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Retrospective Study

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Retrospective evaluation of 155 adult equids and 21 foals with tetanus from Western, Northern, and Central Europe (2000–2014). Part 2: Prognostic assessment

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Abstract

Objective – To identify prognostic variables for adult equids and foals with tetanus.
Design – Multicenter retrospective study (2000–2014).
Setting – Twenty Western, Northern, and Central European university teaching hospitals and private referral centers.
Animals – One hundred fifty-five adult equids and 21 foals with tetanus.
Interventions – None.
Measurements and Main Results – Variables from history and clinical examination were statistically compared between survivors and nonsurvivors (adults: 49 survivors, 85 nonsurvivors; foals: 7 survivors, 10 nonsurvivors). Cases euthanized for financial reasons were excluded. Mortality rates in adults and foals were 68.4% and 66.7%, respectively. Variables associated with survival in adults included: standing, normal intestinal sounds and defecation, voluntarily drinking, eating soft or normal food, lower heart and respiratory rates, high base excess on admission, longer diagnosis time, treatment and hospitalization delay, and mild severity grade. Variables associated with death included: anorexia, dysphagia, dyspnea, low blood potassium concentration on admission, moderate and severe disease grading, development of dysphagia, dyspnea, recumbency and seizures during hospitalization, treatment with glycerol guaiacolate, intravenous fluids, and intravenous glucose solutions. Variables associated with survival in foals included standing on admission, voluntarily eating soft food and drinking, older age, and longer hospitalization delay. Outcome was not different between different tetanus antitoxin (TAT) dosages, although there was a trend of increasing survival rate with increasing TAT dosages. Cases with appropriate vaccination prior to development of tetanus were rare, but had improved outcome and shorter hospitalization.
Conclusions – Prognosis for equine tetanus is poor with similar outcome and prognostic factors in foals and adults. The prognostic assessment of cases with tetanus provides clinicians with new evidence-based information related to patient management. Several prognostic indicators relate to the ability to eat or drink, and more severe clinical signs relate to poor outcome. Increasing intravenous dosages of TAT has no significant effect on outcome, but the positive trend identified may support a recommendation for high intravenous TAT dosages. Further evaluation is warranted.

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Keywords: *Clostridium tetani*, epidemiology, horses, infectious disease, survival

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Abbreviation

TAT tetanus antitoxin

Introduction

The prognosis for tetanus in horses is considered to be poor, but survival rates vary considerably in previously published studies, ranging from 25%[1] to 75%.[2] In diseases with a poor prognosis, recognition of prognostic indicators is valuable for appropriate case management and owner advice. Although the prognosis for equine tetanus was assessed in previous studies,[1–7] few have evaluated specific prognostic factors. The previously published studies suffer from absent or poorly defined case definitions, inclusion or exclusion criteria,[1–5,7] low case numbers and therefore poor statistical power,[1,2,4–6] absence of multivariate statistical analysis,[1,2,4–7] inclusion of only a limited number of variables and no blood parameters,[1,4,5,7] or have excluded cases presented in a terminal state.[5] In addition, most reports only describe cases from before 2000[1–4,7] or do not reflect the current approach in equine medicine in Europe.[5–7] Furthermore, although neonatal tetanus is considered to be a separate entity in human medicine with different prognostic factors compared with adult tetanus,[8] none of the previously published studies determined prognostic factors specifically for foals affected by tetanus.

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Gaby van Galen, Joke Rijckaert, Tim Mair, and Claude Saegerman were chosen according to the amount of work performed.

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Although intensive care techniques were practiced in tetanus cases as early as the 1970s,[9] intensive care monitoring and therapeutic options are now more widely available. Since human tetanus is considered "*a Third World disease that requires First World technology for treating*," with mortality rates inversely correlated to the availability and adequacy of intensive care management,[10–12] recent developments in equine veterinary care may potentially have had a significant impact on survival rates. Moreover, administration of tetanus antitoxin (TAT)[5,13] and different routes of TAT administration are questioned[1,6,13] and data on the effects of TAT on the outcomes in equine patients are very limited. In order to better manage affected horses in an evidence-based manner, more information about the variables that influence outcome in horses are required.

The aims of this study were to identify variables that had an impact on the outcome of adult horses and foals that were recently treated in referral hospitals for tetanus, and to determine whether the outcome of those cases was related to the use of different TAT dosages.

Materials and Methods

Data collection

Through the Atypical Myopathy Alert Group Network[14] and the European College of Equine Internal Medicine, potential scientific collaborators were identified. The following criteria for collaborators were used: (1) Located in Western, Northern, or Central Europe, (2) working in an academic equine referral center or a large, private referral center with a good reputation and interest in scientific research, (3) working in a referral clinic where at least one equine internal medicine specialist (Diplomate ECEIM or ACVIM) is employed. At least one academic clinic was searched and contacted for every country. All collaborators who had diagnosed tetanus cases since the year 2000 and who agreed to collaborate in the study, received a case definition and a detailed, standardized data spreadsheet for specific variables to be retrospectively retrieved from the medical records. Subsequently, all data were gathered and checked by the first author (G. van Galen), and analyzed by the first and last authors (G. van Galen, C. Saegerman).

Case definition

The following case inclusion criteria were used for this study: (1) cases with the clinical diagnosis of tetanus, (2) admitted to the referral hospital of the collaborator, and (3) admitted in the years 2000 to 2014. Since no definitive diagnostic tests are available for tetanus, the diagnosis of tetanus was based on the presence of the most typical

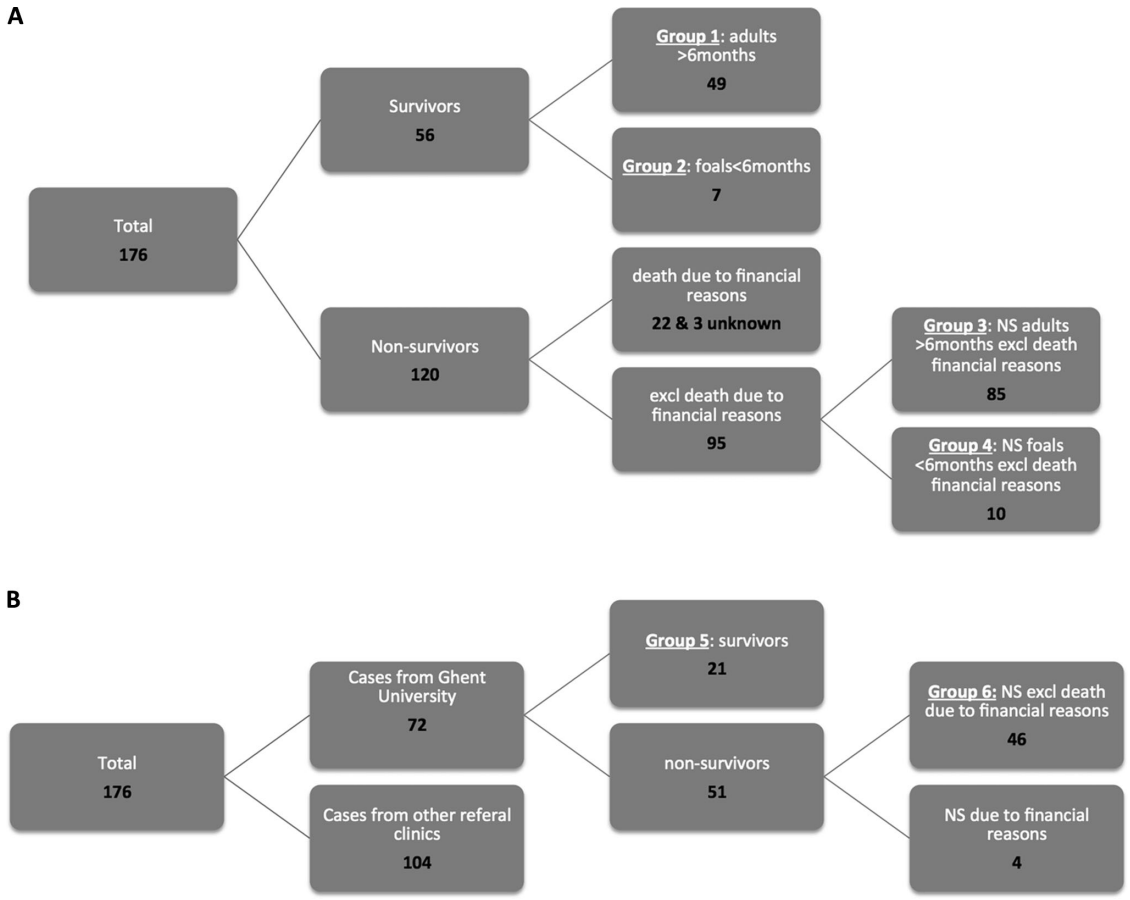

Figure 1: (A and B) Groups of the tetanus cases for statistical comparisons. NS, nonsurvivor.

and consistent clinical signs reported in the published literature (eg, stiffness, trismus, or protrusion of the third eyelid), and the absence of clinical signs, laboratory results and, where applicable, postmortem findings that indicated any other disease that could explain the clinical presentation.[13] Cases with the following findings were excluded from the study: (1) serum biochemical evidence of significant rhabdomyolysis (creatine kinase activity of > 10,000 U/L, with or without myoglobinuria), (2) hypocalcemia (ionized calcium < 1 mmol/L [2 mEq/L], total calcium < 2 mmol/L [4 mEq/L]), (3) signs and laboratory results suggestive of hepatic encephalopathy or significant liver damage (gamma-glutamyl transferase activity > 150 U/L), and (4) signs or result of concomitant examinations suggestive of other neurological conditions.

Retrieved data from reported cases and definitions

Detailed information about the cases was retrieved retrospectively from the medical files with owner informed consent. For a minority of the cases no consent could be obtained because of absence of standard consent contracts on admission and unsuccessful attempts to reach the owner. Demographic- and management-related data, details of the clinical history, clinical examination on admission, complications and clinical signs that developed during hospitalization, treatments and final outcome were detailed in Part 1 of this study.[15]

Groups

Based on resemblance of the clinical parameters in foals older than 6 months and adults, and the fact that all foals should theoretically have received a first vaccination at this age, cases were divided into horses >6 months old (adults) and <6 months old (foals). Figure 1 illustrates a schematic explanation of the division of the tetanus cases in groups based on outcome and age. Group 1 was surviving adult horses, Group 2 surviving foals, Group 3 nonsurviving adult horses, Group 4 nonsurviving foals, Group 5 surviving horses from Ghent University (adults and foals), and Group 6 nonsurviving horses from Ghent University (adults and foals). Cases that were euthanized

due to financial reasons were excluded from all nonsurvivor groups (Groups 3, 4, and 6).

Statistical Methods

Comparisons of surviving and nonsurviving groups

For the prognostic assessment of adult tetanus, Group 1 was compared to Group 3, and for a prognostic assessment of foals with tetanus, Group 2 was compared to Group 4. Additionally, to rule out institute-related bias, a prognostic assessment of cases from Ghent University was performed comparing Group 5 to Group 6. For all statistical comparisons, horses that were euthanized due to financial reasons and variables with a low response rate (<30%) and low incidence were excluded. Statistical analyses were performed using commercial statistical software.[a] $P < 0.05$ was considered significant.

Univariate analysis

To compare the surviving cases versus nonsurviving cases, dichotomous and categorical variables were assessed by odds ratio (OR), and quantitative variables were assessed by a two-sample Wilcoxon rank-sum test. When complete separation (zero cells) occurred, the Firth logit method allowed interference of ORs and confidence intervals. Severity grades were compared between groups with a Fisher's exact test.

Multivariate analysis

All variables with a P-value < 0.05 in the univariate analysis were entered in a multivariate logistic regression model. Two multivariate regressions were performed: one where only the variables from the history and the clinical examination on admission were taken into account, and one where only the variables after admission were taken into account (complementary examinations, complications, and treatments). To assess collinearity, a backward elimination of variables was performed. Variables that induced a modification of OR of >20% were retained in final analysis where the interaction was tested. All pairwise interactions between the variables in the final model were examined for significance (if biologically relevant). Goodness of fit was assessed using the Hosmer–Lemeshow goodness-of-fit test.

Effect of TAT on outcome

The outcome of adult horses (Groups 1 and 3) treated with intravenous TAT was compared with a Fisher's exact test among different categories of total dosage received (<25,000 IU, 25,000–50,000 IU, 50,000–100,000 IU, 100,000–150,000 IU, 150,000–200,000 IU, >200,000 IU).

Results

In total, 185 cases were reported of which 176 cases fulfilled the inclusion criteria for this study. Of those 176 cases, 120 were nonsurvivors and 56 were survivors, giving a survival rate of 31.8% and mortality rate of 68.2%. Survival rate for the adult cases was 31.6% (49/155) and for the foals 33.3% (7/21). Of the nonsurviving cases, 21 died, 22 were euthanized due to financial reasons, and the remainder was euthanized for ethical/humane reasons. Of the survivors, 93.8% were reported to have fully recovered, but 2 horses suffered from sequelae: 1 horse was affected by an unspecified lameness and another by ataxia. Three of the 4 correctly vaccinated horses survived and had mild (2) and moderate (1) disease severity and shorter hospitalization periods (10, 12, and 13 days) than other survivors (average 20.5 days). The one that did not survive was euthanized for ethical reasons, not for financial reasons. Correct vaccination was doubtful since it was recently purchased and the seller assured the new owners that the horse was correctly vaccinated. For a full detailed description of the cases the readers are referred to Part 1 of the study.[15]

Statistical analysis

Comparisons of surviving and nonsurviving groups

Forty-nine equids were allocated to Group 1, 7 to Group 2, 85 to Group 3, 10 to Group 4, 46 to Group 5 and 21 to Group 6 (Figure 1). Variables associated with survival in adult cases were as follows: standing, normal intestinal sounds and defecation, voluntarily drinking, eating soft and/or eating normal food on admission, and mild disease grading. Adult survivors had a significantly lower heart rate, lower respiratory rates, higher blood potassium concentration, higher base excess on admission, and longer diagnosis time, treatment delay and hospitalization delay compared to nonsurvivors. Variables associated with nonsurvival in adults were: anorexia, dysphagia, dyspnea on admission, moderate and severe disease grading, development of dysphagia, dyspnea, recumbency and seizures during hospitalization, treatment with glycerol guaiacolate, intravenous fluids, and intravenous glucose solutions (Tables 1 and 3). Although no statistical significance was identified, a trend was seen ($P = 0.053$) with survivors of the adult group having received a higher total intravenous dosage of TAT than nonsurvivors (survivors mean = 106 IU, range 186 ± 96,176, $n = 42$; nonsurvivors mean = 77 IU, range 164 ± 49,261 IU, $n = 67$; $P = 0.053$).

Variables associated with survival in foals were standing, voluntarily eating soft food, and drinking on admission. Survivors had a significantly older age and

Table 1: Variables that are statistically different between adult surviving and nonsurviving tetanus cases (Group 1 vs Group 3)

	Descriptive data						Statistical comparison S versus NS			
	S ($n = 49$)			NS ($n = 85$)			UVA			MVA
Categorical variables	***n***	***N***	**%**	***n***	***N***	**%**	***P*-value**	**OR**	**CI 95**	***P*-value**
On admission										
Standing	47	49	95.9	71	85	83.5	0.049	4.63	1.01–21.33	
Anorexia	13	43	30.2	49	72	68.1	<0.001	0.20	0.09–0.46	0.026*
Dysphagia	21	46	45.7	52	76	68.4	0.014	0.39	0.18–0.83	
Dyspnea	11	45	24.4	38	68	55.9	0.001	0.26	0.11–0.59	
Normal intestinal sounds	23	37	62.3	10	41	24.4	0.001	5.09	1.92–13.49	
Defecation	27	35	77.1	8	36	22.2	<0.001	11.81	3.87–35.97	0.002*
Grade of severity[x]										
Moderate	20	49	40.8	37	85	43.5	0.005	0.30	0.13–0.69	
Severe	6	49	12.2	37	85	43.5	<0.001	0.07	0.02–0.22	
Complications/clinical signs developing during hospitalization										
Dysphagia	23	48	47.9	65	73	89.0	<0.001	0.11	0.04–0.29	
Dyspnea	7	48	14.6	57	76	75.0	<0.001	0.06	0.02–0.15	
Recumbency	8	48	16.7	62	78	79.5	<0.001	0.05	0.02–0.13	<0.001
Seizures	1	48	2.1	24	78	30.8	0.003	0.05	0.006–0.37	
Treatment										
Glyceryl guaiacolate	3	49	6.1	20	80	25.0	0.012	0.20	0.05–0.70	
IV fluids	36	49	73.5	77	80	96.3	0.001	0.11	0.03–0.40	
Free drinking	44	49	89.8	29	77	37.7	<0.001	14.56	5.18–40.94	<0.001
Voluntary eating normal food	22	49	44.9	13	76	17.1	0.001	3.95	1.74–8.27	
Voluntary eating soft food	32	45	71.1	15	75	20.0	<0.001	9.85	4.18–23.21	
IV glucose	18	49	36.7	47	78	60.3	0.011	0.38	0.18–0.80	

Numerical variables	**Mean**	**SD**	***N***	**Mean**	**SD**	***N***	***P*-value UVA**	***P*-value MVA**
Diagnosing time (days)	2.55	4.09	44	0.55	0.77	84	0.002	
Treatment delay (days)	2.60	4.12	43	0.53	0.77	80	0.001*	
Hospitalization delay (days)	2.92	4.46	44	0.67	0.82	83	0.001	
Heart rate (bpm)	55.51	11.81	47	68.07	19.78	76	0.0008	
Respiratory rate (rpm)	35.30	20.75	40	46.99	26.08	67	0.02	
Potassium (mmol/L or mEq/L)	3.77	0.38	23	3.37	0.33	34	0.0005	
pH	7.40	0.04	18	7.36	0.07	33	0.04**	
Base excess (mmol/L)	2.67	3.18	24	0.03	5.63	50	0.047**	

*Significantly different between groups in the multivariate analysis for variables on history and clinical examination on admission.

**Significantly different between groups in the multivariate analysis for variables on complementary examinations, complications during hospitalization and treatment.

[x]The severity grades were defined as specified in van Galen et al. Part 1.[15]

S, surviving cases; NS, nonsurviving cases; SD, standard variation; OR, odds ratio to survive; CI 95, 95% confidence interval; *N*, number of horses with a response for this specific parameter; n, number of horses with a positive response; UVA, univariate analysis; MVA, multivariate analysis. Group 1, surviving adult horses (>6 months of age); Group 3, nonsurviving adult horses (>6 months of age). For Group 3, all cases that were euthanized due to financial reasons were excluded.

longer hospitalization delay compared to nonsurvivors (Tables 2 and 3).

Variables associated with good outcome in the Ghent University cases were normal defecation, voluntary eating of soft food and free drinking on admission. Those associated with nonsurvival included severe disease grade, development of dysphagia, dyspnea and recumbency during hospitalization, treatment with acepromazine and glycerol guaiacolate administration. Survivors had a significantly longer diagnosis time, treatment delay and hospitalization delay, lower heart rate, higher base excess, and higher pH compared to nonsurvivors (Table 4).

For adult cases, anorexia, defecation, recumbency, and free drinking were retained as prognostic indicators (Table 1). For foals, only voluntarily eating soft food was retained (Table 2). For the Ghent University cases, normal defecation, recumbency, and voluntary eating of soft food were retained (Table 4).

Effect of TAT dosage on outcome

Outcome between the different total received TAT dosages was not significantly different ($P = 0.33$),

Table 2: Variables that are statistically different between surviving and nonsurviving tetanus foals (Group 2 vs Group 4)

	Descriptive data						Statistical comparison S versus NS			
	S ($n = 7$)			NS ($n = 10$)			UVA			MVA
Categorical variables	***n***	***N***	**%**	***n***	***N***	**%**	***P*-value**	**OR**	**CI 95**	***P*-value**
On admission										
Standing	6	7	85.7	2	10	20.0	0.018	24	1.74–330.80	
Treatment										
Free drinking	6	7	85.7	2	8	25.0	0.033	18.0	1.27–255.74	
Voluntary eating soft food	5	7	71.4	0	8	0.0	0.028	37.4	1.49–936.27	0.027[@]

Numerical variables	**Mean**	**SD**	***N***	**Mean**	**SD**	***N***	***P*-value UVA**	***P*-value MVA**
Age (years)	0.32	0.21	7	0.08	0.06	9	0.01	
Hospitalization delay (days)	2.79	2.67	7	0.26	0.62	10	0.03	

*Significantly different between groups in the multivariate analysis for variables on history and clinical examination on admission.
[@]Significantly different between groups in the multivariate analysis for variables on complementary examinations, complications during hospitalization and treatment.S, surviving cases; NS, nonsurviving cases; SD, standard variation; OR, odds ratio to survive; CI 95, 95% confidence interval; *N*, number of horses with a response for this specific parameter; *n*, number of horses with a positive response; UVA, univariate analysis; MVA, multivariate analysis. Group 2, surviving foals (<6 months of age); Group 4, nonsurviving foals (<6 months of age). For Group 4, all cases that were euthanized due to financial reasons were excluded.

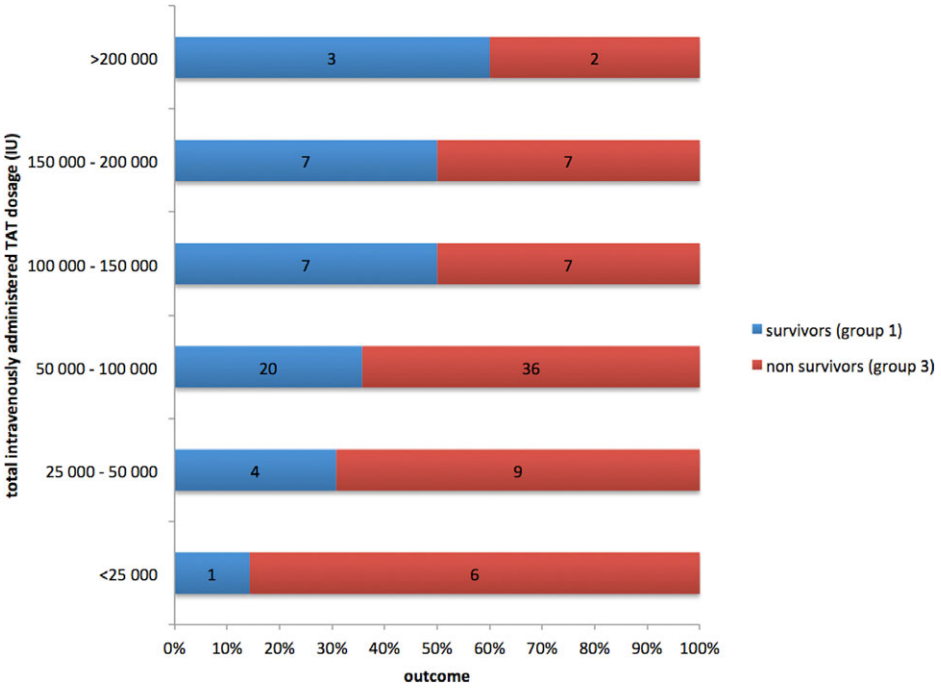

Figure 2: The outcome of adult horses that received intravenous tetanus antitoxin (TAT) according to the total administered dosage. Group 1, surviving adult horses (>6 months of age); Group 3, nonsurviving adult horses (>6 months of age). For Group 3, all cases that were euthanized due to financial reasons were excluded. The outcome was statistically not different between the different dosage groups ($P = 0.33$).

although a trend of increasing survival rate with increasing total dosages was observed, as shown in Figure 2.

Discussion

This study reports a prognostic assessment in a large population of equids with tetanus, providing more recent information on more variables compared to what is available in the literature. Several prognostic indicators for outcome were identified that can assist clinicians in making evidence-based decisions about initiating or continuing treatment. It should be noted that this is a risk analysis and by no means provides clear-cut answers for all clinical cases. Although the presence of a specific poor

Table 3: Comparison of severity grades among survivors and nonsurvivors of tetanus in adult cases (Group 1 and 3) and foals (Group 2 and 4) with a Fisher's exact test

Adult horses

	S ($n = 49$)			NS ($n = 85$)			
	n	***N***	**%**	***n***	***N***	**%**	***P*-value**
Mild	23	49	46.9	9	85	10.6	<0.001*
Moderate	20	49	40.8	37	85	43.5	0.86
Severe	6	49	12.2	37	85	43.5	<0.001*
Very severe	0	49	0.0	2	85	2.4	0.53

Foals

	S ($n = 7$)			NS ($n = 10$)			
	n	***N***	**%**	***n***	***N***	**%**	***P*-value**
Mild	3	7	42.9	3	10	30.0	0.64
Moderate	3	7	42.9	0	10	0.0	0.051
Severe	1	7	14.3	5	10	50.0	0.30
Very severe	0	7	0.0	2	10	20.0	0.49

*Significantly different between groups. The severity grades were defined as specified in van Galen et al. Part 1.[15]

N, number of horses with a response for this specific parameter; *n*, number of horses with a positive response. Group 1, surviving adult horses (>6 months of age); Group 3, nonsurviving adult horses (>6 months of age). For Group 3, all cases that were euthanized due to financial reasons were excluded. Group 2, surviving foals (<6 months of age); Group 4, nonsurviving foals (<6 months of age). For Group 4, all cases that were euthanized due to financial reasons were excluded.

prognostic clinical parameter carries an increased analytical risk for nonsurvival, outcome is not necessarily poor; chance of survival is just expected to be lower than when the specific variable is absent. Therefore, the authors recommend to base irrevocable decisions of euthanasia on the presence of multiple poor prognostic indicators, or when those indicators do not improve following treatment. In addition, the statistically significant differences between survivors and nonsurvivors identified with the univariate analysis do not take into account possible interactions between the different variables tested. Therefore, they might not have a direct effect on outcome. With the multivariate analysis, interactions between variables are taken into account making them more reliable as prognostic factors. In order to optimize use of prognostic variables at different time points in case management, 2 different multivariate analyses were performed. One took into account the variables from history and the clinical examination on admission, reflecting the first veterinary visit and allowing prognostic assessment in an early phase. A second multivariate analysis was undertaken with the variables from concomitant examinations, complications, and treatments, allowing prognostic assessment later on.

The majority of the prognostic indicators identified in the current study are related to the ability to eat or drink, and the subsequent required treatment. Normal intestinal sounds and defecation, and voluntarily drinking and eating soft or eating normal food were associated with good outcome. Anorexia, dysphagia on admission, development of dysphagia during hospitalization, necessity for treatment with intravenous fluids and intravenous glucose solutions, and low blood potassium concentrations were associated with poor outcome. Only few of those variables were retained in the multivariate analysis for each age group, probably because of strong correlation between these variables. Multiple complications related to the gastrointestinal tract were reported in Part 1 of the study (eg, hyperlipemia, gastrointestinal impaction, weight loss, diarrhea, gastrointestinal distension, aspiration pneumonia, and cecal impaction with subsequent rupture).[15] These findings highlight how important a normal functioning gastrointestinal tract is for the outcome of horses suffering from tetanus. Clinicians should support this with close monitoring of the gastrointestinal tract, preventive or early treatment when complications arise and focus on nutritional support. The remaining prognostic factors were predominantly related to severity of neuromuscular dysfunction and respiratory compromise.

In addition to identifying prognostic factors in adult horses with tetanus, the present study also identified prognostic factors for foals with tetanus. The only report of tetanus in the existing literature suggests extremely poor outcomes for foals, with 6 out of 6 reported foals dying.[2] In human and canine neonates with tetanus, the outcome is also worse than in adult cases.[8,16–18] The outcome for foals in the current study is comparable to neonatal human cases (73.2% case fatality).[8] With a mortality rate of 68.4% and 66.7% for adult horses and foals, respectively, there was no significant difference between the outcomes of foals and adults in this study. Only within the foal group itself, younger age was found to be a poor prognostic indicator with all nonsurviving foals being under the age of 2 months. This corresponds with young age at onset of disease (<5–7 days) being a poor prognostic indicator in human neonates affected by tetanus.[8,16]

The overall survival rate in the present study was similar to that recorded in several older equine studies from various countries and continents (41% in Morocco,[5] 23.7% in Brazil,[7] 25% in United States,[1] 32% in Belgium[4]). Survival rates have clearly not improved compared to studies from the 1970s that report equine survival rates of 50%[3] and 77.5%.[2] Artificial ventilation following central muscle relaxation is the critical care technique that improved outcome over time in human beings, but is currently not used in adult horses and could largely explain this discrepancy.[11,12] Although this is a well-established technique for foals,[19] artificial ventilation

Table 4: Demographic, management-related, and clinical variables that are statistically different between surviving and nonsurviving tetanus cases from Ghent university (Group 5 vs Group 6)

	Descriptive data						Statistical comparison S versus NS			
	S ($n = 21$)			NS ($n = 46$)			UVA			MVA
Categorical variables	***n***	***N***	**%**	***n***	***N***	**%**	***P*-value**	**OR**	**CI 95**	***P*-value**
On admission										
Normal defecation	6	8	75	0	9	0	0.02	49.40	2.02–1207	0.02*
Complications/clinical signs developing during hospitalization										
Dysphagia	14	21	66.7	41	44	93.2	0.01	0.15	0.03–0.64	
Dyspnea	4	21	19.0	29	44	65.9	0.001	0.12	0.03–0.43	
Recumbency	2	21	9.5	31	44	70.5	<0.001	0.04	0.009–0.22	0.001@
Grade of severityx										
Severe	0	21	0	21	46	45.7	0.006	0.016	0.0009–0.30	
Treatment										
Acepromazine	14	21	66.7	39	44	88.6	0.04	0.26	0.07–0.94	
Glyceryl guaiacolate	14	21	66.7	39	44	88.6	0.02	0.20	0.050–0.78	
Free drinking	16	21	76.2	6	44	13.6	<0.001	20.27	5.40–76.08	
Voluntary eating soft food	13	21	61.9	2	44	4.5	<0.001	34.13	6.43–181.22	0.003@

Numerical variables	**Mean**	**SD**	***N***	**mean**	**SD**	***N***	***P*-value UVA**	***P*-value MVA**
Diagnosing time (days)	2.0	2.54	21	0.40	0.62	46	0.03	
Treatment delay (days)	2.02	2.52	21	0.41	0.61	45	0.02	
Hospitalization delay (days)	2.48	2.61	21	0.58	0.73	46	0.003	
Heart rate (bpm)	56.80	12.30	20	70.84	22.52	44	0.02	
pH	7.40	0.03	12	7.35	0.07	22	0.04	
Base excess (mmol/L)	3.22	3.06	20	−0.09	5.68	39	0.009	

*Significantly different between groups in the multivariate analysis for variables on history and clinical examination on admission.

@Significantly different between groups in the multivariate analysis for variables on complementary examinations, complications during hospitalization and treatment.

xThe severity grades were defined as specified in van Galen et al. Part 1.[15]

S, surviving cases; NS, nonsurviving cases; SD, standard variation; OR, odds ratio to survive; CI 95, 95% confidence interval; *N*, number of horses with a response for this specific parameter; *n*, number of horses with a positive response; MVA, multivariate analysis. Group 5, surviving horses from Ghent University; Group 6, nonsurviving horses from Ghent University. For Group 6, all cases that were euthanized due to financial reasons were excluded.

was not performed on any of the cases of the current study. Total parenteral nutrition is frequently and easily used in people. In the current study, partial parenteral nutrition was used frequently in the form of intravenous glucose solutions, but total parenteral nutrition was only provided in very few cases (1.4%; see Part 1).[15] Regardless of treatment options, outcome is probably also dictated by the amount of toxin, and the horse is known as one of the most sensitive species to tetanus toxins.[13,20]

The current study shows that fewer prognostic factors could be identified for foals than adults, probably due to the smaller population size. Those factors that were identified for foals, however, were similar to those of adult cases, except for the variable age. Conversely, human neonatal tetanus and adult tetanus have different prognostic factors[15,21,22] than those identified in horses in the current study. Tachycardia was the only variable in the current study that was identified as a poor prognostic indicator in adult equids similar to adult humans.[20,21] Delay in admission of affected equids was found to be a positive prognostic predictor, but is a poor prognostic indicator in people.[16] The association of a longer diagnosis, treatment, and hospitalization delay with survival in horses can be explained by the less severe and less obvious clinical signs in survivors, and therefore delayed recognition of the disease. Treatments associated with poor prognosis in this study (ie, acepromazine, glycerol guaiacolate, intravenous fluids, and intravenous glucose solutions) also do not necessarily have a negative impact on the patient, but patients with more severe disease require additional and different therapeutic support. Therefore, early diagnosis, treatment and hospitalization are still recommended. Prognostic factors identified in the Ghent University cases were largely similar to the rest of the adult population, suggesting that there was no apparent institution-related bias in this study.

Since the number of appropriately vaccinated horses is very low in this study, it seems reasonable to suggest that vaccination provides adequate protection against tetanus, however it does not guarantee full protection. In affected cases, appropriate vaccination prior to development of tetanus seems to lead to less severe clinical

signs, shorter disease period, and good outcome. There is little evidence available on the effect of therapeutic administration of TAT and its dosage in horses. There is currently no consensus with regards to TAT administration, with some authors suggesting a positive effect on the outcome[3] while others suggest that there is no effect.[5,7] TAT will not cross the blood-brain barrier and cannot capture and inactivate bound tetanus toxin, but it neutralizes circulating residual toxin. However, by the time horses show clinical signs, circulating toxin might not be detectable.[13] Although TAT is considered part of the standard treatment in horses,[13] affected individuals are reported to be able to survive tetanus without TAT administration.[3,5] The current study does not show statistical differences in therapeutic TAT use, its route of administration, the timing of the first TAT or the total intravenous administered dosage between survivors and nonsurvivors. A trend, with the *P*-value approaching significance ($P = 0.53$), was seen with survivors having received higher total dosages of TAT than nonsurvivors. The survival rates were not statistically different for horses treated with different total intravenous dosages, though also a trend appeared in this comparison as well. As efficacy cannot be determined via retrospective studies, it is clear that further research is warranted to determine the utility and optimal dosages of TAT in horses with tetanus. Nevertheless, our results may support a recommendation for high intravenous TAT dosages (total dosage >100,000 IU). With regards to intrathecal TAT, too few cases (16) were treated to be able to see a difference between groups for this administration route in the current study.

The most common antimicrobial used in the current study was penicillin. Penicillin has been suggested to have low efficacy for treatment of tetanus patients because of poor penetration into devitalized anaerobic tissue, and deactivation by beta-lactamases produced by coinfecting bacteria. Moreover, it has anti-gamma-aminobutyric acid and therefore proconvulsant activity. One report of human tetanus patients showed a positive effect of metronidazole compared to penicillin with a significantly lower mortality rate, a shorter stay in hospital, and an improved response to treatment,[23] but other reports fail to show significantly superior clinical responses.[22,24] In the current study, a comparison of outcome between horses treated with metronidazole versus those treated with penicillin was not possible because of the few horses that received exclusively metronidazole.

Limitations of this study include its retrospective nature and the large number of reporting clinicians. However, potential bias was limited by the use of standardized data collection sheets and the high response rate for most variables in this study. For this study, a large number of adult horses with tetanus was collected, for a disease currently considered to be rare in Western Europe.[1] The number of foals was limited, and therefore fewer prognostic factors could be identified. Institution-related bias was limited as indicated by performing the prognostic assessment of Ghent University cases only.

In conclusion, this study demonstrates that the outcome of equine tetanus patients is still poor in Europe. Outcome and prognostic factors are similar in foals and adult horses. The prognostic assessment of cases with tetanus provides clinicians with new evidence-based information related to patient management. Several prognostic indicators are related to the ability to eat or drink, and in general more severe clinical signs are associated to poorer outcome. Although positive trends were identified, the study failed to demonstrate a statistically significant effect on outcome for increasing intravenously administered dosages of TAT. Providing more intensive monitoring and more intensive and advanced support to our equine patients may be key to improving the prognosis in the future. The strongest emphasis should remain on prevention through vaccination.

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Footnote

[a] StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.

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