Baseline plasma cortisol and ACTH concentrations and response to low-dose ACTH stimulation testing in ill foals

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**Objective**—To evaluate baseline plasma cortisol and ACTH concentrations and responses to low-dose ACTH stimulation testing in ill foals.

**Design**—Cross-sectional study.

**Animals**—58 ill foals.

**Procedures**—Baseline cortisol and ACTH concentrations and cortisol concentrations after administration of a low dose of cosyntropin were determined within 6 hours after admission. Foals were assigned to 4 groups on the basis of age (≤24 hours vs 1 to 56 days) and presence of septicemia (yes vs no). Values were compared among groups and with values previously reported for healthy foals.

**Results**—Plasma cortisol concentrations 30 and 60 minutes after cosyntropin administration in foals ≤24 hours old were significantly higher than corresponding cortisol concentrations in older foals. In all 4 groups, plasma cortisol concentration 30 minutes after cosyntropin administration was significantly higher than baseline cortisol concentration or concentration 60 minutes after cosyntropin administration. No differences in baseline cortisol or ACTH concentration or in the ACTH-to-cortisol ratio were detected between groups or when ill foals were compared with healthy foals. A small number of ill foals had low baseline cortisol and ACTH concentrations or low responses to cosyntropin administration, compared with healthy foals.

**Conclusions and Clinical Relevance**—Results indicated that most ill foals in the present study population had adequate responses to cosyntropin administration. However, a small subset of ill foals appeared to have dysfunction of the hypothalamic-pituitary-adrenal axis. (*J Am Vet Med Assoc* 2009;234:126–132)

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Relative adrenal insufficiency, defined as inadequate production of cortisol in response to increased demands associated with critical illnesses, has been identified in human patients with sepsis and septic shock. Although RAI has been diagnosed on the basis of low baseline plasma cortisol concentrations in ill patients, the ACTH stimulation test is more commonly used to identify RAI in people because patients with RAI have a blunted response to exogenous ACTH administration. People with RAI have clinical signs associated with inadequate cortisol concentrations, such as hypotension, hemodynamic instability, ongoing inflammation with no obvious source, and hypoglycemia, and nonspecific clinical signs, including weakness, depression, and anorexia. The incidence of RAI in people depends on the underlying disease, severity of illness, and diagnostic criteria used to define RAI.

The incidence of RAI in horses is unknown, although the condition is believed to occur in septic foals. On the other hand, although septicemia is common in foals, adrenal gland dysfunction is reported infrequently. Nevertheless, recent evidence suggests that some foals with sepsis with hypotension that are unresponsive to fluid therapy have abnormally high ACTH concentrations with normal cortisol concentrations, which may be indicative of abnormal adrenal gland function. Foals with evidence of abnormal adrenal gland function have a high mortality rate, and clinical studies in people with RAI have suggested that administration of glucocorticoids may improve the survival rate. Thus, it would be useful to know whether adrenal gland dysfunction and RAI occur in ill foals.

The study reported here was designed to determine whether ill foals examined at a veterinary teaching hospital had evidence of adrenal gland dysfunction or RAI. Specifically, the purposes of the study reported here were to determine baseline plasma cortisol and ACTH concentrations in ill foals and to evaluate responses to low-dose ACTH stimulation testing. We also wanted to determine whether baseline plasma cortisol or ACTH...

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**Abbreviation**

<table>
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<th>RAI</th>
<th>Relative adrenal insufficiency</th>
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Supported by a donation from Acey and Kay Haroldson to the Companion Animal Fund at the College of Veterinary Medicine, Iowa State University.

The authors thank Andrea Dorschner and Sheri Marsden for technical assistance.

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Variables of interest were associated with outcome in foals with various disorders.

Materials and Methods

Animals—The study was designed as a cross-sectional study of a convenience sample of 58 client-owned foals examined at the Iowa State University Veterinary Teaching Hospital during the 2007 foaling season. The study protocol was approved by the Iowa State University Animal Use and Care Committee.

Foals included in the study ranged from 2 hours to 56 days old (mean, 7.9 days; median, 3 days) at the time of initial examination. Breeds represented included Quarter Horse and related breeds (n = 28), Thoroughbred (14), Percheron (6), American Miniature Horse (3), Belgian (2), Icelandic Pony (1), Donkey (1), Standardbred (1), Irish Draft (1), and Shetland Pony (1). There were 32 colts and 26 fillies.

Abnormalities diagnosed while participating foals were hospitalized included septicemia (n = 24), diarrhea (24), partial or complete failure of passive transfer of maternal antibodies (16), urogenital abnormalities (patent urachus, umbilical infection, and uroabdomen; 11), hypoxic-ischemic encephalopathy (7), colic (4), septic arthritis (3), pneumonia (2), seizures (2), neonatal isoerythrosis (2), cellulitis (1), corneal laceration (1), and congenital oral mass (1), with multiple abnormalities identified in some foals. Six foals died while hospitalized, and 2 were euthanatized because of a grave prognosis.

In all foals, a physical examination and clinicopathologic testing were performed at the time of admission. Specific tests were performed at the discretion of the attending veterinarian, but included any or all of the following: CBC, serum biochemical analyses, arterial or venous blood gas analyses, aerobic or anaerobic bacterial culture of blood samples, and measurement of serum immunoglobulin concentration. A sepsis score ranging from 0 to 34 was calculated for all foals.

Septicemia was diagnosed in 24 of the 38 foals included in the study. In 18 of the 24, the diagnosis was made on the basis of results of bacterial culture of blood samples; in the remaining 6, the diagnosis was made on the basis of a sepsis score ≥ 11. Mean sepsis score for the 24 foals with septicemia was 14.6. For the 18 foals in which results of bacterial culture of blood samples were positive, 12 samples yielded a single bacterial species and 6 yielded multiple bacterial species. Bacterial isolates that were obtained included Escherichia coli (n = 5), Actinobacillus equuli (3), Enterococcus durans (3), Streptococcus zooepidemicus (3), Salmonella spp (2), α-hemolytic Streptococcus spp (2), coagulase-negative Staphylococcus spp (2), Corynebacterium spp (2), Enterococcus faecium (1), Pseudomonas spp (1), and Acinetobacter spp (1). Twenty-one of the 24 foals with septicemia were discharged from the hospital, and 3 died or were euthanatized because of a grave prognosis. None were euthanatized because of financial restrictions.

Study protocol—All foals were weighed after the initial clinical examination was performed. Fifty-two of the 58 foals were admitted to the internal medicine service, and a low-dose ACTH stimulation test was performed on the basis of abnormal health status at the time of initial examination; testing was performed within 1 to 6 hours after foals were admitted to the hospital. An ACTH stimulation test was not performed in the remaining 6 foals because these foals were admitted to the emergency service (n = 5) or died (1). However, in these foals, baseline plasma cortisol and ACTH concentrations were measured.

For ACTH stimulation testing, the foal was manually restrained, and a blood sample (3 mL) was collected by means of venipuncture and placed in an evacuated glass tube containing EDTA. Prior to removal of the venipuncture needle, cosyntropin* (0.1 µg/kg [0.045 µg/lb], IV) was administered. Additional blood samples (5 mL) were collected 30 and 60 minutes after administration of cosyntropin and placed in evacuated glass tubes containing EDTA. Initial blood samples were refrigerated until all 3 samples had been collected. Samples were then centrifuged at 210 X g, and plasma was obtained. Plasma samples were frozen at –80°C in plastic tubes until assayed for baseline cortisol and ACTH concentrations and cortisol concentrations 30 and 60 minutes after administration of cosyntropin.

In 22 of the 32 foals that survived > 24 hours, a second ACTH stimulation test was performed between 1 and 5 days after the initial ACTH stimulation test. Foals that underwent a second ACTH stimulation test were randomly selected from among all those foals that survived > 24 hours; limited technical resources did not allow retesting of all 52 foals.

Cosyntropin used for the ACTH stimulation test was acquired as lyophilized powder containing 250 µg of α-24 corticotropin/vial. Each vial was reconstituted according to the manufacturer’s recommendations, resulting in a concentration of 250 µg/mL. This solution was diluted 50-fold with sterile saline (0.9% NaCl) solution, yielding a concentration of 5 µg/mL. Individual 2-mL aliquots were stored frozen at –20°C until used; aliquots that were not used within 1 month were discarded. The cosyntropin dose used for ACTH stimulation testing was selected on the basis of doses used in healthy adult horses and foals.23,24,26

Measurement of plasma cortisol and ACTH concentrations—Plasma total cortisol concentrations were determined by use of a radioimmunoassay kit previously validated for use with equine samples.25 Each sample was analyzed in duplicate, and the mean of the duplicate measurements was reported. The limit of sensitivity was 10 ng/mL, and intra- and interassay coefficients of variation were < 5%.

Plasma ACTH concentrations were determined with an automated analyzer by means of an enzyme-based immunometric assay with chemiluminescent detection previously validated for use with equine samples.26–28 Mean reported intra- and interassay coefficients of variation were 9.3% and 8.1%, respectively.26–28 The limit of sensitivity was 9 pg/mL.

Statistical analysis—Variables of interest were baseline cortisol concentration, baseline ACTH concentration, cortisol concentration 30 minutes after administration of cosyntropin, cortisol concentration 60 minutes after administration of cosyntropin, the change in cortisol concentration from baseline to 30 minutes after administration of cosyntropin, the change in cortisol concentration from baseline to 60 minutes after administration of cosyntropin, and the ratio of baseline ACTH concentration to baseline cortisol concentration. On the basis of published age-related differences in baseline
cortisol concentrations and response to cosyntropin administration in foals, foals were assigned to 1 of 4 groups (ie, foals ≤ 24 hours old without septicemia, foals ≤ 24 hours old with septicemia, foals between 1 and 56 days old without septicemia, and foals between 1 and 56 days old with septicemia). A subset of 30 foals was used to determine baseline cortisol concentrations, and plasma cortisol concentration 30 minutes after administration of cosyntropin. In addition, multiple t tests were used to compare mean values of variables of interest for foals in each group with previously reported mean values for healthy foals and to compare variables of interest between foals that survived and foals that died or were euthanatized. Values for each ill foal were also compared with reported values for healthy foals. All analyses were performed with standard software. Values of P ≤ 0.05 were considered significant.

**Results**

There were 7 foals ≤ 24 hours old that did not have septicemia. Mean age at the time of initial examination was 12.4 hours (range, 6 to 20 hours), and all 7 foals survived to discharge. There were 6 foals ≤ 24 hours old that had septicemia. Mean age at the time of initial examination was 10.3 hours (range, 2 to 24 hours), and 5 of the 6 survived to discharge. There were 27 foals between 1 and 56 days old that did not have septicemia. Mean age at the time of initial examination was 13.2 days (range, 1 to 56 days), and 22 of the 27 survived to discharge. Finally, there were 18 foals between 1 and 56 days old that had septicemia. Mean age at the time of initial examination was 4.8 days (range, 1 to 13 days), and 16 of the 18 survived to discharge.

**Baseline plasma cortisol concentration**—Baseline plasma cortisol concentration did not differ significantly among the 4 groups of foals (Table 1), nor were any differences detected when values for each group were compared with previously reported values for healthy foals. Overall, for 10 of the 58 (17%) foals, baseline cortisol concentration was within the range of values previously reported for healthy foals, whereas for 30 (52%) foals, baseline cortisol concentration was higher than the range of values previously reported for healthy foals, and for 18 (31%) foals, baseline cortisol concentration was lower than the range of values previously reported for healthy foals (Table 2). Baseline cortisol concentration was measured in an age group before the administration of cosyntropin, and foals without baseline cortisol concentration were compared with previously reported values for healthy foals.

### Table 1—Baseline plasma cortisol and ACTH concentrations, ratio of baseline ACTH concentration to baseline cortisol concentration, and response to administration of cosyntropin (0.1 µg/kg [0.045 µg/lb], IV) in ill foals.

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline Cortisol (ng/mL)</th>
<th>ACTH (pg/mL)</th>
<th>ACTH-to-cortisol ratio</th>
<th>30 minutes Cortisol (ng/mL)</th>
<th>ACTH (pg/mL)</th>
<th>Change in cortisol (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62.0 ± 42.7 (11.7–143.3)</td>
<td>21.0 ± 18.1 (12.9–62.1)</td>
<td>0.40 ± 0.25 (0.19–0.92)</td>
<td>109.4 ± 42.4 (64.9–186.3)</td>
<td>117.2 ± 59.3 (50.9–167.9)</td>
<td>44.0 ± 16.5 (14.9–60.8)</td>
</tr>
<tr>
<td>2</td>
<td>73.7 ± 39.5 (28.1–121)</td>
<td>182.1 ± 317.1 (13.1–824)</td>
<td>1.76 ± 2.51 (0.41–6.81)</td>
<td>102.4 ± 50.3 (43.7–183)</td>
<td>43.5 ± 31.3 (4.7–58)</td>
<td>23.7 ± 28.5 (10.8–89.5)</td>
</tr>
<tr>
<td>3</td>
<td>38.4 ± 36.6 (2.3–183)</td>
<td>28.9 ± 15.7 (11.4–58.6)</td>
<td>1.55 ± 2.34 (0.11–12.34)</td>
<td>58.6 ± 44.4 (5.5–208)</td>
<td>41.4 ± 46.6 (6.7–224.7)</td>
<td>20.0 ± 16.0 (2.3–58.5)</td>
</tr>
<tr>
<td>4</td>
<td>60.2 ± 65.0 (15.5–269.3)</td>
<td>199.7 ± 373.3 (10.2–1,250)</td>
<td>3.23 ± 2.09 (0.36–7.45)</td>
<td>83.8 ± 14.2 (20.4–151)</td>
<td>66.5 ± 38.0 (11.8–143)</td>
<td>17.4 ± 24.8 (–37.0–65.1)</td>
</tr>
<tr>
<td>Healthy ≤ 24 hours old</td>
<td>32.0 ± 9.6</td>
<td>16.0 ± 7.1</td>
<td>0.6 ± 0.4</td>
<td>81.6 ± 9.8</td>
<td>51.6 ± 9.8</td>
<td>26.0 ± 5.0</td>
</tr>
<tr>
<td>Healthy (3–56 days old)</td>
<td>26.5 ± 3.5</td>
<td>31.1 ± 4.7</td>
<td>1.23 ± 0.41</td>
<td>36.0 ± 3.7</td>
<td>24.7 ± 3.0</td>
<td>9.5 ± 2.1</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD (range). Group 1 = Foals ≤ 24 hours old without septicemia (n = 7). Group 2 = Foals ≤ 24 hours old with septicemia (n = 6). Group 3 = Foals between 1 and 56 days old without septicemia (n = 2). Groups 4 = Foals between 1 and 56 days old with septicemia (n = 18).

* Cortisol concentration after administration of cosyntropin (data represent values for 6 group 1 foals, 6 group 2 foals, 23 group 3 foals, and 17 group 4 foals).*

† Change in cortisol concentration, compared with baseline concentration. Values previously reported.‡

$^a$Within a group, mean concentration was significantly (P < 0.05) higher than baseline concentration or concentration measured 60 minutes after cosyntropin administration. $^b$ Mean concentration was significantly (P < 0.05) higher than mean cortisol concentration for group 3 foals. $^c$ Mean concentration was significantly (P < 0.05) higher than mean cortisol concentration for group 4 foals.

### Table 2—Numbers of ill foals with baseline cortisol and ACTH concentrations, ratios of baseline ACTH concentration to baseline cortisol concentration, and changes in cortisol concentration 30 and 60 minutes after administration of cosyntropin higher than, within, and lower than reported ranges for healthy foals.

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline Cortisol</th>
<th>Baseline ACTH</th>
<th>ACTH-to-cortisol ratio</th>
<th>Change in cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Normal</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>1</td>
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<tr>
<td>3</td>
<td>14</td>
<td>11</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

See Table 1 for key.
Baseline plasma ACTH concentration and ACTH-to-cortisol ratio—Baseline plasma ACTH concentration and the ratio of baseline ACTH concentration to baseline cortisol concentration did not differ significantly among the 4 groups of foals (Table 1), nor were differences detected when values for each group were compared with previously reported values for healthy foals. In addition, mean ACTH-to-cortisol ratio was not significantly different between foals with and without septicemia. For 16 of the 58 (28%) foals, baseline ACTH concentration was within the range of values previously reported for healthy foals, whereas for 21 (36%) foals, baseline ACTH concentration was higher than the range of values previously reported for healthy foals, and for 21 (36%) foals, baseline ACTH concentration was lower than the range of values previously reported for healthy foals (Table 2). Baseline ACTH concentration and the baseline ACTH-to-cortisol ratio were not significantly different between the 50 foals that survived and the 8 foals that died or were euthanatized.

Low-dose ACTH stimulation testing—Plasma cortisol concentrations 30 (adjusted \( P = 0.02 \)) and 60 (adjusted \( P = 0.03 \)) minutes after cosyntropin administration in foals \( \leq 24 \) hours old were significantly higher than corresponding cortisol concentrations in older foals (Table 1). In addition, in all 4 groups, plasma cortisol concentration 30 minutes after cosyntropin administration was significantly (adjusted \( P < 0.02 \)) higher than baseline cortisol concentration or concentration 60 minutes after cosyntropin administration. Results of ACTH stimulation testing (ie, plasma cortisol concentrations 30 and 60 minutes after cosyntropin administration and change in cortisol concentrations 30 and 60 minutes after cosyntropin administration, compared with baseline concentration) were not significantly different between foals with and without septicemia or between foals in the present study and healthy foals. However, for foals between 1 and 56 days old, cortisol concentrations 30 (adjusted \( P = 0.004 \)) and 60 (adjusted \( P = 0.005 \)) minutes after cosyntropin administration were significantly higher for the 22 foals that survived than for the 5 foals that died or were euthanatized.

For 14 of the 52 (27%) foals in which ACTH stimulation testing was performed, the change in plasma cortisol concentration 30 minutes after administration of cosyntropin was within the range of values previously reported for healthy foals, whereas for 23 (44%) foals, the change in concentration was higher than the range of values previously reported for healthy foals, and for 15 (29%) foals, the change in concentration was lower than the range of values previously reported for healthy foals (Table 2). Similarly, for 9 (17%) foals, the change in plasma cortisol concentration 60 minutes after administration of cosyntropin was within the range of values previously reported for healthy foals, whereas for 24 (46%) foals, the change in concentration was higher than the range of values previously reported for healthy foals, and for 19 (37%) foals, the change in concentration was lower than the range of values previously reported for healthy foals. In 3 foals between 1 and 56 days old that had septicemia, cortisol concentration was decreased, compared with baseline concentration, 30 minutes after cosyntropin administration (concentration decreased by 0.1, 1.8, and 37.02 ng/mL). A decrease in cortisol concentration was not observed in foals in the other 3 groups.

Low-dose ACTH stimulation tests were repeated in 22 foals, including 4 foals \( \leq 24 \) hours old without septicemia, 5 foals \( \leq 24 \) hours old with septicemia, 7 foals between 1 and 56 days old without septicemia, and 6 foals between 1 and 56 days old with septicemia. Testing was repeated in 6 of the 15 foals in which cortisol concentrations 30 minutes after cosyntropin administration were lower than the range of values for healthy foals, and in all 6, results of ACTH stimulation testing were within ranges previously reported for healthy foals. For 8 of the remaining 16 foals in which ACTH stimulation testing was repeated, cortisol concentration 30 minutes after cosyntropin administration was higher than the range previously reported for healthy foals, whereas for 6 foals, concentration was within the range previously reported for healthy foals, and for 2, concentration was less than the range previously reported for healthy foals.

Discussion

Activation of the hypothalamic-pituitary-adrenal axis occurs in ill foals, and it is reasonable to expect cortisol and ACTH concentrations to be similar to or higher than values for healthy foals of similar age.\(^{10,14}\) Recent studies\(^{10,14}\) have suggested that baseline cortisol concentrations are commonly high in foals with septicemia, but that some foals may have relatively deficient cortisol concentrations, particularly in relationship to ACTH concentrations (high ACTH-to-cortisol ratio). Results of the present study suggested that baseline cortisol and ACTH concentrations and results of low-dose ACTH stimulation testing in ill foals were generally not substantially different from values previously reported\(^{21}\) for healthy foals. However, a small subset of ill foals had a low baseline plasma cortisol concentration or blunted response to cosyntropin administration, which suggested dysfunction of the adrenal gland. Few measured variables were associated with outcome in the present study, but a higher cortisol concentration in response to cosyntropin administration was associated with a positive outcome in foals at 1 to 56 days of age. Results from this study also demonstrate that ill foals \( \leq 24 \) hours old have a significantly higher cortisol concentration 30 and 60 minutes after cosyntropin administration, compared with older foals. Furthermore, cortisol concentration 30 minutes after administration of cosyntropin at the dose used in the present study resulted in a higher mean cortisol concentration in all groups of foals, compared with mean cortisol concentration measured at baseline or 60 minutes after cosyntropin administration, which suggested that this dose may be appropriate for future investigations of adrenal gland dysfunction and RAI in foals.

In the present study, we did not detect any significant differences in mean baseline plasma cortisol concentration among the 4 groups of foals or between...
values for these foals and values previously reported for healthy foals. This is in contrast to results of a previous study\textsuperscript{14} in which cortisol concentration was significantly higher in septic foals than in healthy foals. A possible explanation for this discrepancy is that 86\% (50/58) of the foals in the present study survived to discharge, compared with only 61\% of the foals in the previous study.\textsuperscript{4} In people, there is a linear relationship between plasma cortisol concentration and severity of illness,\textsuperscript{9,13} and the higher survival rate in the present study may suggest that foals were not as critically ill. In addition, the large degree of variation in plasma cortisol concentration in the present study made it difficult to identify significant differences.

One method used to identify RAI in people is a single random baseline cortisol concentration.\textsuperscript{1,3,7} However, the lowest appropriate cortisol concentration a person should have in response to illness is unknown and varies from 1 individual to the next and with the extent of illness.\textsuperscript{1,5} Thus, the cutoff for cortisol concentration used to diagnose RAI in critically ill people with conditions such as sepsis, hypotension, hypoxemia, or trauma ranges from 100 to 250 ng/mL.\textsuperscript{1,4,10,13} In the present study, 69\% (40/58) of the foals had baseline cortisol concentrations within or higher than the range previously reported for healthy foals, and only 31\% (18/58) had concentrations lower than this range. Seventeen of the 18 (94\%) foals with low baseline cortisol concentrations, compared with concentrations for healthy foals, were between 1 and 56 days old, and 13 of these 18 (72\%) foals also had low ACTH concentrations (all 13 were between 1 and 56 days old). Thus, we were able to identify a subset of foals, all of which were between 1 and 56 days old, with a low baseline cortisol concentration associated with a low ACTH concentration. A low baseline cortisol concentration in conjunction with a low ACTH concentration may imply dysfunction at the level of the hypothalamus or pituitary gland. However, the clinical importance of low baseline cortisol and ACTH concentrations in ill foals and whether low concentrations are related to RAI are not known at this time.

Although we did not detect a significant difference in baseline ACTH concentration between foals with and without septicemia in the present study; some foals with septicemia had extremely high ACTH concentrations. Circulating concentrations of endotoxin and cytokines, such as interleukin-1 and tumor necrosis factor-\(\alpha\), may be high in septic foals and have been shown in other species to activate the hypothalamic-pituitary-adrenal axis.\textsuperscript{1,3,5} In addition, experimental infusion of endotoxin into healthy mares has been associated with increases in concentrations of corticotropin-releasing hormone and ACTH.\textsuperscript{39} High baseline ACTH concentrations in foals may also be associated with hypotension resulting from sepsis. In 1-week-old foals in which hypotension was induced by infusing sodium nitroprusside, plasma ACTH concentration increased from a range of 40 to 50 pg/mL to a range of 100 to 200 pg/mL after 20 minutes.\textsuperscript{39} On the other hand, baseline ACTH concentration was low in 6 of the 24 (25\%) foals in the present study with septicemia. The reason for this is uncertain, but may be related to the time at which blood samples were collected in relation to the course of illness. People with sepsis or severe trauma demonstrate biphasic activation of the hypothalamic-pituitary-adrenal axis, with cortisol and ACTH concentrations high during the initial phase and cortisol concentration high but ACTH concentration paradoxically low during the secondary phase.\textsuperscript{3,18,41} Other possible causes of low baseline ACTH concentrations in the present study include blunted ACTH release as a result of high interleukin-6 and tumor necrosis factor-\(\alpha\) concentrations, depletion of the releasable pool of ACTH, or negative feedback on ACTH release because of high cortisol concentrations.\textsuperscript{1,44-46} As was the case for baseline cortisol concentrations, a high degree of variability in baseline ACTH concentration was found in the present study, particularly among foals with septicemia. By contrast, previous studies\textsuperscript{14,15,47,48} have found minimal variation in baseline cortisol and ACTH concentrations in healthy foals.

The ACTH-to-cortisol ratio has been used to evaluate function of the pituitary-adrenal axis in people.\textsuperscript{43,49} In children with meningococcal disease,\textsuperscript{43} for instance, the highest values for the ACTH-to-cortisol ratio were observed in patients with the most severe disease and were a result of high ACTH and low cortisol concentrations. Similarly, in a previous study,\textsuperscript{14} the mean ACTH-to-cortisol ratio was significantly higher in septic foals that did not survive than in septic foals that did survive. On the other hand, in the present study, the ACTH-to-cortisol ratio was not significantly different between foals with and without septicemia or between foals that survived and foals that died or were euthanatized.

The low-dose ACTH stimulation test has been used in various species to evaluate adrenocortical function during critical illness.\textsuperscript{7,9,10,24} In the present study, we found age-related differences in cortisol concentration 30 minutes after cosyntropin administration, with concentrations significantly higher in foals ≤ 24 hours old than in foals 1 to 56 days old. Age-related differences have been reported in other studies\textsuperscript{23,33,41} involving foals and have been attributed to a heightened response of the adrenal cortex to ACTH associated with birth. We also found that in all 4 groups, mean cortisol concentration 30 minutes after cosyntropin administration was significantly higher than baseline cortisol concentration or concentration 60 minutes after cosyntropin administration, suggesting that ill foals were able to produce cortisol in response to cosyntropin.

For 37 of 52 (71\%) foals in the present study, plasma cortisol concentration 30 minutes after cosyntropin administration was higher than or within the range of values previously reported for healthy foals. However, the remaining 15 (29\%) foals, including 11 with and 4 without septicemia, had evidence of adrenal dysfunction characterized by a low plasma cortisol concentration 30 minutes after cosyntropin administration. Of interest, 12 of these 15 foals had a high baseline cortisol concentration. Thus, it is possible that these 15 foals had a low response to cosyntropin administration because cortisol secretion was already so high. We also found that 3 foals with septicemia had a decrease in cortisol concentration, compared with baseline concentration, 30 minutes after cosyntropin administration, suggesting that
some septic foals may have a severely blunted response. However, additional studies with a larger population of foals are needed to determine whether this pattern of response represents RAI. In foals with a poor response to cosyntropin administration in which a second ACTH stimulation test was performed, the response to cosyntropin administration was similar to that reported for healthy foals, suggesting that adrenocortical function may recover over the clinical course of disease.

For foals between 1 and 56 days old in the present study, cortisol concentrations 30 and 60 minutes after cosyntropin administration were significantly higher for foals that survived than for foals that died or were euthanatized. This suggests that maintenance of a functional adrenal cortex facilitates survival and that a heightened response to cosyntropin administration may be associated with a more favorable prognosis. We did not identify any other factors in the present study that were significantly associated with outcome. This is in contrast to results of a previous study in which the ACTH-to-cortisol ratio was significantly higher in non-survivors than in survivors. In part, the lack of significant differences in the present study may be explained by the high survival rate of septicemic foals and the small sample size. Large variations in baseline cortisol and ACTH concentrations were observed in the present study, which is similar to results of previous studies involving foals and people. Interestingly, none of the foals that died in the present study had a low baseline cortisol concentration or blunted response to cosyntropin administration. Rather, septicemic foals that died had high baseline cortisol and ACTH concentrations, high ACTH-to-cortisol ratios, and exaggerated responses to cosyntropin administration.

One limitation of the present study was the low number of foals in each of the groups, making it difficult to detect significant differences among groups even if they existed. Thus, additional studies with larger numbers of foals would be beneficial. Additionally, many studies of adrenal dysfunction and RAI in people involve patients with severe sepsis (eg, sepsis with multiorgan dysfunction) and septic shock (ie, severe sepsis with refractory hypotension). Although sepsis was diagnosed in 24 (41%) foals in the present study, no widely accepted criteria for the diagnosis of severe sepsis or septic shock have been established in equine medicine, nor were efforts made to categorize foals in the study as such. It is possible that the incidence of adrenal dysfunction may be higher in foals with more severe sepsis, but further studies documenting disease severity are necessary.

In summary, we did not identify any significant differences in mean baseline plasma cortisol and ACTH concentration or in mean baseline ACTH-to-cortisol ratio between foals with and without septicemia in the present study. However, values varied widely, suggesting that clinicians should be cautious in evaluating single random measurements of cortisol or ACTH concentration. Importantly, foals with a low baseline cortisol concentration may not necessarily have RAI, as 16 of the 18 foals in the present study with low baseline cortisol concentration had appropriate responses to cosyntropin administration. Similarly, foals with a high baseline cortisol concentration may not necessarily have a functional hypothalamic-pituitary-adrenal axis or may have attained maximal cortisol secretion. On the other hand, in foals between 1 and 56 days old, cortisol concentrations 30 and 60 minutes after cosyntropin administration were significantly higher for foals that survived than for foals that died or were euthanatized, suggesting that results of ACTH stimulation testing may be useful in establishing a prognosis in ill foals.

References

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