Approach to Fever of Unknown Origin in the Horse

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Abstract: In the horse, approaching a fever of unknown origin can sound like a daunting task. However, by reviewing the history, specific physical examination findings, and diagnostic testing, one can reach a diagnosis in the majority of cases.

Keywords: Fever, FUO

Definition:

Proposed in 1961, the human medicine definition of a fever of unknown origin (FUO) included the following criteria:¹

1. Fever higher than 101 °F on several occasions

2. Persisting without diagnosis for three or more weeks

3. One or more weeks of investigation in hospital

Veterinarians have tended to adopt these criteria, but using species-specific temperature ranges. In the horse, this is higher than 101.5 °F. Additionally, veterinarians expand the third criteria to include cases where a diagnosis has not been reached after one week of routine diagnostic testing, or after three days of investigation in the hospital. More commonly though, FUO in a horse is defined as a fever that cannot be localized to a body system based on initial physical examination or diagnostic test findings.

Mechanisms of Fever:²
The anterior hypothalamus controls the thermoregulatory mechanisms that usually maintain normal temperature and also control temperature changes during a fever. A fever can originate from infectious, inflammatory, immune-mediated, or neoplastic disease, or other injury. These states stimulate endogenous pyrogens that stimulate the anterior hypothalamus and initiate a prostaglandin mediated response. Elevation of the thermostatic set point and activation of autonomic, endocrine, and behavioral responses result in fever.

The most commonly implicated endogenous pyrogens include cytokines such as interleukin-1 and interleukin-6, interferon, and tumor necrosis factor, which are produced by leukocytes and other cells. Toll-like receptors, produced by macrophages and dendritic cells, have also been associated, as they can affect the hypothalamus independent of the cytokine pathway.

Evaluation:

*Documenting Fever*

Characterizing the fever pattern can be achieved by charting the rectal temperature at least twice daily.

An intermittent fever is characterized by diurnal variation in which a peak temperature elevation of at least 1.5 °F occurs, followed by a decline in temperature. Sometimes that decline falls within the normal temperature range and sometimes not. Most intermittent fevers peak in the late afternoon/evening and decline in the mornings, but not all.

Remittent fevers are characterized by several days of fever followed by several days of normal temperatures, with the cycle continuing to repeat.

As it sounds, sustained fevers are characterized by constantly raised, unvarying temperatures.
Each fever pattern can point you towards possible causes. For instance, intermittent fevers are often associated with infectious or neoplastic differential diagnoses. Remittent fevers are often noted in blood-borne protozoal diseases, or with equine infectious anemia virus. Finally, sustained fevers may be more commonly observed with drug administration or certain toxicities. It is important to note that these are not hard-and-fast rules, but more guidelines, to help direct the clinician in one direction or another.

History

As with all cases, the importance of obtaining a thorough history cannot be stressed enough. A general management history and medical history should be obtained, ideally utilizing open-ended questions that allow the client to expand on potentially useful information as much as possible. After gathering a more general history, specific questions about the farm and the individual should be asked. Examples include, but are not limited to, questions about housing, diet, vaccination status, parasite control programs, travel history, movement of horses on/off the farm, etc.

Physical Examination

True FUO occurs in the absence of other clinical signs. However, there are occasionally subtle localizing signs, so a complete physical examination should be performed to evaluate all body systems. Additionally, in some cases, the cause of fever is revealed later as localizing clinical signs develop. In those cases, repeated physical examinations are useful to identify early changes. The following are some examination tips which can be particularly helpful in cases of FUO.
- Cardiovascular examination: Mucous membrane color, capillary refill time, scleral injection, jugular pulsation, pitting subcutaneous edema, palpable temperature changes of the extremities, and cardiac auscultation are the most common circulatory physical exam parameters that should be evaluated. Auscultation should be performed in a quiet environment, paying careful attention to evaluate for the rate, cardiac sounds, rhythm, and the presence of any murmurs. The heart should be auscultated bilaterally. Arrhythmias usually necessitate an electrocardiogram (ECG) except in the case of type II atrioventricular block, a normal finding in horses. Murmurs should be graded according to intensity (I to VI), site, phase of cardiac cycle, and character. Many times endocarditis can present as a FUO. However, it should be noted, some subacute or chronic cases may not present with murmurs, and measuring cardiac troponin or echocardiography may be the only means of diagnosis.

- Respiratory examination (including rebreathing examination): Respiratory rate and effort, air flow through both nostrils, presence of nasal discharge, cough, checking for halitosis, and percussion of the sinuses should all be evaluated. Additionally, auscultation at rest should be performed in a quiet environment, listening to the trachea and the entire lung field on both sides. Evaluate for bronchovesicular sounds throughout and evaluate for the presence of any increased or decreased bronchovesicular sounds, crackles, or wheezes. Since respiratory disease is a common cause of fever, and respiratory abnormalities are not always be apparent on resting exam, it is also important to include a rebreathing examination in your evaluation. A bag should be placed over the muzzle, being sure to prevent sucking of the bag into the nostrils as the horse inhales. Alternatively, having someone block airflow through the nostrils can achieve similar
results. Tolerance of the rebreathing exam, auscultation of the trachea and the entire lung field on both sides, and recovery ability should all be evaluated.

-Lymph node palpation: Palpate carefully for any increases in size, sensitivity, symmetry, or rupture.

-Oral exam (visual and ideally manual, i.e. sedated and with speculum): The horse should be observed for normal prehension, chewing/drinking, and swallowing if possible. Subjective assessment of tongue tone can be made by grasping the tongue. A sedated dental exam allows for evaluation of malocclusions or dental abnormalities such as missing or damaged teeth, tooth root abscess, or injury to soft tissues in the mouth.

-Ophthalmic examination: A pen light, ophthalmoscope, and fluorescein dye should be utilized to evaluate the conjunctiva, cornea, anterior chamber, pupil and iris, lens, vitreous, and retina.

-Musculoskeletal and lameness evaluation: Evaluate body condition, muscling, symmetry, synovial effusion, response to musculoskeletal palpation, or any lameness appreciated.

-Neurologic examination: Evaluate attitude, posture, head carriage, complete cranial nerve exam, spinal reflexes, tail and anal tone, and gait/proprioception deficits.

-Abdominal palpation per rectum: Approximately 40% of the abdomen is palpable, and allows for evaluation of portions of the gastrointestinal tract, left kidney, urogenital structures, any enlarged lymph nodes, or abdominal masses.
- Urogenital: Abdominal palpation per rectum (above), or manual palpation, plus speculum exam in mares, can help evaluate the urogenital systems. It is also important to exteriorize the penis/sheath in all males and palpate both testicles in stallions.

Further Diagnostic Evaluation:

Overall, the prevalence of FUO is thought to be decreasing due to improved diagnostic testing availability. The list below includes examples, which may not apply to every case.

- Labwork (minimum database): A minimum database should be evaluated on all patients, including complete blood count (with blood smear evaluation for blood-borne organisms), fibrinogen concentration, biochemistry profile, and urinalysis (+/- urine culture).

- Labwork (additional testing): Additional testing may include bile acid concentration and/or ammonia concentration (if there is concern for decreased liver function), serum amyloid A concentration (to be serially monitored in cases with inflammatory conditions), cardiac troponin concentration (if there is concern for cardiac disease), coombs test or antinuclear antibody testing (in cases of hemolytic anemia, red blood cell autoagglutination, or suspecting other immune-mediated disease), or serum protein electrophoresis/immunoelectrophoresis (used to further classify hypo- or hyper-gammaglobulinemia).

- Fecal testing: Fecal egg count, fecal float, and culture/PCR for infectious differentials are indicated in cases with intermittent/chronic/acute diarrhea, weight loss, or evidence of gastrointestinal protein loss.

- Imaging: Thoracic ultrasonography and/or radiography and/or airway endoscopy are indicated in cases with persistent nasal discharge, cough, abnormal auscultation of the
thorax, or persistently increased respiratory rate/effort. Abdominal ultrasonography
and/or radiography are indicated in cases with gastrointestinal clinical signs such as colic,
gastric reflux, or diarrhea, as well as cases with abnormal liver or kidney function tests,
or suspected abdominal masses. Echocardiography is indicated in cases with cardiac
murmurs or dysrhythmias. Ultrasonography and/or radiography of specific areas with
musculoskeletal heat, pain, or effusion are also indicated.

- Trans-tracheal wash: Submission for cytology, culture, PCR (ex. EHV-5) is indicated in
cases with persistent nasal discharge, cough, abnormal auscultation or percussion of the
thorax, or persistently increased respiratory rate/effort.

- Broncho-alveolar lavage: Submission for cytology is indicated in cases with persistent
nasal discharge, cough, abnormal auscultation of the thorax (particularly if wheezes are
appreciated), or exercise intolerance.

- Thoracocentesis: Fluid evaluation, cytology, and/or culture are indicated in cases with
evidence of pleural effusion on auscultation/percussion or ultrasonography.

- Abdominocentesis: Fluid evaluation, cytology, +/- culture is indicated in cases with
abdominal pain, abnormal rectal examination (such as small intestinal distension,
enlarged lymph nodes, or palpable abdominal mass), or increased free fluid in the
abdomen on ultrasonography.

- Synoviocentesis: Fluid evaluation, cytology, and culture is indicated in cases with
localized synovial structure heat, pain, or effusion.

- Serology: Testing for infectious diseases common in the geographic area or the specific
patient population is indicated.
- Fine needle aspirate or biopsy for cytology/culture/histopathology: Indicated in cases with enlarged lymph nodes, accessible masses, vesicular or ulcerative skin lesions, liver abnormalities, +/-kidney abnormalities. Intestinal mucosa biopsy (duodenal or rectal biopsy) is indicated in cases of hypoproteinemia despite normal kidney and liver diagnostics, chronic weight loss, chronic diarrhea, or cases with thickened bowel wall on ultrasonography.

- Cerebrospinal fluid tap: Fluid analysis, cytology, culture, specific disease testing is indicated in cases with neurologic signs localized to the central nervous system.

- Blood culture: Indicated in cases with intermittent fever (particularly neonates with failure of passive transfer), cases with neutropenia or neutrophilia, increased fibrinogen, or cases with cardiac murmurs and/or valve lesions on echocardiography suspicious of bacterial endocarditis.

In cases that truly have no subtle localizing signs, beginning with a minimum database, fecal examination, and serologic tests appropriate to the geographic location is recommended. If positive finding are noted there, one can pursue more specific diagnostic tests. If no abnormalities are noted, performing thoracic and abdominal ultrasound and/or radiography is recommended next.

Differential Diagnoses:

In general, patients with FUO are usually exhibiting atypical presentations of common diseases. In a case series, 43% were due infectious causes, 22% due to neoplastic processes, 6.5% due to immune-mediated diseases, 19% had miscellaneous causes, and 9.5% remained undiagnosed.³

Treatment Options:
In some cases, a specific diagnosis cannot be found, or diagnostic testing must be discontinued. In these cases, different treatments may be trialed without a confirmed diagnosis. Options may include antibiotics, anti-inflammatory medications, or immunosuppressive therapy. While this can resolve clinical signs and sometime confirm a suspected diagnosis, it also carries substantial risk and should only be performed with close monitoring.

Conclusion:

FUO cases are often time consuming and challenging, and may incur a large expense for clients. By careful evaluation of history and physical examination findings, and following an ordered, problem-oriented approach, one is able to reach a diagnosis in 90% of cases.  

References:

