Uveal Inflammation in Septic Newborn Foals

M. Leiva, T. Peña, L. Armengou, C. Cesarini, and L. Monreal

Background: Septicemia in humans is described as a leading cause of uveitis, which eventually can induce blindness.

Hypothesis/Objectives: Uveal inflammatory findings could be related to sepsis severity in newborn foals and might be used as an indirect indicator for survival.

Animals: Seventy-four septic foals, 54 nonseptic foals, and 42 healthy foals.

Methods: Prospective observational clinical study. A detailed blinded, ophthalmic examination was performed by boarded ophthalmologists on all admitted newborn foals. Foals were grouped as septic (when blood culture resulted positive or the sepsis score was ≥14), nonseptic, and controls. Based on blood culture results, the septic group was subdivided into bacteremic and nonbacteremic foals.

Results: Blood culture was performed in 62/74 septic foals, from which 35 (56%) were bacteremic and 27 (44%) were nonbacteremic. Anterior uveitis was diagnosed in a significantly (P < .005) higher number of septic/bacteremic foals (14/35, 40%) than in septic/nonbacteremic foals (5/27, 19%), nonseptic foals (4/54, 7%), and control foals (0%). Anterior chamber fibrin was only observed in 4/14 (29%) septic/bacteremic foals with anterior uveitis. Anterior uveitis was also associated with posterior uveitis in 6/35 (19%) septic/bacteremic foals. The diagnosis of uveitis was related to nonsurvival (P = .001, odds ratio = 6.2, 95% confidence interval = 2.1–18.2).

Conclusions and Clinical Importance: Anterior uveitis is highly prevalent in septic newborn foals, especially in those with a positive blood culture, and it should be considered as a survival prognostic factor.

Key words: Chorioretinitis; Equine; Eye; Neonate; Sepsis; Survival indicator; Uveitis.

In adult horses the ocular examination in the diagnosis of systemic diseases is greatly underused.1 This fact is even more evident in newborn foals, in which a complete ocular examination is not routinely included in the physical examination although ocular signs are commonly observed.1

Septicemia is the principal cause of morbidity and mortality in neonatal foals.2–6 Similar to human neonates, septic newborn foals can have bacterial seeding in many locations, such as joints, lung, or the eye.7–14 Ocular manifestations of septicemia can be divided into nonspecific and specific. The nonspecific findings are associated with the general situation of the foal (dehydration, starvation, and so on) and include entropion, blepharitis, conjunctivitis, and corneal ulcers. The specific ocular manifestations of septicemia are mainly related to the poor equine blood-aqueous barrier (BAB)1,15,16 and include anterior uveitis, chorioretinitis, retinal detachment, and optic neuritis.7–14 Anterior uveitis is considered the most frequently reported ocular finding in septic foals1 and is characterized by lacrimation, blepharospasm, photophobia, corneal edema, conjunctival hyperemia, ciliary injection, changes in iris color, miosis, hypotony, and inflammatory products in the anterior chamber.17 These products can be subtle in the form of aqueous flare, or gross with fibrin clots, hypHEMA, or hypopion. Posterior segment lesions may also be observed in these foals when the anterior segment is spared, and they are typical embolic lesions of multifocal hemorrhages, exudates, and focal retinal detachments.13 In some cases, severe intraocular inflammation can induce blindness.1 Thus, diagnosis and treatment of early intraocular inflammation in septic newborn foals is strongly recommended.

Gram-negative bacteria are the most frequently isolated agents in septic newborn foals.15 However, to our knowledge no relationship has been established previously between the type of organism and the incidence and severity of uveitis in the affected foals.

The purpose of this study was to report uveal inflammatory findings in septic newborn foals when they are examined by boarded ophthalmologists and to determine whether these ocular lesions are related with outcome. Our hypothesis was that the severity of uveal disorders in septic foals may be related with sepsis...
severity and might be used as an indirect indicator for survival.

Material and Methods

Foals

In this prospective observational clinical study, all newborn foals younger than 21 days of age admitted to the Equine Teaching Hospital of Barcelona from May 2003 to February 2008, on which a detailed ophthalmic examination was performed, were included. Those healthy newborn foals accompanying their sick dams were also included in the study and used as controls. Health of these control foals was confirmed based on clinical history, physical examination, and blood work routinely performed during their hospitalization (CBC, and plasma biochemistry, serum IgG concentration or both).

Sick foals were then grouped as septic and nonseptic. Foals were included in the septic group when blood culture resulted positive, the sepsis score performed on admission was ≥14 or both. For this study, diagnosis of uveitis made by ophthalmologists was not used in the sepsis score. The septic group of foals was subsequently divided according to blood culture results in bacteremic (blood culture resulted positive) and nonbacteremic (blood culture resulted negative). For classification according to blood culture results, septic foals, in which blood culture was not performed on admission because of previous systemic antibiotic administration by referral veterinarians, were not used. The nonseptic group included the remainder sick foals, which included neonates with a sepsis score <14 and a negative blood culture. These foals had different diagnoses, such as failure of transfer of passive immunity, colic, or hypoxic-ischemic encephalopathy.

Neonates were also grouped by outcome into survivors (discharged alive) and nonsurvivors (died or euthanized during hospitalization because of poor prognosis). Those foals that were discharged because of financial constraints were not included for this purpose. For the nonsurvival group, postmortem examination findings were also recorded to confirm diagnosis.

Ophthalmic Examination

A detailed bilateral ophthalmic examination was performed by boarded ophthalmologists (M.L. and T.P.) in scotopic conditions in all foals (including sick and healthy neonates) without any previous information on clinical history and diagnosis to reduce any bias in the ophthalmic examination findings. In order to minimize foal’s stress during the ocular examination, they were manually restrained and maintained all the time in the mare’s visual area. Examinations were always performed within 16 hours after admission.

Menace response, dazzle reflex, palpebral reflex, and pupillary light reflexes were evaluated in every foal. Diffuse transillumination and slit lamp biomicroscopic examination were performed. Intraocular pressure (IOP) measurements were obtained by application of rebound tonometry, and values were recorded. For each foal, recorded IOP value was an average of 3 successive tonometry readings. Only means with a low standard deviation (SD ≤ 5%) were considered. Indirect ophthalmoscopy was performed in every foal after 15 minutes of instilling 1 drop of topical tropicamide. Direct ophthalmoscopy was performed when needed.

Exudative anterior uveitis was defined as the presence of aqueous flare, fibrin, hypopyon, and/or hyphema. Other minor ocular signs, such as corneal edema, decreased IOP, miosis, keratic precipitates, and synechia, were also considered. Based on the severity of the aqueous flare and the amount of fibrin, hypopyon, and/or hyphema, anterior uveitis was then classified into different grades (mild, moderate, and severe), as reported. Posterior uveitis or chorioretinitis was diagnosed if one or more of the following signs were observed by ophthalmoscopy: white perivascular opacities, areas of grayish or brownish discoloration in the tapetal fundus, grayish to white lesions in the nontapetal area, or opaque/translucent retina with subretinal exudate.

Statistical Analysis

Results

Animal

During the study period, 128 sick newborn foals and 42 healthy newborn foals were examined. Seventy-four of the sick foals were included in the septic group and 54 foals in the nonseptic group. Among the 74 septic foals, 35 neonates were considered as bacteremic and 27 neonates as nonbacteremic; blood culture was not performed in 12 neonates. The septic group included foals with different manifestations, such as enteritis, pneumonia, polyarthritis, meningoencephalitis, and abscesses in the umbilical remnant. The nonseptic group included foals with failure of transfer of passive immunity, hypoxic-ischemic encephalopathy, colic, immaturity, and other nonseptic metabolic disorders. The sepsis score of all these foals was <11. All groups had similar sex, age, and breed distribution (Table 1), except for the bacteremic group, which was significantly younger (P = .003) than nonbacteremic foals.

Uveal Findings

Bilateral anterior uveitis was diagnosed in 19/74 septic foals (26%) and in 4/54 nonseptic foals (7%), while it was not seen in any control foal (Table 2). The Fisher’s exact test showed that the uveitis was diagnosed in a significantly (P = .01) higher number of septic foals when compared with the nonseptic group. Among the 19 septic/uveal-affected neonates, 14 foals were bacteremic (74%) and 5 foals were nonbacteremic (26%).

In the nonseptic group, severe anterior uveitis was detected in 3 foals with hypoxic-ischemic encephalopathy and mild anterior uveitis was seen in 1 foal with several congenital bone malformations and trauma. In the septic/nonbacteremic group, moderate anterior uveitis was diagnosed in 2 foals with bronchopneumonia and hypoxic-ischemic encephalopathy (Fig 1) and in 1 foal with enteritis. Mild bilateral anterior uveitis was diagnosed in 1 foal with enteritis and in another foal with pneumonia,
hypoxic-ischemic encephalopathy, and renal failure. In the septic/bacteremic group, severe anterior uveitis was associated with meningoencephalitis in 2 foals (Fig 2), with enteritis in other 2 foals, and with polyarthritis in 1 foal. Moderate uveitis was seen in 2 foals with pneumonia, 1 foal with enteritis, and 1 foal with polyarthritis. Mild anterior uveitis was observed in 2 foals with enteritis and the 3 remaining foals had meningoencephalitis, pneumonia, and polyarthritis, respectively.

The presence of fibrin in the anterior chamber was only detected in 4 septic/bacteremic foals. Among those, 3 foals had a severe amount of fibrin associated with a severe anterior uveitis, and 1 foal showed mild amount of fibrin associated with a mild anterior uveitis. In the severely affected foals, the amount of fibrin precluded the ability to perform ophthalmoscopic examination on admission (Fig 3). Hyphema or hypopion was not seen in any foal.

Table 1. Incidence and severity of uveitis in newborn foals.

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<thead>
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<td>Control Foals (n = 42)</td>
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<td>Sex</td>
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<tr>
<td>Sex</td>
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<tr>
<td>20 males</td>
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<tr>
<td>22 females</td>
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<tr>
<td>Age (mean, range)</td>
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<td>7.7 days (1–21)</td>
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<tr>
<td>Breed</td>
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<tr>
<td>36 Andalusians</td>
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<tr>
<td>3 Cross-breds</td>
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<tr>
<td>2 Arabians</td>
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<td>1 Holstein</td>
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<td>1 Lusitanian</td>
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</table>

The initial general therapeutic approach included topical nonsteroidal drugs (flurbiprofen), wide spectrum antibiotics (neomycin, polymycin B, and gramicidin), short action mydriatics (tropicamide), and protective artificial tears (carbomer). Tissue plasminogen activator was not needed in any case. In some cases, the use of atropine was needed during the beginning of treatment in order to induce mydriasis. When signs of anterior uveitis began to improve, the frequency of medication was reduced accordingly, and topical treatment was maintained 1 week longer after all clinical signs were resolved. In general, anterior inflammatory signs had a good progression and no adverse sequelae were observed in surviving foals. Intracocular inflammation was not completely resolved in nonsurvivors, showing different degrees of aqueous flare and fibrin on the anterior chamber.

**Ocular Treatment and Progression**

Concomitant with systemic specific treatments, uveitic foals also were topically treated to reduce pain and minimize the intraocular damage associated with uveitis. The initial general therapeutic approach included topical nonsteroidal drugs (flurbiprofen), wide spectrum antibiotics (neomycin, polymycin B, and gramicidin), short action mydriatics (tropicamide), and protective artificial tears (carbomer). Tissue plasminogen activator was not needed in any case. In some cases, the use of atropine was needed during the beginning of treatment in order to induce mydriasis. When signs of anterior uveitis began to improve, the frequency of medication was reduced accordingly, and topical treatment was maintained 1 week longer after all clinical signs were resolved. In general, anterior inflammatory signs had a good progression and no adverse sequelae were observed in surviving foals. Intracocular inflammation was not completely resolved in nonsurvivors, showing different degrees of aqueous flare and fibrin on the anterior chamber.

**Blood Culture Results**

Blood culture was performed in 62/74 septic foals, from which 35 (56%) resulted bacteremic and 27 (44%) nonbacteremic. Among the bacteremic foals, 14/35 neonates (40%) presented with bilateral uveal inflammatory signs. In these foals, the most commonly isolated agent was *Escherichia coli* (9/14 foals; 64%). In 2 of these foals, *E. coli* isolation was cocultured with other bacteria, such as *Enterobacter aerogenes* and *Providencia stuartii*. In the

Table 2. Incidence and severity of uveitis in newborn foals.

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<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Sex</td>
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<td>0 (0%)</td>
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<td>1 (1+), 3 (3+3)</td>
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<td>0 (0%)</td>
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Data expressed as number of foals (%).

Severity grading: +1, mild; +2, moderate; +3, severe.

aBlood culture was not performed because these foals were already receiving systemic antibiotics on admission.

bFundus examination could not be performed in 3 foals because of severity of anterior chamber signs.
remainder bacteremic/uveal-affected animals \((n = 5)\), different bacteria were isolated, such as *Klebsiella pneumoniae*, *Alcaligenes faecalis*, *Plesiomonas shigelloides*, *Citrobacter youngae*, and *Pasteurella* spp.

In the bacteremic/nonuveal-affected foals \((n = 21)\), the most frequently isolated agents were *E. coli* (8 foals), *Pasteurella* spp. (5 foals), *K. pneumoniae* (4 foals), and *Streptococcus* spp. (2 foals). Other less commonly isolated agents were *Clostridium perfringens* and *Enterobacter cloacae*. In 2 foals, *E. coli* isolation was associated with *Klebsiella* spp. and *Pasteurella* spp., respectively.

**Outcome**

For the outcome evaluation, 1 septic nonbacteremic and 2 bacteremic neonates were excluded because of financial constraints; from them, 1 bacteremic foal had anterior uveitis. From the remainder 125 sick foals, 104 were survivors (83.2%) and 21 nonsurvivors (16.8%). The case fatality rate differed between groups, being 0% in the control group, 4% (2/54) in the nonseptic group and 27% (19/71) in the septic group (Fisher’s exact test, \(P < .001\)). Among the septic group, the case fatality rate was 30% in bacteremic foals (10/33) and 35% in nonbacteremic foals (9/26). In the bacteremic group, the case fatality rate in foals with anterior uveitis was 54% (7/13), while it was 15% in foals without anterior uveitis (3/20). In the septic/nonbacteremic group, the case fatality rate in foals with anterior uveitis was 60% (3/5), while it was 29% (6/21) in foals without anterior uveitis. In the septic/bacteremic group, the case fatality rate in foals with chorioretinitis was 83% (5/6), while it was 19% (5/26) in foals without posterior uveitis (fundus examination could not be performed in 1 septic bacteremic foal) (Table 3).

Nonsurvivors had a significantly higher rate of uveitis \((P < .001)\), fibrin clots in the anterior chamber \((P = .015)\), and chorioretinitis \((P < .001)\) (Table 3). Uveitis was significantly more severe in nonsurvivors (Mann-Whitney U-test, \(P < .001\)). Diagnosis of uveitis was an independent risk factor for a poor prognosis when adjusted by age (odds ratio \([\text{OR}] = 6.2\), 95% confidence interval \([\text{CI}] = 2.1–18.2\); \(P = .001\)). After a multivariate model approach, adjusting presence of uveitis by age and subtype of sepsis, the effect of uveitis as a risk factor was lower (OR = 4.3, 95% CI = 1.3–14.5; \(P = .0194\)) although the previous conclusion was not altered, and the interaction with subtype of sepsis was not significant \((P = .924)\). These results show that presence of uveitis is a good predictor of poor prognosis for survival with independence of results of subtype of sepsis. However, in the final multivariate model when adjusted by blood culture and age, uveitis was a better predictor of death.

**Discussion**

Uveitis has been commonly associated with human sepsis and it has been considered as an indirect predictor for survival in neonatal medicine.\(^{19–22}\) In foals, although it is generally accepted that uveitis may be a frequent finding in septic neonates, there are no studies establishing its real incidence and clinical relevance. The present study shows that the incidence of uveitis in septic foals is
high, and that uveitis is related with poor prognosis in newborn foals.

By definition, the neonatal period in human medicine includes the 1st 4 weeks of the postnatal period. In equine medicine, although there are no data about the specific duration of the neonatal period, it is generally accepted as a similar period. Taking into consideration previous studies on newborn foals, a period of 21 days was considered for the purpose of this study.

Because of the necessity of early diagnosis and treatment of sepsis for a good outcome, reliable and rapidly available tests for diagnosis of infection are desirable. Positive blood cultures are the only definitive ante-mortem test of bacteremia, but a minimum of 24 hours is usually required for preliminary results. A sepsis scoring system, initially developed and proposed by Brewer and Koterba, has been used by many referral and teaching hospitals as an overall approach to the diagnosis of bacterial infection in the neonatal foal. By assigning numerical values to a number of clinicopathologic variables, including ocular signs, the authors devised a sepsis scoring system with a high sensitivity and specificity compared with confirmed sepsis by blood culture. More recently, the accuracy of this system has been questioned, but it still remains a valuable and frequently used clinical tool. This study confirms that a complete ocular examination should routinely be performed in sick foals and uveal findings can be used for prognosis of survival.

All microorganisms able to induce septicemia can theoretically enter BAB and blood-retinal barrier (BRB) inducing different degrees of intraocular signs. These signs will depend mainly on the severity of BAB/BRB damage, being the fenestrated BAB more predisposed to endogenous damage than the nonfenestrated BRB. During the preantibiotic era, human newborns with sepsis were well-known to be at risk for severe ocular involvement, particularly for endogenous panophthalmitis. Since the introduction of antimicrobial drugs, the severity of septicemia and related ocular signs has decreased.

Although septic uveitis is rarely diagnosed in adult horses, it is commonly seen in newborn foals, especially those that have had inadequate transfer of immunoglobulins and those with other immunodeficiencies. Ocular signs in septic horses can be present unilaterally or bilaterally. Among all the septic-uveitic foals of the study, no unilateral cases were diagnosed, although an asymmetrical presentation was frequently observed. The incidence of bilateral uveitis was significantly higher in septic foals (26%) than in the nonseptic (7%) or control (0%) groups. This finding is not surprising given the importance of the vascular endothelium in the pathogenesis of sepsis and the already known weakness of the equine BAB. Among the septic foals, bacteremic neonates had a higher incidence of uveitis (40%) than non-bacteremic neonates (19%). This finding suggests that uveitis could be considered as a component of the non-specific inflammatory response syndrome. Further studies are needed to determine whether the intraocular findings are immuno-mediated or associated with the intraocular presence of the infectious organism.

The presence of fibrin clots in the anterior chamber and chorioretinitis were specific findings of septic/bacteremic foals, indicating that the severity of BAB/BRB damage in septic foals might be greater than in nonseptic foals. The high capacity for fibrin production in neonatal foals is already known, and in severe cases it can even fill the complete anterior chamber, preventing adequate funduscopic examination. That was the case of severely affected foals in this study, and it could have led to the underestimation of the diagnosis of chorioretinitis. If not treated, the fibrin can induce corneal or lens sequelae, inducing different degrees of hemeralopia or even blindness. Moreover, in our study bilateral chorioretinitis in septic foals was less frequently diagnosed than anterior uveitis, being mainly diagnosed in foals with a severe form of anterior uveitis. This fact could be related with the weakness of the BAB to endogenous damage when compared with BRB. In all cases chorioretinitis was located around the optic nerve head, coinciding with the most permeable point of the BRB.

Although both Gram-positive and -negative microorganisms have been previously related with anterior uveitis in newborn foals, in this study only Gram-negative bacteria were detected in the uveitic-bacteremic foals. Some studies in humans suggest that infections caused by Gram-positive organisms are associated with much lower inflammatory response than Gram-negative induced sepsis. Because of the low number of Gram-positive septic foals in the present study, it was not possible to elucidate the exact reason for the lack of Gram-positive-induced uveitis. Particular etiologies of bacteremia are in part dependent on the age and concurrent disease status of the animal. The most frequently isolated organism in this study was E. coli (64%), which had previously shown its avidity for uveal tissue. The pathogenicity of E. coli in the eye has not been clearly established yet. Ocular disease could be associated with direct bacterial spreading to the uveal

Table 3. Uveal findings in 125 sick newborn foals regarding outcome.

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<th>Survival Foals (n = 104)</th>
<th>Nonsurvival Foals (n = 21)</th>
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<tbody>
<tr>
<td>Anterior uveitis</td>
<td></td>
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</tr>
<tr>
<td>(n = 22)</td>
<td>(4 nonseptic foals)</td>
<td>(7 septic/bacteremic foals)</td>
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<tr>
<td>(6 septic/bacteremic foals)</td>
<td>(3 septic/nonbacteremic foals)</td>
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<td>(2 septic/nonbacteremic foals)</td>
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<tr>
<td></td>
<td>1 (1%)</td>
<td>3 (14%)</td>
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<tr>
<td></td>
<td>(1 septic/bacteremic foal)</td>
<td>(3 septic/bacteremic foals)</td>
</tr>
<tr>
<td>Fibrin in anterior chamber (n = 4)</td>
<td>5 (24%) a</td>
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<tr>
<td>Posterior uveitis</td>
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<tr>
<td>(n = 6)</td>
<td>(1 septic/bacteremic foal)</td>
<td>(5 septic/bacteremic foals)</td>
</tr>
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</table>

Data expressed as number of foals (%). A fundus examination could not be performed in 3 nonsurvival foals because of the severity of anterior chamber signs.
tissue or with local vascular alterations induced by secondary endotoxemia, causing inflammation and exudation of proteins and cells into the aqueous humor. Further studies are needed to determine whether Gram-negative bacteria resulting uveitis is a consequence of direct bacterial action or of immune-mediated injury driven by the microbial heteroantigen. As far as the authors are aware, no previous studies have related newborn uveitis to equine recurrent uveitis in the adult.

During the last years, improvements have been made in the diagnosis and treatment of sepsis in neonatal foals, but methods for accurately predicting survival are still rarely reported.1,7,17,19,33 In our study a significant poor outcome for the septic-uveitic foals was observed when compared with nonuveitic foals. This is an easily understandable fact if ocular signs are considered as one of the nonspecific inflammatory responses commonly related with the clinical condition. The present findings expressly do not support the use of uveitis as the only prognosis factor for survival, but do suggest a poor prognosis of survival for affected foals.

It is a common practice to perform a complete ocular examination in all septic human patients.19,21 Unfortunately, ophthalmologic examinations in horses are not routinely performed, what might underdiagnose many ocular disorders. Findings of this study remark the clinical relevance of performing a complete ocular examination in all sick foals, in order to help in the diagnosis and prognosis of uveal diseases, as well as to guarantee visual soundness.

The fact that bacteremic foals were statistical younger than nonbacteremic foals in this study might be related with an early referral of the former neonates and the delayed referral in those receiving antibiotics in the stud. However, this result did not affect the analysis for survival of uveitic foals.

In conclusion, this study shows that uveitis is a frequent ocular disorder detected in septic newborn foals. Furthermore, the study suggests that uveitis can be used as an indirect marker of severity in septic neonates, as well as an independent predicting prognosis factor for survival.

Footnotes
koKa SL-14, KoWa Company, ToKyoo, JapaN
Tonopen XL, Mentor, Norwell, MA
Care, Tioslat, Helsinki, Finland
Heine Omega 180, Herrsching, Germany
Colircusı´tropicamida, Alco´n cusı´, Barcelona, Spain
3.5 Coaxial Ophthalmoscope, Welch Allyn, Juning, Germany
SPSS Inc, Chicago, IL

References