DEFINITION
In human medicine, the definition of a fever of unknown origin (FUO) was proposed in 1961 and included the following criteria.
1. Fever higher than 101 °F on several occasions
2. Persisting without diagnosis for more than 3 weeks
3. At least 1 week of investigation in hospital
Veterinarians occasionally adopt these guidelines, using species specific temperature ranges and expansion of the 3rd criteria to include patients in which a diagnosis has not been obtained after a week of routine diagnostics, or after 3 days of diagnostic tests in hospital. However, more commonly, we refer to a FUO as a patient with a fever that cannot be localized to a body system based on physical examination, or initial diagnostics.

MECHANISMS OF A FEVER
The anterior hypothalamus controls thermoregulatory mechanisms that are responsible for maintaining normal temperature and temperature changes during the febrile response. A fever is the result of a complex pathway and can be initiated by infectious, inflammatory, and neoplastic disease, or other injury states. These diseased states stimulate peripheral endogenous pyrogens which reach the hypothalamus and initiate a prostaglandin mediated response. The result is an elevation of the thermostatic set point and activation of endocrine, autonomic and behavioral responses leading to a fever. The endogenous pyrogens are cytokines that are produced by leukocytes and other cells, such as tumor necrosis factor (TNF), interleukin (IL-1, IL-6) and interferon (IFN). The IL-1 family (particularly IL-1α and IL-1β) are considered to be the most important pyrogenic cytokines. Toll-like receptors (TLRs) have also received attention as fever stimulants. Expressed by a variety of cells, such as macrophages and dendritic cells, TLRs in response to LPS can affect the hypothalamus independent of the cytokine pathway.
A number of laboratory studies have also implicated the vagal nerve as having a role in fever induction. Vagotomized laboratory animals have shown a reduced febrile response to intraperitoneal LPS.

EVALUATION OF A FEBRILE PATIENT

History
Prior to performing a physical examination, and as with any patient, the importance of thorough history taking cannot be emphasized enough. General medical history and specific questions about the individual and the farm should be asked. Examples of these include diet, housing, vaccination and parasite control programs, travel history and movement of other horses on and off the farm should be asked.
Physical Examination
A true FUO exists in absence of localizing clinical signs, however some signs may be subtle. Nonspecific clinical signs include lethargy, inappetence and weight loss. In most cases, the cause of a fever becomes evident as further clinical signs develop, therefore repeating the physical examination frequently can help pick up on subtle and early clinical signs.

While we expect veterinarians to have the ability to perform a physical examination, there are particular aspects of the physical examination that can be forgotten. Some examples are listed here. These will be expanded on in the presentation.

1. Respiratory evaluation and the rebreathing examination: A rebreathing examination should be part of a general physical examination as respiratory disease is a common source of a fever, but may not be apparent on resting examination. Selecting an ideal location or environment to perform the respiratory evaluation is important. Slight background noise or movement of the nervous horse can interfere with auscultation findings. Specialized equipment is not necessary, a trash bag or obstetrical sleeve is sufficient. Alternatively, having someone block airflow through the nostrils will achieve similar results.

2. Cardiac auscultation: thorough cardiac auscultation involves more than just listening to the heart rate. I have dealt with several cases of endocarditis which present as FUOs. Cardiac auscultation should be done in a quiet environment. Care should be taken however because murmurs may not be evident in horses with subacute or chronic endocarditis. In these cases, cardiac troponin and echocardiography may be the only means to diagnose the condition.

3. Lymph node palpation: enlarged lymph nodes may point towards an infection or neoplasia
4. Abdominal palpation per rectum
5. Musculoskeletal and lameness evaluation: Shifting leg lameness has been associated with bacterial endocarditis and immune mediated diseases which may present as a FUO.
6. Neurologic examination
7. Visual and manual oral exam
8. Sinus percussion
9. Ophthalmic examination

Differential Diagnosis
It is well recognized that patients with FUO are not usually suffering from an unusual disease, but rather exhibit atypical manifestations of common diseases. Most cases of a FUO are due to an infectious cause. Neoplastic, immune-mediated and autoimmune diseases are other common causes.

Diagnostics
It is thought that the prevalence of cases defined as having a FUO is decreasing due to advancing diagnostic technology and the increasing number of veterinary practices with
sufficient diagnostic capability. Some case examples will be presented that highlight diagnostic approaches to FUOs. The below list gives some examples of diagnostic tests, many of which may not be pertinent to every case.

1. Laboratory tests: CBC and morphologic evaluation of a blood smear for blood borne parasites, fibrinogen, serum amyloid A, biochemical profile, cardiac troponin, urinalysis. Also coombs test and antinuclear antibody testing for immune-mediated diseases.

2. Serum protein electrophoresis and immunoelectrophoresis can further classify hypo- or hyperproteinemia

3. Diagnostic imaging: thoracic and abdominal ultrasound and radiography, echocardiography

4. Abdominocentesis: fluid evaluation, cytology, culture

5. Transtracheal aspirate: cytology, culture, PCR (e.g. EHV-5)

6. Blood culture

7. Serologic testing for various infectious diseases common to the area or patient population

8. Fecal testing: e.g. PCR for Salmonella

9. Biopsy: Rectal and mucosal (infiltrative bowel disease), lymph nodes, masses, skin lesions

10. CSF analysis: fluid analysis, culture, specific disease testing.

CONCLUSION

FUO cases can often present as time consuming and challenging patients (and a large expense for your client). By forming an ordered, problem-oriented approach, unnecessary diagnostics can be avoided and you will be able to reach a diagnosis in 90% of cases. This presentation will include a number of case examples.

References available on request