Clinical use of plasma lactate concentration. Part 2: Prognostic and diagnostic utility and the clinical management of hyperlactatemia

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Abstract:

Objective – To review the current literature pertaining to the use of lactate as a prognostic indicator and therapeutic guide, the utility of measuring lactate concentrations in body fluids other than blood or plasma, and the clinical management of hyperlactatemia in dogs, cats and horses.

Data Sources – Articles were retrieved without date restrictions primarily via PubMed, Scopus and CAB Abstracts as well as by manual selection.

Human and Veterinary Data Synthesis – Increased plasma lactate concentrations are associated with increased morbidity and mortality. In populations with high mortality, hyperlactatemia is moderately predictive in identifying non-survivors. Importantly, eulactatemia predicts survival better than hyperlactatemia predicts death. Consecutive lactate measurements and calculated relative measures appear to outperform single measurements. The use of lactate as a therapeutic guide has shown promising results in people but is relatively uninvestigated in veterinary species. Increased lactate concentrations in body fluids other than blood should raise the index of suspicion for septic or malignant processes. Management of hyperlactatemia should target the underlying cause.

Conclusion – Lactate is a valuable triage and risk stratification tool that can be used to separate patients into higher and lower risk categories. The utility of lactate concentration as a therapeutic target and the measurement of lactate in body fluids shows promise but requires further research.

Keywords: Lactate, Hyperlactatemia, Lactic Acidosis, Mortality, Effusion, Dog, Cat, Horse, Prognosis

Abbreviations:

AUROC – Area under the receiver operating characteristic curve

APPLE - Acute patient physiologic and laboratory evaluation

Calculated median – Median we manually calculated from published data when not reported

CI – Confidence interval

CSF – Cerebrospinal fluid

ED – Emergency department

GDV – Gastric dilation and volvulus

IMHA – Immune-mediated hemolytic anemia

ICU – Intensive care unit[LAC] – Lactate concentration/s

NPV – Negative predictive value

OR – Odds ratio

PPV – Positive predictive value

ScvO₂ – Central venous oxygen saturation

SD – Standard deviation

SIRS – Systemic inflammatory response syndrome

Introduction:

Increased lactate concentrations ([LAC]) are associated with increased disease severity, morbidity and mortality in many ill and injured human and veterinary populations.^{1,2} The first part of this review³ discussed the physiology, pathophysiology and measurement of lactate. This second part evaluates the clinical utility of lactate as a prognostic indicator and therapeutic guide, the value of measuring lactate concentrations in body fluids other than blood, and the clinical management of hyperlactatemia.

Terminology

There is some confusion in the literature regarding the terminology used to describe the measurement of [LAC]. To encourage standardization and to clarify our intended meaning, the following definitions are used:

Admission [LAC]: The first sample obtained as soon as practicable on admission to a facility.

Initial [LAC]: The first sample obtained; usually, but not necessarily, on admission.

Single, subsequent time point: A single, [LAC] measurement performed subsequent to the first.

Serial [LAC]: One or more subsequent lactate measurements following the first.

Relative measure: A variable calculated by comparing 2 or more [LAC] measurements over time e.g. absolute change, % change

Lactate clearance: Although used in the literature to refer to a decrease in [LAC] over time, the term “clearance” specifically refers to, and should be reserved for, the rate at which a substance is removed from the blood or body, expressed as volume per unit time eg, mL/min. The term

“disappearance rate” has been suggested as more correct for the decrease in [LAC] over time.

But to improve clarity and specificity of meaning, it is preferable to refer to the specific relative measure (listed above) and avoid the inappropriate use of “clearance.”

Lactate as a Prognostic Indicator

Human Medical Literature

The association between admission hyperlactatemia and poor outcome has been demonstrated repeatedly across a range of patient populations in the human medical literature. Of 15,179 trauma patients, mortality was 22.7% in people presenting with [LAC] > 6 mmol/L compared to just 2.26% in patients with [LAC] < 6 mmol/L.⁴ Similarly, in 5,360 people presenting to an ED, 7-day mortality was 2.9% in patients with a [LAC] < 2 mmol/L at admission, 7.8% for patients with [LAC] of 2-3.9 mmol/L, and 23.9% when admission [LAC] was 4.0 mmol/L or greater.⁵ As a predictor of death, higher cut-offs for [LAC] are inherently associated with lower sensitivities but higher specificities while lower cut-offs are more sensitive but less specific. For example, in people presenting to the ICU or ED with hypotension, admission [LAC] >6 mmol/L, >4mmol/L and >2 mmol/L had a sensitivity of 42%, 62%, and 88% and a specificity of 100%, 87% and 44% in predicting non-survival.⁶ Nevertheless, a systematic review reported areas under the receiver operating characteristic curve (AUROC) for admission [LAC] as a marker of non-survival that ranged from poor to excellent (0.56 to 0.98).⁷ Without accounting for study quality or weighting for study population size, the authors of the current review calculated a median AUROC of 0.71 from those data indicating moderate prognostic accuracy overall. Positive and negative predictive (PPV and NPV) values also vary considerably between studies, an effect that is at least partially due to different mortalities in the populations studied. In the aforementioned systematic review, PPVs of admission [LAC] ranged from 4 to 97% (calculated median 33%) and NPVs ranged between 61 and 100% (calculated median 94%).⁷

Serial and calculated relative [LAC] measurements may provide more robust prognostic information than measurement at a single time point. In human patients with polytrauma, survival was 100% when [LAC] normalized within 24-hours of hospital admission.⁸ Survival decreased to 78% if [LAC] remained increased for 48 hours following admission and to just 14% if [LAC] remained increased beyond 48 hours.⁸ Similarly, mortality was 60% in patients with severe sepsis that demonstrated <10% decrease in [LAC] within the first 6 hours of treatment compared to 19% in those with ≥10% decrease in [LAC] over the same time period.⁹ Reported AUROC values for the ability of persistent hyperlactatemia to discriminate survivors from non-survivors range from 0.62 to 0.86 (calculated median 0.80).⁷ Reported PPVs for persistent hyperlactatemia vary from 12-100% (calculated median 68%), and reported NPVs vary from 52-100% (calculated median 87%).⁷ These results are comparable with the most well developed illness severity scoring systems (eg, APACHE IV, MPM0-III, and SPS3) which are also reported to have highly variable AUROC values (median 0.81, range 0.62 to 0.92).¹⁰

Measurement of [LAC] appears to offer additional value as a marker of disease severity beyond traditional hemodynamic variables such as blood pressure and central venous oxygen saturation (ScvO₂). In 28,150 patients with severe sepsis, normotensive patients presenting with [LAC] >4mmol/L were as likely to die (29.0%) as patients presenting with hypotension but with [LAC] < 4 mmol/L (29.3%).¹¹ This illustrates that high [LAC] can be a poor prognostic indicator even in the absence of clinically apparent hypotension. In the same study, mortality was 44.5% in patients with [LAC] >4 mmol/L and hypotension compared to 23.3% in normotensive patients with [LAC] <4mmol/L. People in septic shock who achieved a target of ScvO₂ ≥ 70% but not a ≥ 10% reduction in lactate per 2-hour period had a 41% mortality.¹² In

contrast, mortality was only 8% in those who achieved the lactate target but not the ScvO₂ target.¹²

In summary, the association between increased [LAC] and mortality is well established in the human medical literature. Overall the predictive power of [LAC] is moderate, but varies from poor to excellent depending on the target population and the lactate measure used. In populations with relatively high mortality, [LAC] can effectively identify the group of patients at greater risk of non-survival, while in populations with low mortality, high [LAC] is associated with a high false positive rate and does not effectively predict outcome.^{5,13} A low lactate concentration is a better predictor of survival than a high lactate is of death.

Veterinary Literature

Most of the veterinary studies evaluating [LAC] as a prognostic indicator have been conducted in dogs or horses with fewer studies in cats. Presently, there are few highly powered, large-scale studies in the veterinary literature on which to base recommendations for using [LAC] measurements in patient evaluation and management. In an effort to provide some general guidelines, a literature search of PubMed, Scopus and CAB Abstracts performed for this review identified 35 clinical studies that investigated [LAC] as a prognostic indicator in dogs and cats.¹⁴⁻⁴⁸ As in the human medical literature,⁴⁹ there was marked heterogeneity in study sizes, study populations, mortality, and selected lactate cut-off points making comparison across studies challenging. Most, if not all, of the selected veterinary studies were hampered by relatively small sample sizes and, in many cases, the impact of euthanasia on prognostic variables was difficult or impossible to quantify.

Dogs

Despite these limitations, the association between increased admission or initial [LAC] and mortality is well documented in dogs. From the available clinical studies that contained sufficient data for analysis, non-surviving dogs had significantly higher [LAC] than survivors in 18 of 22 studies.¹⁴⁻³⁵ Studies that found significantly higher [LAC] in non-survivors were in: dogs with blunt or penetrating trauma,^{14,15} sepsis or systemic inflammatory response syndrome (SIRS),¹⁶⁻¹⁸ spontaneous hemoabdomen,¹⁹ immune-mediated hemolytic anemia (IMHA),²⁰ Babesiosis,²¹⁻²³ heartworm,²⁴ general illness or injury,^{25,26} gastric dilatation and volvulus (GDV),²⁷⁻³⁰ and following cholecystectomy.³¹ A significant difference in [LAC] between survivors and non-survivors was not found in 4 of 22 studies: dogs with GDV,³² blunt trauma,³³ Babesiosis³⁴ and soft tissue infections.³⁵ Notably, [LAC] was a significant predictor of mortality in the Acute Patient Physiologic and Laboratory Evaluation (APPLE) scoring system which is a rigorous, veterinary, disease severity scoring system.^{36,37} In the 12 clinical studies in which mortality was reported, dogs with [LAC] above study-specific cut-offs always had a higher mortality than dogs with [LAC] below the cut-offs.^{17,20-22,27,28,30,32,38-41} Across those studies, the difference in mortality ranged from 5 to 99% (calculated median 29%).

Indicators of diagnostic performance (sensitivity, specificity, PPV, NPV and accuracy) for [LAC] measurements as a predictor of mortality in dogs were extracted or calculated from 14 studies (Tables 1, 2 and 3).^{16,17,20-22,27,28,30,32,38-42} Population size across those 14 studies ranged from 20 to 173 dogs with mortality ranging between 4.5 and 71.6%. Performance of [LAC] was assessed for admission or initial samples, typically pre-surgical or prior to fluid resuscitation (Table 1), samples collected at a single, subsequent time point during hospitalization other than

admission (Table 2), and relative [LAC] measurements (Table 3). Variance between studies was assessed by pooling the proportions of reported PPV, NPV and Accuracy by using the Freeman Tukey arcsine square root transformation method. A fixed-effects meta-analysis was then performed and weighted using the inverse of the variance⁵⁰ using commercially available software.^a

Depending on the cut-off value used and timing of sample collection, sensitivity, specificity, PPV and NPV varied considerably between studies. Nevertheless, these data convincingly demonstrate consistently high NPVs compared to PPVs (ie, that low lactate predicts survival much better than high lactate predicts death). In those studies in which it was reported, the AUROC for initial and admission [LAC] to correctly predict outcome ranged from 0.66 to 0.89 (calculated median 0.71). For single subsequent and relative [LAC] measurements, the AUROC for predicting outcome ranged between 0.66 and 0.98 (calculated median 0.86). Using accuracy as an overall measure of predictive performance, [LAC] had a moderate prognostic ability. Measurement of [LAC] at a single, subsequent time point appeared to outperform [LAC] measured at admission and relative measurements (Overall accuracy: 87.8%, 69.8% and 80.3%, respectively). Determining the ideal timing of subsequent sample collection and the respective ideal cut-off value requires further studies on specific diseases and conditions. It is important to emphasize that, because no effort was made to account for qualitative differences between studies, readers are cautioned in over-applying these data to their own clinical populations. Nevertheless, dogs with persistent hyperlactatemia appear to be at greater risk of death.

Cats

Few clinical studies have evaluated [LAC] as a prognostic indicator in cats and the results differ. In 102 cats requiring intravenous fluid therapy, an admission [LAC] > 4.0 mmol/L was associated with lower survival (17/27: 63% vs 20/22: 91%) and increased median duration of hospitalization (48 hrs, Range 3-123 vs 24 hrs, Range 8-183) compared to eulactatemic cats.⁴³ Cats with [LAC] > 4.0 mmol/L and a decrease of $\geq 30\%$ within 8 hours of admission had a higher survival (9/10: 90%) than those where [LAC] decreased < 30% (1/6: 17%). In 111 cats presenting to an ED,⁴⁴ 123 sick cats hospitalized for emergency care,⁴⁵ and in 51 cats with septic peritonitis,⁴⁶ [LAC] was not significantly different between non-survivors and survivors. In contrast, in 26 cats with septic peritonitis⁴⁷ and in 600 cats admitted to an ICU, non-survivors had significantly higher [LAC] compared to survivors.³⁶ In the latter study, [LAC] could discriminate between the two groups with an AUROC of 0.70, indicating moderate prognostic accuracy.⁵¹ Furthermore, in 39 hypotensive cats admitted to an intensive care unit, cats with normal initial [LAC] had a 66% mortality rate compared to 92.6% in those with [LAC] ≥ 2.5 mmol/L (overall mortality 85%).⁴⁸

Overall, it appears that the association between increased [LAC] and mortality in cats may be less consistent than in dogs, horses and people. One plausible explanation is that lactate might increase exponentially in cats with increasing severity of disease rather than in a linear fashion. Hence, cats with mild to moderate compromise may exhibit only mild increases in lactate such that more cats with marginally increased [LAC] would die compared to other species. Additional studies are required to further characterize how lactate increases in cats with worsening disease severity and further elucidate its prognostic value.

Horses

Most studies assessing the value of [LAC] as a prognostic indicator in horses have focused on adult horses with gastrointestinal disease or neonatal foals admitted to ICUs.⁵²⁻⁶¹ In both groups, a high admission [LAC] was consistently associated with non-survival although admission [LAC] does not accurately predict outcome in all equine populations. In 250 adult horses with a range of emergent conditions, including 152 horses with a primary presenting complaint of colic, the odds ratio (OR) for non-survival increased by 29% for every 1 mmol/L increase in admission [LAC].⁵² Admission [LAC] is also consistently higher in non-surviving equine neonates when compared to survivors.⁵³⁻⁵⁸ In a prospective study enrolling 643 foals at 13 referral centers, the risk of death increased by 14% for every 1 mmol/L increase in admission [LAC]. The odds ratios (OR) for death were greater for some patient groups, for example, those with a major diagnosis of 'sepsis', 'unspecified enterocolitis', 'unspecified colic' or 'respiratory disease'.⁵⁸ An admission [LAC] <6 mmol/L had a sensitivity of 84%, a specificity of 83% and a PPV of 96% in predicting survival to discharge in horses with a large colon volvulus.⁵⁹ For hospitalized equine neonates, the sensitivity and specificity of admission [LAC] in predicting survival to discharge are typically modest (60 to 75%) and there is considerable overlap between [LAC] in surviving and non-surviving foals.^{53,54,58} Nevertheless, three recent studies enrolling between 112 and 643 foals reported that using a cut-off for admission [LAC] of between 4.4 and 6.9 mmol/L can accurately predict outcome in 79 to 86% of cases.^{53,54,58} As in dogs and people, the underlying disease almost certainly influences the prognostic utility of admission [LAC] and a study in horses with colitis (mortality 25%) found no association between admission [LAC] and survival.⁶⁰

Horses in which [LAC] remains increased or decreases very slowly in the face of appropriate therapy have lower survival.^{52,53,57,60,61} In 250 horses presented for emergency evaluation, the OR for non-survival increased from 1.29 (95% CI 1.17 - 1.43) for every 1 mmol/L increase in [LAC] at admission to 49.90 (95% CI 6.47 - 384.82) at 72 hours after admission.⁵² In

horses with colitis, serial absolute [LAC] and relative measures were superior to admission [LAC] in predicting outcome.⁶⁰ A decrease in [LAC] of $\geq 30\%$ by 4-8 hours after admission or a decrease of $\geq 50\%$ by 24 hours after admission was associated with survival.⁶⁰ Sensitivity for the percent decrease in [LAC] to predict survival ranged between 82 and 91% while specificity ranged between 40 and 50%.⁶⁰ In contrast, in horses with a broader range of gastrointestinal diseases, the percent decrease in [LAC] between admission and select time points had poor prognostic accuracy.^a When [LAC] is measured serially in hospitalized equine neonates, consistently higher values are found in non-survivors when compared to survivors at least over the first 72 hours of hospitalization.^{53,57,58} Serial [LAC] measurement in foals appears to improve prognostication: outcome was accurately predicted in about 86% of cases using an admission [LAC] of 6.9 mmol/L but accuracy increased to 94% using a cut-off of 3.2 mmol/L 24 hours after admission.⁵⁸ In addition, an admission [LAC] cut-off of 4.4 mmol/L had a sensitivity of 63% and specificity of 63% for prediction of survival in foals but both sensitivity and specificity improved using lower [LAC] cut-offs at 24 and 48 hours after admission.⁵⁷

When using [LAC] as a prognostic indicator in individual clinical cases, recommendations to the owner should be couched in relatively conservative terms eg for dogs or horses with severe hyperlactatemia it may be appropriate to say “complications are more likely.” In agreement with the human medical literature, there is good evidence in both species to suggest that a normal [LAC] is a better predictor of survival than a high [LAC] is of death. Dogs and horses with normal [LAC] at admission are highly likely to survive as demonstrated by the generally high NPVs reported by most studies. While higher [LAC] can indicate a poorer prognosis, an increased [LAC] at any time during hospitalization should never be used as sole justification to withhold treatment or recommend euthanasia. As an example, the mortality in dogs with GDV presenting with moderately or markedly increased [LAC] was 13 to 57% higher than in dogs presenting with normal to mildly increased [LAC].^{27,28,30,32,39,41} However, 79% of

dogs with [LAC] ≥ 4.1 mmol/L,²⁸ 65% of dogs with [LAC] ≥ 5.9 mmol/L,³² and 58% of dogs with [LAC] ≥ 6.0 mmol/L⁴¹ survived with treatment. Furthermore, 54% of dogs with admission [LAC] ≥ 9.0 survived to discharge following treatment.³⁰ In the future, even when ideal cut-offs have been identified for specific conditions, the clinician will still never know whether an individual patient is in the, let's say, 5% of patients that will survive or the 95% that will die. Further research is required before firmer recommendations can be made about the predictive value of lactate as a marker of mortality in cats.

Lactate compares well with other predictors of outcome or measures of disease severity in veterinary medicine including those requiring more input variables and that are more cumbersome to use. As previously mentioned, reported AUROCs for [LAC] as a predictor of mortality in dogs range from 0.66 to 0.98. Reported AUROCs for the veterinary survival prediction index 2 (SPI2) that requires 7 variables, range from 0.61-0.77.⁶²⁻⁶⁴ Reported AUROCs for the APPLE score vary between 0.78 and 0.93 for the 10-variable score^{37,64,65} and 0.85 to 0.95 for the 5-variable score.^{36,66} Finally, the AUROC was 0.91 for the 6-variable animal trauma triage score (ATT).^{42,67} Irrespective of the current evidence base, in all species, hyperlactatemia warrants increased suspicion for severe underlying disease, a comprehensive diagnostic approach, and increased time and resource allocation, particularly when it persists despite treatment.

Lactate as a Therapeutic Guide

Human Medical Literature:

Oxygen derived variables are considered important indices of tissue blood flow and oxygen utilization.⁶⁸⁻⁷¹ As such, several of these variables, including [LAC], have been investigated as

therapeutic guides and indicators of the restoration of tissue blood flow. Human ICU patients prospectively randomized to receive therapy targeting a decrease in [LAC] by $\geq 20\%$ per 2-hour period had a mortality of 33.9%, while mortality in the standard care group was 43.5%.⁷² Although this difference was not statistically significant in the initial analysis, after adjusting for risk factors, in-hospital mortality was significantly lower in the group targeting a reduction in [LAC] with a hazard ratio of 0.61 (95% CI, 0.43-0.87). Patients in the [LAC] targeted group also had lower Sequential Organ Failure Assessment (SOFA) scores, required less inotropic and ventilator support, and were discharged earlier than the control group.⁷² In human patients with severe sepsis or septic shock and an initial lactate ≥ 4.0 mmol/L, using mandated serial lactate monitoring to guide therapy significantly reduced 28-day mortality compared to measurement of only initial [LAC] (23.5% vs 39.6%).⁷³ The group in which [LAC] was serially measured also had lower 24-hour SOFA scores, and shorter hospitalization, mechanical ventilation and vasopressor dependency times.⁷³ Similarly, patients with septic shock subsequent to pneumonia were randomly allocated to receive standard early-goal directed therapy (EGDT), EGDT targeting a [LAC] reduction of 10%, or EGDT targeting a [LAC] reduction of 30%.⁷⁴ Illness severity scores, 28-day mortality and length of ICU stay were significantly reduced in the 2 groups targeting [LAC] reduction with the 30% [LAC] reduction group demonstrating the greatest benefit.⁷⁴ In a meta-analysis that included four randomized controlled trials, inclusion of [LAC] reduction in the treatment of septic patients significantly reduced the risk of death (relative risk ratio 0.65, 95% CI, 0.49-0.85).⁷⁵ In contrast, other studies have documented reduced patient morbidity without significantly different mortality between patient groups.^{76,77} Human patients with sepsis and hypoperfusion resuscitated with a protocol targeting either a [LAC] reduction of 10% or $ScvO_2 \geq 70\%$ in addition to CVP and MAP had similar mortality, indicating non-inferiority between the two strategies.^{78,79} This suggests that [LAC] could be effectively used to guide resuscitation in septic patients when more expensive or

invasive monitoring techniques are either not available or inappropriate. Inclusion of targeted [LAC] reduction to the Surviving Sepsis Campaign bundle decreased mortality from 24.5% to 17.9% in patients with severe sepsis or septic shock who achieved the therapeutic targets.⁸⁰ Lactate normalization was subsequently added to the 2012 Surviving Sepsis Campaign guidelines⁸¹ and has remained a part of the recently updated 2016 guidelines.⁸²

The human medical literature supports [LAC] reduction as a useful, non-invasive resuscitation marker in critically ill patients. Treatment protocols incorporating [LAC] reduction have been associated with lower morbidity and mortality but the ideal target for lactate reduction remains unknown.⁸³ In some studies, administered treatments⁷⁸ and rate of lactate reduction⁷² were similar between treatment groups despite outcome benefits in those receiving lactate targeted therapy. This may suggest that lactate targeted therapy may positively influence patient outcomes by promoting increased clinician concern, more frequent patient re-evaluation, and perhaps more individualized resuscitation efforts.

Veterinary Literature

Experimental trials in animals have also demonstrated that normalization of traditional hemodynamic parameters including heart rate and blood pressure do not necessarily guarantee adequate oxygen delivery at the capillary level.⁸⁴⁻⁸⁶ In a recent prospective, observational trial including 30 dogs in hypovolemic or septic shock, central venous [LAC] remained ≥ 2 mmol/L in 7/30 (23%) of patients and ScvO₂ remained $< 70\%$ in 11/30 (38%) of patients despite normalization of traditional hemodynamic parameters including heart rate and blood pressure.⁸⁷ These results highlight the importance of using multiple clinical end points to assess the efficacy of shock resuscitation.

Although there is evidence that lactate-guided therapy is associated with improved outcomes in some patient groups in the human medical literature, there are currently insufficient data to make specific recommendations as to how and when lactate-guided therapy should be implemented in veterinary medicine. The use of [LAC] measurement as a component of a protocolized therapeutic strategy has been prospectively evaluated in 30 dogs that met the criteria for severe sepsis or septic shock due to pyometra, but conclusions regarding the superiority of including [LAC] measurements could not be made from this report as a control group was not included.¹⁶ Given that persistent hyperlactatemia has been consistently associated with increased mortality in veterinary patients, it seems reasonable to suggest that persistent hyperlactatemia should trigger careful re-evaluation of the patient. Hyperlactatemia secondary to simple, volume responsive hypoperfusion should rapidly resolve with restoration of circulating volume. As the half-life of lactate in healthy animals is estimated to be 20-60 minutes⁸⁸⁻⁹² it seems reasonable to expect lactate concentrations to decrease by 50% every 1-2 hours and to expect resolution of hyperlactatemia within 6-12 hours. When hyperlactatemia is persistent or decreasing more slowly than anticipated, volume status should be reassessed and treated accordingly. If the patient is deemed volume replete, interventions should be directed at other ways to optimize oxygen delivery as clinically indicated eg, transfusion therapy, oxygen support, inotropes). Once efforts to improve oxygen delivery have been exhausted, causes of Type B hyperlactatemia should be considered.³

Measurement of Lactate in Other Body Fluids

Peritoneal Effusion

Studies in both human and veterinary medicine have evaluated peritoneal fluid [LAC] to differentiate septic from aseptic and benign from malignant abdominal disease.⁹³⁻¹⁰³ In people,

normal [LAC] in abdominal effusions cannot be reliably used to exclude septic or surgical abdominal disease.^{93,94} Further, although an increase in peritoneal [LAC] supports the presence of intra-abdominal pathology, peritoneal [LAC] alone cannot definitively discriminate between sepsis and malignancy.⁹⁵

Experimentally, peritoneal fluid [LAC] increases markedly and rapidly following intestinal strangulation in dogs but does not increase with non-ischemic bowel obstructions.^{96,97} Similarly, peritoneal fluid [LAC] in horses with strangulating intestinal obstructions was significantly higher (8.45 ± 5.52 mmol/L [mean $\pm$ SD], n=39) than in horses with non-strangulating obstructions (2.09 ± 2.09 mmol/L, n=87).⁹⁸ In this study, a peritoneal fluid [LAC] ≥ 4 mmol/L at admission was significantly associated with the presence of a strangulating intestinal lesion (OR 3.8, 95% CI 1.1-12.7).⁹⁸ In healthy horses, the ratio of peritoneal fluid [LAC] to blood [LAC] (PFL:BL) is normally less than 1.⁹⁹ A PFL:BL ratio of greater than 1 was significantly associated with the need for surgery (OR 3.1, 95% CI 1.1-9.0) in one study in horses¹⁰⁰ but was unreliable in another.¹⁰¹ In another, 52/54 (96%) horses with a PFL:BL ratio of less than one had a simple (non-strangulating) lesion and 47/54 (87%) of those horses survived to discharge.⁹⁸

Generally, dogs and cats with septic peritonitis have higher abdominal fluid [LAC] than those without but there is considerable overlap between groups.^{102,103} In one small study (n=19), peritoneal fluid [LAC] > 2.5 mmol/L was 100% sensitive and 91% specific identifying septic peritonitis in dogs¹⁰³ and a difference of > 2.0 mmol/L between abdominal fluid and blood [LAC] had a sensitivity of 63% and a specificity of 100%.¹⁰³ The apparently high sensitivities and specificities from this study are very likely biased because of the low subject

numbers detecting a lower number of false positives and false negatives and so should be used with great caution. The same study reported findings from 18 cats: abdominal fluid [LAC] > 2.5 mmol/L was 67% sensitive, 67% specific and 67% accurate in detecting septic peritonitis and a difference of > 0.5 mmol/L between blood and peritoneal fluid [LAC] was 78% sensitive, 78% specific and 78% accurate.¹⁰³

As both leukocytes¹⁰⁴ and neoplastic cells¹⁰⁵⁻¹⁰⁷ are known to produce lactate, it is possible that aseptic but highly inflammatory or neoplastic effusions may also be associated with increased peritoneal [LAC]. Hence, abdominal fluid [LAC] may not be able to reliably differentiate abdominal sepsis from other highly inflammatory abdominal processes such as severe pancreatitis or neoplastic disease. Further, the presence of abdominal drains is associated with a high peritoneal fluid [LAC]^{108,109} so the absolute peritoneal fluid [LAC] and PFL:BL ratio should be considered unreliable in the diagnosis of abdominal sepsis when using samples collected from abdominal drains.^{108,109}

Synovial Fluid

Several studies in people have reported significantly higher synovial fluid [LAC] in people with non-gonococcal septic arthritis, seropositive rheumatoid arthritis, and microcrystal-induced arthropathies compared to seronegative rheumatoid arthritis, degenerative or gonococcal arthritis with variable overlap between groups.¹¹⁰⁻¹¹³

Normal synovial fluid [LAC] in dogs has been reported as 2.8 ± 0.6 mmol/L (mean $\pm$ SD, n=17)¹¹⁴ and 1.7 ± 0.44 mmol/L (mean $\pm$ SD, n=6).¹¹⁵ Normal synovial fluid [LAC] in horses has been reported as 2.0 ± 0.76 mmol/L (mean $\pm$ SD, n=6)¹¹⁶ and 2.2 (2.0-2.9) mmol/L [median (range), n=8].¹¹⁷ Mean synovial fluid [LAC] was significantly higher in dogs with septic arthritis (mean $\pm$ SD, 8.9 ± 2.1 mmol/L, n=8) compared to normal dogs (mean $\pm$ SD, 2.8 ± 0.6 , n=17), dogs

with osteoarthritis (mean $\pm$ SD, 3.2 ± 1.3 , $n=30$) or immune-mediated inflammatory arthritis (mean $\pm$ SD, 2.8 ± 0.6 mmol/L, $n=19$).¹¹⁴ Synovial fluid lactate was not correlated with nucleated cell count, and [LAC] ≥ 6.5 mmol/L was able to discriminate patients with septic arthritis with 100% sensitivity (95% CI 63%-100%) and 100% specificity (95% CI 95%-100%).¹¹⁴ There was also no significant difference detected in synovial fluid lactate concentration between 6 dogs with osteoarthritis secondary to spontaneous cranial cruciate rupture (mean $\pm$ SD, 2.3 ± 0.85 mmol/L) and 6 normal dogs (1.7 ± 0.44 mmol/L).¹¹⁵ In one small study in horses, 10 with septic arthritis had a median synovial fluid [LAC] of 9.9 (range 4.2-11.1) mmol/L ($n=10$) whereas 3 with non-septic arthritis had a median synovial fluid [LAC] of 2.9 (range 2.6-3.4) mmol/L.¹¹⁶ Although mean synovial fluid [LAC] was higher in 6 horses with experimentally induced septic arthritis compared to 6 controls, there was significant overlap between groups beyond 24 hours after bacterial inoculation and synovial fluid total nucleated cell count was a more robust marker of septic arthritis.¹¹⁷

These preliminary data suggest that an high synovial fluid [LAC] in dogs might help differentiate septic from immune-mediated arthritis and osteoarthritis which may be particularly helpful given that joint cultures are often unreliable in the diagnosis of septic arthritis in dogs.¹¹⁸ Albeit uncommon, the impact of erosive arthritis (rheumatoid arthritis) on synovial fluid [LAC] is presently unknown and is a potential confounder. In horses, it is unclear if synovial fluid [LAC] can provide additional diagnostic value beyond that obtained from total nucleated cell counts and differentials, particularly given the low incidence of immune mediated arthritis in this species. To the authors' knowledge, the utility of synovial fluid lactate in cats has not been investigated.

Cerebrospinal Fluid

Bacterial production of lactate is believed to account for only 10% of CSF [LAC] in cases of bacterial meningitis, with the majority originating from neurons, glial cells and leukocytes.¹¹⁹⁻¹²¹ In people, brain hypoxia and vascular compromise (ie, intracranial hemorrhage, mass lesions, trauma, stroke, seizures, hypoglycemic coma) also increase cerebral spinal fluid (CSF) [LAC].^{122,123} When confounding conditions have been excluded, CSF [LAC] can differentiate septic from aseptic meningitis.^{119,120,124,125} In a meta-analysis including 33 studies and 1885 people, the measurement of CSF [LAC] had a pooled sensitivity of 93% (95% CI 0.89-0.96) and specificity of 96% (95% CI 0.93-0.98) in discriminating septic from aseptic meningitis using a cut-off of 3.9 mmol/L.¹²⁶ Similarly, in a meta-analysis that included 25 studies and 1692 people but excluded those with central nervous system (CNS) disease that could increase CSF [LAC] (eg, stroke, seizures, cerebral hypoxia, brain trauma), CSF [LAC] had a pooled sensitivity of 96% (95% CI, 0.95-0.98), specificity of 94% (95% CI, 0.93-0.96) and AUROC of 0.984 in differentiating septic meningitis from aseptic meningitis.¹²³ Consequently, empirical antimicrobial therapy is recommended in post-operative neurosurgical patients if CSF [LAC] is ≥ 4.0 mmol/L.^{121,127} CSF lactate cannot be used to rule out bacterial meningitis in patients previously treated with antimicrobials.¹²⁶

The reference interval for CSF [LAC] in horses has been stated as 1.92 ± 0.12 mmol/L (atlanto-occipital space) and 2.3 ± 0.21 mmol/L (lumbosacral space).¹²⁸ Healthy cats have CSF [LAC] of 1.16 ± 0.06 ¹²⁹ and in healthy dogs it has been reported as 1.1-2.0 mmol/L,¹³⁰ 0.42-1.8 mmol/L,¹³¹ and 1.9 ± 0.61 mmol/L (mean $\pm$ SD).¹³² Increased CSF lactate has been documented in dogs following experimental intracerebral and subarachnoid hemorrhage^{133,134} and in cats following experimental spinal cord trauma and brain injury.^{135,136} In horses, increased CSF [LAC] has been observed with brain abscesses, Eastern Equine Encephalomyelitis and head trauma¹³⁷ and in a horse with bacterial meningitis.¹³⁸ CSF [LAC] does not effectively differentiate dogs

with intervertebral disc herniation from those without, nor is it predictive of outcome.¹³⁹ CSF [LAC] is correlated with plasma [LAC] in dogs with intracranial disease and CSF [LAC] is higher in dogs with worse neurological scores, however, CSF [LAC] could not accurately identify dogs with intracranial disease.¹³⁰ To the authors' knowledge, there are no clinical investigations into CSF lactate as a marker of septic meningitis in dogs or cats and additional studies may be warranted to determine the diagnostic utility of measuring CSF [LAC] in horses with neurological disease.

Pericardial Effusion

[LAC] has been measured in the pericardial fluid of dogs in an effort to distinguish neoplastic from non-neoplastic effusions. Median pericardial fluid [LAC] was significantly higher in dogs with neoplasia (9.2 mmol/L, range 1.9-12.5 mmol/L, n = 28) but overlapped with values obtained from dogs with non-neoplastic effusions (3.7 mmol/L, range 1.3-12.7 mmol/L, n = 13).¹⁴⁰ The difference between peripheral blood [LAC] and pericardial fluid [LAC] was also not useful, in part because 61% of all dogs with pericardial effusion were hyperlactatemic. To our knowledge, [LAC] in pericardial effusions have not been evaluated in cats or horses.

Dystocia

In people, fetal distress during parturition can be identified by measuring [LAC] from fetal scalp or umbilical cord blood.^{141,142} Umbilical vein [LAC] in 70 puppies from 17 parturitions was higher in pups delivered vaginally compared to pups delivered via elective C-section.¹⁴³ Further, umbilical vein [LAC] was higher in pups that died within 48 hours (mean $\pm$ SD, 12.2 $\pm$ 6.7 mmol/L) when compared to surviving pups (6.55 $\pm$ 3.3 mmol/L). Mean $\pm$ SD umbilical [LAC] in "severely stressed" pups (low APGAR (Appearance, Pulse, Grimace, Activity, Respiration) score)

at birth was 8.6 ± 5.2 mmol/L compared to 7.5 ± 3.6 mmol/L in those with a medium APGAR score and 4.6 ± 1.4 mmol/L in healthy pups (high APGAR score). For comparison, jugular lactate from healthy, 4 day old pups is 3.83 ± 1.38 (mean $\pm$ SD) mmol/L.¹⁴⁴ [LAC] measured from the amniotic sacs of 95 puppies¹⁴⁵ was highest for stillborn pups, lower for pups born via vaginal delivery and lowest in pups born via elective C-section; however, a significant difference between surviving pups and those that died within 48 hours was not detected.¹⁴⁵

Amniotic fluid and umbilical blood [LAC] were measured during parturition in 62 mares delivering healthy foals and 19 mares that delivered sick foals.¹⁴⁶ Umbilical blood [LAC] did not differ between healthy and sick foals. Interestingly, amniotic fluid [LAC] was significantly higher in mares delivering healthy foals (median 14.99 mmol/L, range 12.68 – 16.03 mmol/L) when compared to mares delivering sick foals (median: 12.61 mmol/L; range 11.45 – 14.18 mmol/L). The authors speculated that the lower amniotic fluid [LAC] might indicate placental insufficiency and inadequate fetal energy provision since lactate is an important energy substrate for the fetus and is supplied by placental production.¹⁴⁶

Clinical Management of Hyperlactatemia

When faced with a patient with hyperlactatemia, it is important to remember that an increase in [LAC] may be an indicator of underlying disease but is not, in and of itself, harmful.³ If the cause of hyperlactatemia is physiologic, such as exercise or a brief, uncomplicated epileptic seizure, treatment to correct the hyperlactatemia is not indicated. In these patients, [LAC] should decrease quickly following cessation of muscle activity, eg, decreasing by 50% per hour or normalizing within 1-2 hours.⁸⁸⁻⁹² Conversely, if the hyperlactatemia is a consequence of a pathologic process, therapy should primarily be directed at the underlying cause. Although the

origins of hyperlactatemia in shock are likely multifactorial, the most common cause of hyperlactatemia in veterinary emergency practice is, almost certainly, tissue hypoperfusion. Regardless of the underlying cellular mechanisms, restoration of tissue perfusion typically results in a rapid and profound decrease in [LAC] in patients with hypoperfusion-induced hyperlactatemia. Persistently increased [LAC] following apparent optimization of oxygen delivery or hyperlactatemia without evidence of impaired tissue perfusion raises concern for occult shock or causes of Type B hyperlactatemia. Although these suggestions are logical and not particularly contentious, further research is necessary to definitively support them.

Interpreting [LAC] in conjunction with other markers of tissue metabolism may help to unravel the origins of hyperlactatemia in specific patients. For example, in the absence of increased muscle activity, increased [LAC] in conjunction with low venous oxygen content or saturation or high venous carbon dioxide tension suggests inadequate tissue oxygen delivery (via macrocirculatory compromise, microcirculatory compromise, and rarely anemia or hypoxia).¹⁴⁷⁻¹⁵² Alternatively, an increased lactate concentration in conjunction with an increased peripheral venous oxygen concentration may suggest reduced oxygen extraction (for example due to mitochondrial dysfunction with impaired oxygen utilization such as in SIRS) or microcirculatory shunting.^{153,154} Epinephrine-induced upregulation of Na⁺-K⁺-ATPase and extramitochondrial glycolysis may be an under recognized cause of hypokalemia and should be considered when faced with hyperlactatemia with concurrent hypokalemia.^{155,156}

Macrocirculatory derangements should be treated with intravenous fluid therapy, blood products, supplemental oxygen, vasopressors and inotropic support as appropriate.¹⁵⁷ The ideal strategies to diagnose and treat microcirculatory and mitochondrial derangements have not

been defined. Although not readily available for use in clinical practice, microcirculatory monitoring techniques such as sidestream microscopy are presently under investigation¹⁵⁸⁻¹⁶⁰ and therapies to improve microcirculatory flow such as dobutamine, nitrates and calcium sensitizers are also being evaluated.^{161,162} Research is also ongoing into interventions targeting mitochondrial dysfunction including cofactor supplementation, mitochondrial anti-oxidants, reactive oxygen species scavengers and mitochondrial membrane stabilizers.¹⁶³⁻¹⁶⁶ The ideal therapy for microcirculatory and mitochondrial dysfunction remains elusive with conflicting data from both experimental and clinical trials.¹⁶⁷⁻¹⁶⁸ Cofactor supplementation with thiamine is a safe and rational adjunctive treatment for hyperlactatemia given that thiamine pyrophosphate is a cofactor for pyruvate metabolism. Discontinuation of drugs that might promote hyperlactatemia (eg, epinephrine, corticosteroids) should be considered if clinically appropriate when managing patients with unexplained hyperlactatemia to help distinguish between persistent hypoperfusion and Type B2 hyperlactatemia. In some patients, unexplained hyperlactatemia might indicate malignancy (among other Type B causes) and supports the need for further diagnostics and specific therapy.

Based on the evidence available to date, specific pharmacologic intervention to accelerate lactate metabolism or inhibit lactate production is not recommended and may be harmful.¹⁶⁹⁻¹⁷⁴ Although a number of pharmacologic agents including dichloroacetate (a pyruvate dehydrogenase activator),¹⁷¹⁻¹⁷⁷ ouabain (an Na⁺-K⁺-ATPase inhibitor),¹⁷⁸⁻¹⁸⁰ and β -adrenergic antagonists^{178,181} effectively reduce [LAC], reductions in mortality have been inconsistent. Indeed, some studies have documented increased organ dysfunction and higher mortality associated with these interventions.¹⁷¹⁻¹⁷⁴ This may be because lactate is an important alternative cellular energy source, especially for tissues such as the myocardium and brain during periods of stress.¹⁸⁰⁻¹⁸³

The use of buffers such as sodium bicarbonate to treat the acidosis that often accompanies hyperlactatemia is also controversial and potentially harmful. Sodium bicarbonate has the potential to cause hyponatremia, hyperosmolality, ionized hypocalcemia, overshoot alkalosis, and hypercarbia, as well as intracellular and CSF acidosis.¹⁸⁴⁻¹⁹⁰ Sodium bicarbonate can also promote lactate production by upregulating the glycolytic enzyme phosphofructokinase.¹⁹¹⁻¹⁹⁶ A number of experimental animal studies have documented bicarbonate therapy to be of no benefit or detrimental in the management of hyperlactatemia,^{191,194} and the administration of bicarbonate in people with hyperlactatemia is associated with increased mortality without significant improvement in hemodynamic variables.¹⁹⁷⁻²⁰⁰ Other alkalinizing therapies that have been investigated include tris(hydroxymethyl)aminomethane (THAM), carbicarb, dialysis, and selective sodium-hydrogen exchanger 1 inhibitors^{169,188,200,201} with the latter potentially showing some early promise for the treatment of hypovolaemic shock.²⁰¹

Conclusion

The human medical and veterinary literature demonstrates that increased [LAC] is associated with increased morbidity and mortality. Overall, in populations with sufficiently high mortality, increased lactate is moderately predictive in identifying non-survivors and serial lactate measurements and relative measures appear to outperform single measurements. Importantly, a normal [LAC] predicts survival better than a high one predicts death. Consequently, lactate is a valuable triage and risk stratification tool that can be used to separate patients into higher and lower risk categories, but hyperlactatemia does not justify withholding resources or performing euthanasia because a significant number of patients with increased [LAC] will survive with

therapy. The use of lactate as a therapeutic guide has shown promising results in people but data are sparse in veterinary species. Increased [LAC] in body fluids other than blood should raise the index of suspicion for septic or malignant processes. Hyperlactatemia is a protective response so treatment of hyperlactatemia should be directed at the underlying cause.

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Footnotes:

- a. Tennent-Brown B, Beck J, Firestone S and Wilkins PA. Lactate area as a prognostic indicator in horses with gastrointestinal disease. J Vet Emerg Crit Care. 2015;25(S1):S19.
- b. StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

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Table 1: Sensitivity (Sn), specificity (Sp), positive (PPV), negative (NPV) predictive values and accuracy for admission or initial lactate concentration [LAC] in predicting non-survival in dogs. The precise timing of the initial measurement of [LAC] was not always specified but occurred before surgery or the initiation of fluid therapy. Mortality includes both dogs that died and dogs that were euthanized; animals that were euthanized on the basis of financial constraints were not always excluded from analysis. Values were calculated from the available data by the authors of the current review if not provided in the study itself.

		N	Mortality (%)	[LAC] Cut-off (mmol/L)	Sensitivity and Specificity (%)	Positive and Negative Predictive Values (%)	Accuracy (%)
De Papp <i>et al.</i> , 1999	Retrospective; GDV	101	13.9	> 6.0	Sn: 92.9 Sp: 79.3	PPV: 41.9 NPV: 98.6	81.2
Nel <i>et al.</i> , 2004	Prospective; babesiosis	90	12.2	> 2.5	Sn: 81.8 Sp: 54.4	PPV: 20.0 NPV: 95.6	57.8
Jacobson <i>et al.</i> , 2005	Prospective; babesiosis	20	25.0	Increased*	Sn: 80.0 Sp: 53.3	PPV: 36.4 NPV: 88.9	60.0
Stevenson <i>et al.</i> , 2007	Prospective; systemically ill	80	12.5	> 2.3	Sn: 60.0 Sp: 68.6	PPV: 21.4 NPV: 92.3	67.5
Holahan <i>et al.</i> , 2010	Retrospective; IMHA	173	23.1	> 4.4 (ROC Analysis)	Sn: 60.0 Sp: 76.7	PPV: 43.6 NPV: 86.4	72.8

Zacher <i>et al.</i> , 2010	Retrospective; GDV	64	23.4	≥ 9.0	Sn: 73.3 Sp: 73.5	PPV: 45.8 NPV: 90.0	73.4
Green <i>et al.</i> , 2011	Retrospective; GDV	84	11.9	≥ 4.1 (ROC Analysis)	Sn: 90.9 Sp: 60.3	PPV: 23.7 NPV: 97.8	63.9
				≥ 6.0	Sn: 50.0 Sp: 74.3	PPV: 20.8 NPV: 91.7	71.4
Conti-Patara <i>et al.</i> , 2012	Prospective; severe sepsis/septic shock	30	36.7	≥ 3.15	Sn: 63.6 Sp: 84.2	PPV: 70.0 NPV: 80.0	76.7
				≥ 3.30	Sn: 54.6 Sp: 89.5	PPV: 75.0 NPV: 77.3	76.7
Green <i>et al.</i> , 2012	Retrospective; GDV	101	15.8	≥ 6.0	Sn: 62.5 Sp: 75.3	PPV: 32.3 NPV: 91.4	73.2
Israeli <i>et al.</i> , 2012	Prospective; GDV	65	21.5	Increased§	Sn: 64.3 Sp: 43.1	PPV: 23.7 NPV: 81.5	47.7
				> 6.0	Sn: 64.3 Sp: 66.7	PPV: 34.6 NPV: 87.2	66.2
				> 7.2 (ROC Analysis)	Sn: 57 Sp: 80	PPV: 44 NPV: 87	75
Santoro Beer <i>et al.</i> , 2013	Retrospective; GDV	73	10.9	≥ 7.4 (ROC Analysis)	Sn: 75 Sp: 89	PPV: 46 NPV: 98	88
Hall <i>et al.</i> , 2014	Prospective; trauma	111	4.5	≥ 4.0	Sn: 80	PPV: 8	57

				(ROC Analysis)	Sp: 56	NPV: 98	
Cortellini <i>et al.</i> , 2015	Retrospective; septic peritonitis	81	35.8	> 4.0	Sn: 37.9 Sp: 92.3	PPV: 73.3 NPV: 72.7	72.8
Ateca <i>et al.</i> , 2015	Retrospective; critical illness with hypotension	67	71.6	≥ 2.0	Sn: 64.6 Sp: 63.2	PPV: 81.6 NPV: 41.3	64.2
Overall (95% CI)					Sn: 64.7 (58.7 - 70.6) Sp: 71.7 (69.0 - 74.4)	PPV: 35.0 (30.7 - 39.4) NPV: 90.3 (88.0 - 92.4)	69.8 (67.3 - 72.2)

* Admission [LAC] greater than approximately 3.2 mmol/L (reference range determined from 10 healthy dogs).

§ Admission [LAC] greater than 4.2 mmol/L which was the upper limit of reference interval determined in 79 healthy dogs.

Table 2: Sensitivity (Sn), specificity (Sp), positive (PPV), negative (NPV) predictive values and accuracy for lactate concentration [LAC] measured at a single, subsequent time point other than admission in predicting non-survival in dogs. Mortality includes both dogs that died and dogs that were euthanized; animals that were euthanized on the basis of financial constraints were not always excluded from analysis. Values were calculated from the available data by the authors of the current review if not provided in the study itself.

		N	Mortality*	[LAC] Cut-off (mmol/L)	Sensitivity and Specificity (%)	Positive and Negative Predictive Values (%)	Accuracy (%)
Nel <i>et al.</i> , 2004	Prospective; babesiosis	87	8 deaths	> 2.5 at 8 hours	Sn: 87.5 Sp: 78.5	PPV: 29.2 NPV: 98.4	79.3
		87	8 deaths	> 5.0 at 8 hours	Sn: 50.0 Sp: 96.2	PPV: 57.1 NPV: 95.0	92.0
		81	5 deaths	> 2.5 at 16 hours	Sn: 100 Sp: 85.5	PPV: 31.3 NPV: 100	86.4
		81	5 deaths	> 5.0 at 16 hours	Sn: 100 Sp: 97.4	PPV: 71.4 NPV: 100	97.5
		79	4 deaths	> 2.5 at 24 hours	Sn: 100 Sp: 88.0	PPV: 30.8 NPV: 100	88.6
		79	4 deaths	> 5.0 at 24 hours	Sn: 75.0 Sp: 100	PPV: 100 NPV: 98.7	98.7
Stevenson <i>et al.</i> , 2007	Prospective; systemically ill	80	10 deaths	> 2.3 at 6 hours	Sn: 60.0 Sp: 88.6	PPV: 42.9 NPV: 93.9	85.0
Zacher <i>et al.</i> , 2010	Retrospective; GDV	64	15 deaths	≥ 5.6 post- resuscitation	Sn: 80.0 Sp: 83.7	PPV: 60.0 NPV: 93.2	82.8
		24	11 deaths	≥ 6.4 post- resuscitation	Sn: 90.9 Sp: 76.9	PPV: 76.9 NPV: 90.9	83.3
Cortellini <i>et al.</i> , 2015	Retrospective; septic peritonitis	76	26 deaths	> 2.5 post- operatively	Sn: 46.2	PPV: 66.7	73.7

					Sp: 88.0	NPV: 75.9	
		24	13 deaths	> 2.5 at 6 hours	Sn: 76.9	PPV: 100	87.5
					Sp: 100	NPV: 78.6	
		55	19 deaths	> 2.3 at 6 hours	Sn: 68	PPV: 81	84
				(ROC analysis)	Sp: 92	NPV: 84	
		54	22 deaths	> 2.4 at 12 hours	Sn: 54	PPV: 100	81
				(ROC analysis)	Sp: 100	NPV: 76	
Overall (95% CI)					Sn: 71.2 (62.9 - 79.0)	PPV: 62.5 (54.6 - 70.1)	87.8 (85.4 -
					Sp: 92.3 (90.1 - 94.3)	NPV: 96.0 (94.2 - 97.5)	90.0)

*Number values indicate the number of deaths in the subset of animals evaluated.

§Subset-analysis of dogs with a high (> 9.0 mmol/L) presenting [LAC]

¶Precise timing of sample not specified but occurred post-resuscitation

Table 3: Sensitivity (Sn), specificity (Sp), positive (PPV), negative (NPV) predictive values and accuracy for relative [LAC] measurements in predicting non-survival in dogs. Mortality includes both dogs that died and dogs that were euthanized; animals that were euthanized on the basis of financial constraints were not always excluded from analysis. Values were calculated from the available data by the authors of the current review if not provided in the study itself.

		N	Mortality*	[LAC] Cut-off (mmol/L)	Sensitivity and Specificity (%)	Positive and Negative Predictive Values (%)	Accuracy (%)
Nel <i>et al.</i> , 2004	Prospective; babesiosis	43	7 deaths	Decrease in [LAC] ≤ 50% at 8 hours	Sn: 71.4 Sp: 83.3	PPV: 45.5 NPV: 93.8	81.4
		38	4 deaths	Decrease in [LAC] ≤ 50% at 16 hours	Sn: 75.0 Sp: 79.4	PPV: 30.0 NPV: 96.4	78.9
Stevenson <i>et al.</i> , 2007	Prospective; systemically ill	28	6 deaths	Decrease in [LAC] < 50% at 6 hours	Sn: 83.3 Sp: 68.1	PPV: 41.7 NPV: 93.8	71.4
Zacher <i>et al.</i> , 2010	Retrospective; GDV	64 [¶]	15 deaths	Decrease in [LAC] ≤ 42.2% (ROC Analysis)	Sn: 100 Sp: 61.2	PPV: 44.1 NPV: 100	70.3
		24 ^{§¶}	11 deaths	Δ[LAC] ≤ 4.0 mmol/L (ROC Analysis)	Sn: 81.8 Sp: 92.3	PPV: 90.0 NPV: 85.7	87.5
		24 ^{§¶}	11 deaths	Decrease in [LAC] ≤ 42.5%	Sn: 100	PPV: 84.6	91.7

				(ROC Analysis)	Sp: 84.6	NPV: 100	
Cortellini <i>et al.</i> , 2015	Retrospective; septic peritonitis	18	12 deaths	Persistent ↑[LAC] post-op (> 2.5 mmol/L)	Sn: 91.7 Sp: 100	PPV: 100 NPV: 85.7	94.4
		20	-	Decrease in [LAC] ≤ 21% at 6 hours (ROC Analysis)	Sn: 54£ Sp: 91£	-	-
		18	-	Decrease in [LAC] ≤ 42% at 12 hours (ROC Analysis)	Sn: 82£ Sp: 100£	-	-
Overall (95% CI)					Sn: 93.3 (84.2 - 99.1) Sp: 77.3 (70.3 - 83.6)	PPV: 61.3 (51.0 - 71.1) NPV: 96.8 (92.3 - 99.6)	80.3 (74.8 - 85.3)

*Number values indicate the number of deaths in the subset of animals evaluated.

§Subset-analysis of dogs with a high (> 9.0 mmol/L) presenting [LAC]

†Precise timing of second sample not specified but occurred post-resuscitation

£Values not included in calculation of overall test performance as insufficient data available

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