RISK FACTORS FOR LARGE COLON VOLVULUS IN THE UK

Keywords: horse, large colon volvulus (LCV), strangulating, survival, colic.

Word Count: 4934
Summary

Reasons for performing study: Risk factors for large colon volvulus (LCV) in the horse have not been previously reported. Knowledge of these risk factors may allow the introduction of measures that could be taken to minimise the incidence of LCV.

Objectives: To investigate risk factors for LCV in the horse.

Methods: A prospective, multi-centre, un-matched case-control study was conducted over a 24-month period in the UK. Data on 69 cases and 204 control horses, from 4 veterinary hospitals, were obtained via telephone questionnaires. Multivariable logistic regression was utilised to identify associations between horse and management-level variables and the likelihood of LCV.

Results: We identified increasing height, multiple colic episodes in the previous 12 months and mares, with a greater odds ratio in mares that had previously foaled, to be associated with increased risk of LCV. Receiving medication, (excluding anthelmintic treatment), in the previous 7 days and quidding behaviour were also associated with increased risk.

Management-level variables associated with greater risk of LCV were an increase in the hours of stabling in the previous 14 days, an increasing number of horses on the premises, and 3 or more people involved in the horse’s care. Variables related to nutrition associated with increased risk of LCV were being fed hay, being fed sugar-beet, a change in pasture in the previous 28 days, and an alteration in the amount of forage fed in the last 7 days.

Conclusions: This study has identified factors that may assist in the recognition of horses with increased risk of LCV and factors that might be altered to minimise the incidence of LCV.
Potential relevance:Clinicians can utilise this information to identify horses at risk of LCV and to provide evidence-based advice to owners of these horses.
Introduction

Large colon volvulus (LCV) is one of the most painful and rapidly fatal causes of colic in the horse [1] and in some hospital populations represents between 10 and 20% of horses with colic undergoing exploratory laparotomy [2, 3]. LCV is associated with considerable postoperative mortality and morbidity [4, 5], making identification of susceptible individuals and prevention very desirable.

Multiple epidemiological studies have identified risk factors associated with colic in general [6, 7, 8, 9, 10], and risk factors associated with specific types of colic. Specific types of colic that have been investigated include strangulation of small intestine by pedunculated lipomas [11, 12], ileal impactions [13, 14], simple colonic obstruction/distension colic (SCOD) [15], impaction colic [16, 17] and epiploic foramen entrapment [18, 19]. Factors identified include horse-level factors, for example height or breed, and modifiable management-level factors, such as exercise regime, diet, feeding, turnout, dental care and anthelmintic treatment.

Identification of risk factors for LCV may aid in the understanding of disease causality and has the potential to allow implementation of disease prevention strategies to reduce the incidence of LCV. There are no published reports investigating risk factors specific for LCV. Anecdotal evidence suggests the incidence of LCV is increased in Warmblood breeds [20] and in mares in the post-partum period [20, 21]. Risk factors for SCOD include a recent change in exercise programme, transport in the preceding 24 hours and crib-biting/windsucking behaviour [15], and one could hypothesise that these are also risk factors for LCV, as in some cases of LCV, volvulus is proceeded by displacement or impaction of
The incidence of LCV has been shown to follow a seasonal pattern, with peaks in the spring and autumn [23]. This pattern coincides with periods of management change but its identification does not elucidate specific determinants of LCV [23].

The aim of this study was to identify horse and management-level risk factors for LCV in the UK. We hypothesised that the post-partum period in broodmares, dietary change, alteration in exercise regime and crib-biting/windsucking behaviour would be associated with increased risk of LCV.

Materials and methods

Study design

A prospective, multi-centre, unmatched, case-control study was conducted to identify associations between horse and management-level variables and LCV. Four equine hospitals in the United Kingdom were selected on the basis of their caseload, level of surgical expertise and willingness to participate in the study. Prior to data collection, the study was approved by the University of Liverpool’s ethics committee. Sample size estimation was performed using WinEpiscope 2.0 (www.clive.ed.ac.uk/winepiscope). This indicated that 60 cases and 180 unmatched controls would have 80% power to detect odds ratios of 2.5 or greater, with 95% confidence, assuming 20% exposure in controls. Data from cases and controls were collected between 1st February 2010 and 1st February 2012. To ensure the cases and controls were unmatched on time, 10 controls were recruited during each month of the study.
Case and control definition and selection

Cases of LCV, ≥270 degrees, diagnosed on exploratory laparotomy or at post-mortem examination at the collaborating hospitals, were recruited onto the study. Cases were identified by the surgeon, based on the degree of colon wall and mesocolon oedema, the colour of the serosa, and by palpation of the position of the large colon. The first author was notified of a case and, if the owner was willing to participate, they were contacted by telephone to complete a questionnaire (Supporting item 1, available online). Questionnaires were conducted as soon as possible after exploratory laparotomy, according to clients’ and collaborating hospitals’ requests. In the majority of cases this was within 48 hours of surgery, although in a minority of cases the questionnaire was conducted within the seven days post-surgery.

Control horses were chosen by randomly selecting a client from a list of all clients seen at the collaborating hospitals in the previous year. Due to variation in caseload between the collaborating hospitals, (and therefore variation in size of client list), the number of clients selected as controls from each hospital was proportional to the caseload of that hospital. To maximise compliance clients were initially sent details of the study by post, and then contacted by telephone. A control ‘horse’ (horse or pony) was randomly selected from the horses in the client’s care. To avoid selection bias, horses that would not undergo surgical treatment of colic, if it were deemed necessary, were excluded from the study population. In this instance, another horse in the client’s care was randomly selected, or if no suitable horses were available, a new control client was chosen [15].
Data collection

Data were collected using questionnaire format, which was conducted by one of two investigators over the telephone. The questionnaire was designed utilising information from previous epidemiological studies investigating colic, and hypothesised biologically plausible risk factors [6, 15, 18] (see Supporting item 1, available online). The questionnaire was divided into a number of sections: Signalment and use, medical history, breeding history, premises details, stabling and turnout, nutrition, exercise and transport, behaviour and preventive healthcare. The questionnaire was carefully constructed and piloted to ensure that it was concise and straightforward to complete, in order to maximise compliance and to facilitate the collection of valid, quality data. Data were entered onto a data capture form (Teleform v9, Verity Inc.) and a database was created using a data entry scanner (Fujitsu fi-4120C2).

To evaluate survival and post-operative colic in the cases of LCV, owners of horses that were discharged from a hospital were contacted, quarterly for the first year following surgery, and bi-annually thereafter. Details regarding any post-operative colic and, if the horse was no longer alive, the reason for death and date of death, were recorded.

Statistical analysis

All variables were screened for univariable association with LCV. The functional form of the relationships between continuous variables and the outcome (LCV) were explored using generalised additive models (GAM) [24]. Prior to multivariable analysis, all variables were
assessed for correlation using Spearman’s rank correlation coefficients. Where Spearman’s rank correlation coefficient was >0.8 the most statistically significant or biologically plausible variable was selected.

Variables showing evidence of univariable association with outcome (p ≤ 0.3) were evaluated in a multivariable logistic regression model, which was constructed using a backwards, stepwise elimination procedure [12]. Variables with >20% of missing values were excluded from the initial model-building procedure. Variables remained in the model if they significantly improved the fit (p ≤ 0.05), assessed using the likelihood ratio statistic. Four sub-models were initially created and the variables identified in each of these sub-models were then pooled and used to develop a final effects model [9]. All variables considered for initial inclusion in the four sub-models were forced back into the model to ensure no significant or confounding variables had been excluded. Variables with >20% missing values were also re-tested in the model. Biologically plausible interaction terms for variables remaining in the final model were assessed. The fit of the model was assessed using the Hosmer-Lemeshow goodness of fit test statistic. Scaled changes in the regression coefficient for each observation (delta betas) were used to evaluate potential leverage by individual observations for each variable [12]. The model was re-run excluding observations with large delta-beta values (>0.4 or <-0.4) to evaluate their influence on parameter estimates. The critical probability for all analyses was set at 0.05.

Results

Descriptive statistics and univariable analysis
Over the two-year study period, 69 cases of LCV and 204 controls were recruited. Of the 280 clients randomly selected to provide a control horse, 23 could not be contacted (due to a change of telephone number or no answer on repeated occasions), 25 did not have a horse that would undergo surgery, and 28 did not wish to participate. This resulted in completion of the questionnaire in 73% of controls and 97% of cases.

Of the 69 cases of LCV 81% (n=56) recovered from anaesthesia. Of those that survived surgery 82% (n=46) were discharged from the hospital and of these 52% (24) had a colic episode reported following discharge. Of the horses that suffered a colic episode following discharge, 33% (n=8) were euthanased as a result.

Univariable analyses identified a large number of variables that were significantly associated with LCV and are shown in Supporting item 2 (available online). Due to the small number of controls that had previously foaled (25/204) it was not possible to investigate the association between time since foaling and LCV. Of the cases of LCV that had foaled previously 72% (21/29) had foaled within the proceeding 90 days. Examination of GAM plots for continuous variables indicated that a linear fit was appropriate (Figure 1 and Supporting item 3 [available online]).

Multivariable analysis

The final multivariable logistic regression model is shown in Table 1. We identified increasing height, multiple colic episodes in the previous 12 months, Hospital 3, and mares,
with a greater odds ratio in mares that had previously foaled, to be associated with increased risk of LCV. Management variables associated with an increased likelihood of LCV were an increase in the hours of stabling in the previous 14 days, an increasing number of horses on the premises, and 3 or more people involved in the horse’s care. Receiving medication, (excluding anthelmintic treatment), in the previous 7 days, and the horse being noted to quid in the previous 90 days increased the likelihood of LCV. Variables related to nutrition associated with increased risk of LCV were being fed hay, being fed sugar-beet, a change in pasture in the previous 28 days, and an alteration in the amount of forage fed in the last 7 days.

No significant biologically plausible multiplicative interaction was found between the variables in the final model. The Hosmer-Lemeshow test statistic was 6.76 (P = 0.6, 8 degrees of freedom) indicating no evidence of poor fit. Removal of influential individual observations with large delta-betas had little effect on coefficients, showing the model was stable and all observations were retained.
Discussion

This study is the first major epidemiological investigation into horse and management-level risk factors for LCV in the horse. Broodmares, horses that have suffered multiple colic episodes in the previous year, and taller horses are at increased risk of LCV. Others factors identified to significantly increase the risk of LCV include quidding behaviour, feed types and feeding practices, and stabling and turnout. This research provides owners and clinicians with evidence-based information on horses at increased risk of LCV, and on factors that might be altered with the aim of reducing the incidence of LCV.

Mares, and in particular broodmares, were found to be at increased risk of LCV; In the present study broodmares were 13 times more likely to develop LCV compared to males (stallions and geldings). Of the cases of LCV that were broodmares, 72% (21/29) had foaled within the last 3 months. This supports the work of Kaneene et al. [8] who found foaling to be significantly associated with increased likelihood of colic in general. A sudden increase in the potential space within the abdomen may explain why mares in the post-partum period are at increased risk. In addition, a variety of management changes occur around the time of foaling, which may increase the risk of LCV in the post-partum period. There is currently limited research detailing the incidence of colic in general, or the incidence of specific gastrointestinal lesions in the post-parturient mare [25]. Colic in the post-parturient period will not only effect the mare, but may also have an impact on the neonatal foal, and on conception rates, with financial and welfare implications. Further work is required to investigate colic, and in particular LCV, in broodmares in the post-partum period.
A proportionally large potential space within the abdomen may also explain why increasing height was associated with increased risk of LCV. For example, in this study, a horse of 173 cm (17 hh) was 8 times more likely to develop LCV compared to a pony of 137 cm (13.2 hh). Horses of greater height were also associated with an increased risk of epiploic foramen entrapment and this was likewise thought to reflect anatomical differences in the relative dimensions within the abdomen [18, 19]. Alternatively the increased risk of LCV with increasing height may be a reflection of differences in the management of ponies and horses; however, this is less likely, since the study took into account potential confounders such as stabling, nutrition and exercise. Previously it has been suggested that the incidence of large colon displacement or volvulus is increased in Warmblood breeds [20]. In this study breed was not statistically significant in the final model. However, height did remain in the final model; this may explain why Warmbloods have previously been associated with increased risk of LCV, compared to other, smaller breeds.

In the present study, horses that had a history of multiple colic episodes within the preceding year were 9 times more likely to develop LCV compared to horses that had not. Hillyer et al [15] reported an increased risk of SCOD in horses with a history of previous colic. These findings may suggest a sub-population of horses exists with underlying gastrointestinal dysfunction affecting the large colon. The density of the interstitial cells of Cajal is reduced in horses with large colon disorders compared to control horses; further studies are required to elucidate mechanisms regulating ICC density and to assess the pathophysiological significance of these findings [26, 27]. Alternatively, it may be that inherent differences between individuals’ intestinal microbiota predispose certain horses to recurrent colic and LCV. It has been demonstrated that in horses with simple colonic disruption and distension (SCOD) colic there is a relative abundance of Streptococci and Lactobacci and a decrease
in the proportion of *Fibrobacter spp* [28]. Novel culture-independent DNA sequencing technology has revolutionized the approach to the characterization of human intestinal microbiome [29] and has opened new doors to the understanding of disease pathophysiology and to the development of new treatment approaches [30]. DNA sequencing technology may prove to be a valuable technique in the horse, allowing exploration of differences between the microbiome of healthy horses and horses suffering from recurrent colic or LCV or displacement.

Horses that had received medication, other than a routine anthelmintic, in the previous 7 days were at increased risk of LCV. A requirement for medication may be associated with a requirement for management change or physiological derangements, such as pain or inflammation. Furthermore, some medications, such as antimicrobials or non-steroidal anti-inflammatories, may alter colonic microbiota and pH [31, 32, 33, 34], which may explain the increased risk of LCV in those horses that have recently received medication.

A number of alterable management variables were found to increase the risk of LCV. Horses who had an increase in stabling in the previous 14 days were at increased risk. Stabling or reduced time at pasture has been identified as a risk factor for colic in other studies [10, 35, 36], including large colon disorders [15, 17] and large intestinal motility is reduced in stabled horses compared to those kept at grass [37]. Increased stabling results in alteration of diet and reduction in activity. Exercise alters gastrointestinal function by decreasing dry matter digestibility of feed, and reducing mean retention time [37, 38, 39]. Our results indicate that where possible pasture turnout should be encouraged, particularly in horses at increased risk of LCV.
Horses with 3 or more carers were at increased risk of LCV. This was also identified as a risk factor for large colon impaction in donkeys [17] and may be due to less consistent feeding or management. It has been previously shown that horses whose owners provide their care are at decreased risk of colic [9, 40]; this was attributed to more consistent care. The finding that increased numbers of horses on premises is associated with increased likelihood of LCV may also be attributed to a lack of consistency or individuality in feeding and management.

Horses that exhibited quidding behaviour in the previous 90 days were 8 times more likely to develop LCV compared to horses that had not (OR 7.77, 95%CI 1.82 – 33.15). Quidding behaviour is often indicative of dental pathology, which has been found to increase the risk of SCOD and recurrent colic in the horse, and of large colon impaction in donkeys [15, 17, 41]. The presence of a dental abnormality on the previous dental examination was not significantly associated with increased risk of LCV; this may be due to the fact that this was owner reported, or because the presence of quidding behaviour is indicative of a relatively severe dental abnormalities. Further research is required to investigate the association of specific dental pathologies with various types of colic and to investigate the cause of these associations. Reduced mastication of feed may lead to ingestion of longer length dietary fibre passing to distal portions of the gastrointestinal tract, increasing the risk of impaction [41, 42], or to an alteration in the nutritional composition of ingesta reaching the large colon [41]. Altered mastication of feed can be prevented or reduced by regular, quality dental care. It is important to provide continued education for horse owners, veterinarians and dental technicians should be educated regarding the provision of dental care.
Feeding sugar-beet in the previous 28 days increased the risk of LCV. Tinker et al. (1997) [7] identified that processed concentrates, such as pellets or sweet feeds increased the risk of colic. Feeding hydrolysable and rapidly fermented carbohydrate, leads to an overgrowth of acidophilic Streptococci and Lactobacilli, an increased concentration of lactate, a reduction in the pH of the luminal environment and a subsequent decrease in the fibrolytic bacterial species [43, 44, 45, 46]. The species that proliferate in a starch rich environment not only produce excess lactate but also large amounts of CO$_2$ which will cause distension and potentially volvulus of the large intestine [47]. Changes in colonic microbiota and pH in response to a change in diet may also explain the increased risk of LCV associated with a recent change in pasture or change in the amount of forage fed.

This study identified that horses fed hay, rather than haylage or grass, had an increased the risk of LCV. Management practices or changes, can result in alteration of the luminal environment of the large colon, resulting in dysmotility, impaction and gaseous distension, potentially leading to large colon displacement or volvulus [27, 47, 48, 49, 50]. One could hypothesise that increased dry matter content of hay, compared to haylage or grass [51], might predispose horses fed hay to impactions and potentially to LCV.

The long-standing reputation of Hospital 3 for referrals for colic surgery may have resulted in horses, with a potentially surgical colic episode that would otherwise have been referred to a different hospital, being referred to Hospital 3, resulting in a referral bias. This may explain the increased risk of LCV associated with Hospital 3.
The multi-centre nature of the study increased the number of cases collected during the study period and allowed investigation of risk factors for LCV in the UK horse population, rather than in one referral population. Multivariable analysis allows investigation of the simultaneous effect of multiple variables on a particular outcome, in this case large colon volvulus; however, associations identified in this study may be due to other unmeasured covariates. Extrapolation of the findings to other horse populations should be done with caution; worldwide differences in genetics, management practices, nutrition and seasonal conditions may influence risk factors for LCV [6, 23].

In conclusion, this novel research has identified factors associated with increased risk of LCV. Mares that have previously foaled, horses with a history of multiple colic episodes in the last year, taller horses and horses that have received medication in the previous seven days are all at increased risk of LCV. Management alterations, that might reduce the incidence of LCV, include increasing turnout, not feeding sugar-beet, feeding haylage or grass rather than hay, providing quality dental care to prevent quidding and minimising the number of individuals caring for a horse. Clinicians can utilise the information provided by this study to identify horses at risk of LCV, and to provide evidence-based advice to owners of these horses.
<table>
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<th>Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>Likelihood ratio</th>
<th>p-value</th>
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**Table 1.** Multivariable logistic regression model of risk factors for large colon volvulus in 69 horses from four UK hospitals.
Figure 1. Use of generalised additive models to demonstrate the functional form of the relationship between a) number of horses and b) height with the outcome (log odds of LCV). The plots show the fitted curves with 95% confidence intervals (dashed lines) and the rug plots along the x-axis represent the number of data points. The P-value is a chi-square test for non-linearity.

Manufacturers Details

1 Verity Inc., River Forest, Illinois, USA.

2 Fujitsu, London, UK.


**Supporting item 1.** Telephone questionnaire conducted with cases and controls.

**Supporting item 2.** Univariable associations of categorical and continuous variables with LCV $\geq$270 degrees.

**Supporting item 3.** Use of generalised additive models to demonstrate the functional form of the relationship between a) hours of stabling in a day and b) number of times transported in a week with the outcome (log odds of LCV). The plots show the fitted curves with 95% confidence intervals (dashed lines) and the rug plots along the x-axis represent the number of data points. The P-value is a chi-square test for non-linearity.