INVESTIGATION OF FEVER IN HORSES: THE OBVIOUS AND THE NOT SO OBVIOUS

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Introduction

Measurement of body temperature forms an essential part of the physical examination. An increased temperature is a common clinical complaint which can accompany a variety of infectious and non-infectious diseases in horses. In many situations, a detailed history, accompanied by a careful physical examination and appropriate diagnostics will determine the cause of the fever. However, in a small number of cases, despite these investigations, the cause of the fever remains elusive, and advanced diagnostic techniques, or therapeutic trials may be required. Investigation of a fever with no obvious cause can be both challenging and frustrating, and in some cases is only solved on the post mortem table.

What is a fever?

Fever is defined as a regulated elevation in thermal set point, or more simply, an increase in body temperature. Whilst in most situations, a horse with an elevated rectal temperature will have a fever, in rare situations (see below) a diagnosis of hyperthermia, which involves a loss of the ability to regulate body temperature, is made.

The average normal temperature of an adult horse is 38°C (100.5°F)
The normal temperature of a foal is slightly higher, ranging from 37.8°C to 38.9°C. (100 to 102°F)

In both adults and foals, the temperature can vary between morning and evening by up to 1°C, with the lowest temperature typically in the morning, and the highest in the late afternoon.

Regulation of body temperature

Body temperature is regulated via neurons within the hypothalamus which sense changes in core body temperature. When an increase in body temperature is sensed, behavioural and physiological responses are initiated to lose heat.

Hyperthermia

If there is a loss of the ability to dissipate heat, hyperthermia can occur. Hyperthermia differs from a true fever in that the regulatory set point is unchanged. Situations in which hyperthermia may occur include:

- Anhidrosis
- Sustained or high intensity exercise
- Heat stroke
- CNS disorders
- Drug or toxin reactions

Several syndromes in foals which result in hyperthermia have been reported. The aetiology is unclear, although it is likely due to a lack of ability to regulate body temperature. A syndrome of idiopathic or transient tachypnoea, accompanied by an increased rectal temperature, has been reported in Clydesdale, miniature horses, Thoroughbred and Arabian foals. Clinical signs usually develop within several days of birth, and can last for several weeks. The clinical signs appear to be worse during warm and humid weather, and it is this presumed that the increased respiratory rate occurs in an attempt to dissipate heat. There is no specific treatment, although maintaining foals in a cool environment, clipping and providing cool water can help. Most foals will grow out of this syndrome. More recently, a similar syndrome has been reported in Friesians, Belgians and other draft horse/draft-cross foals. The syndrome appears similar to that affecting neonatal foals, although clinical signs can be delayed until 6 weeks of age or older. Infectious causes of an increased temperature, in particular sepsis and Rhodococcus pneumonia should be ruled out before making a diagnosis of idiopathic hyperthermia/tachypnoea.

Pathogenesis of 'true' fever

In the vast majority of situations, an increased rectal temperature will be due to a true fever, rather than hyperthermia. Fever is most commonly caused by infectious conditions, in particular viral and bacterial infections, although it can be a component of many inflammatory, immune-mediated and neoplastic conditions.

In response to infection or inflammation, cytokines, which are cell to cell signals, are produced by cells such as monocytes/macrophages, neutrophils and lymphocytes. These cytokines, or endogenous pyrogens, include IL-1, TNF, interferon and IL-6. These pyrogens act within the brain to produce prostaglandins, which ultimately results in an increase in the regulatory set point within the hypothalamus, causing an increased core temperature. This response is controlled so that the temperature does not continue to increase – for example, TNF acts via a negative feedback mechanism to prevent further TNF release. The importance of prostaglandins in the development of fever explains why NSAIDs such as flunixin are typically effective at reducing a fever.

Should we always 'treat' a fever?

The beneficial effects of fever

Fever is part of the physiologic response to invasion of infectious agents. An increased core temperature is an important part of the defence mechanism against the invading organism. The presence of a fever enhances host defences via a number of different mechanisms, including increased activity of phagocytic cells and lymphocytes and increased sequestration of iron.

The adverse effects of fever

However, temperatures above 41°C can result in adverse effects, including increased catabolism and cytokine dysregulation.

Because of the potentially beneficial effects of a fever, I typically will not 'treat' a fever with NSAIDs unless it appears to be making the horse depressed and inappetant. I also find that if I use NSAIDs then it can also interfere with my ability to monitor response to treating the initiating cause of the fever, as a return to a normal rectal temperature would suggest improvement.

Investigation of a fever

The aim of the initial investigation should be to

1. Determine whether this is an individual animal problem, or part of a herd problem.
2. Determine whether, based on the history and PE findings, a diagnosis can be made
3. Determine a list of differential diagnoses if a definitive diagnosis cannot be made
4. Determine what, if any diagnostic tests need to be submitted
5. Determine what, if any, treatment is necessary

The first step in answering these questions is to establish as complete a history as possible, both for this horse and also any in contact horses, and then to perform a complete physical examination.

1. Determine whether this is an individual animal problem, or part of a herd problem.

It is essential to establish as early as possible in the diagnostic process whether this is the only horse affected, or whether other horses are showing similar clinical signs. Early identification of contagious diseases such as Strangles or influenza can help prevent a widespread outbreak. The owner of the horse being examined may not know if other horses are affected, especially in a shared barn, so questioning barn/yard owners or managers may be useful. Travel history of all horses on the yard is also important – older horses in particular may become subclinically infected with agents such as S equi and influenza virus, acting as silent shedders without showing clinical signs. Vaccination history is an important part of the history, however, vaccinated animals can still become infected and shed organisms.

2. Determine whether, based on the history and PE findings, a diagnosis can be made

In some situations, after establishing the history and performing a physical exam, a diagnosis may be made. Clinical experience, as well as classic clinical signs/history is used on these occasions. Examples would include a horse with clinical signs such as draining submandibular lymph nodes, respiratory stridor and fever that has been in contact with a new arrival to the yard. A diagnosis of Strangles can be made at this point, although diagnostic tests could be used to definitively confirm the diagnosis.

3. Determine a list of differential diagnoses if a definitive diagnosis cannot be made

In many situations, identification of the major body system affected will allow a list of differential diagnoses to be constructed even if a definitive diagnosis cannot be made. For example, the major differentials for a horse with abdominal discomfort, fever and loose faeces would include enterocolitis, peritonitis, abdominal abscess and possibly abdominal neoplasia.

4. Determine what, if any diagnostic tests need to be submitted

Diagnostic tests can be used to further refine the differential diagnosis list. Since most owners will not be willing to pay for all possible diagnostic tests, targeted testing will probably be required. There are two

main aims in this situation. Firstly, testing for diseases that may be contagious, exotic or zoonotic. Secondly, testing to help guide treatment and establish a prognosis. The aim of the testing will vary according to the list of differentials. For example, a horse that has recently been imported from Italy which is showing ataxia, fever, hyperaesthesia and depression may be infected with West Nile virus, and should be tested. Testing for WNV in a horse which comes from a closed yard situated in a country with no evidence of WNV infection, with no history of travel but similar clinical signs would not be appropriate, although haematology, acute phase proteins and CSF analysis may be appropriate to rule out bacterial meningitis. In either case, EHV1 infection could be a differential, and has potential impact not only on the individual horse, but also all in contact horses, so testing for EHV1 would be appropriate.

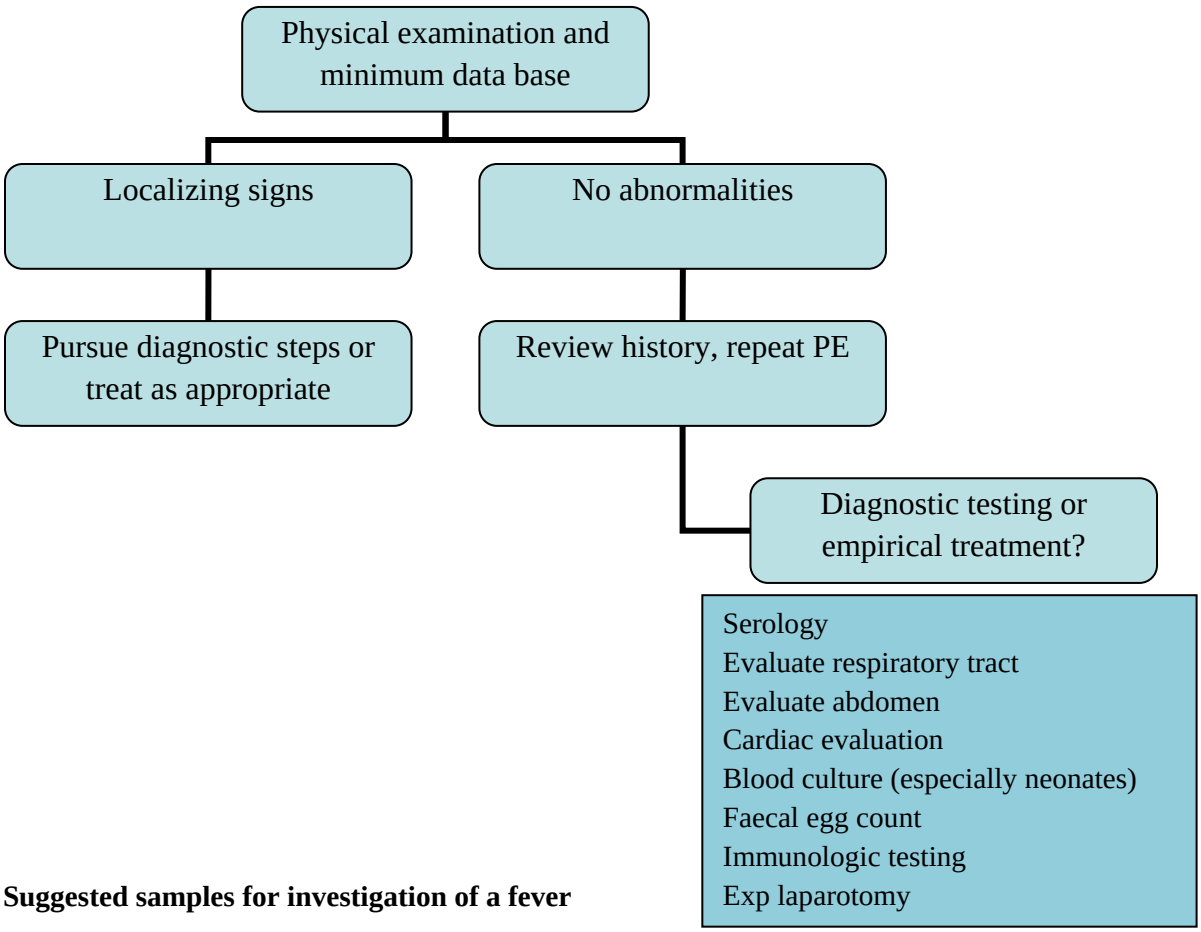
5. Determine what, if any, treatment is necessary

In an ideal world, we would have clients who were happy to pay for whatever diagnostic tests we thought appropriate, and we would have access to tests that would provide rapid results. The reality of the situation however, is that we are usually forced to make a treatment decision after performing only a physical examination. The majority of fevers are caused by infectious causes, but determining whether it is a virus or bacteria (or fungus) can be more challenging. In addition, even if it is a primary viral disease, a secondary bacterial infection cannot be ruled out. Whether or not to use antibiotics before further diagnostics become available, or even instead of performing diagnostic testing, will be determined by severity of clinical signs and thus the risk of NOT treating, client finances, and logistical considerations such as when test results will become available, and when you will next be able to see the horse. If antibiotics ARE used, the choice of drug should be based on the most likely bacteria to cause the disease/clinical signs, the available route of administration (eg your client may not be happy to give intra-muscular injections) and your clinical experience with similar cases. If no response is seen within 3-4 days of these first line antibiotics, further diagnostic testing is recommended.

The fever of unknown origin

Fever of unknown origin (FUO) exists when a fever is prolonged and there are no specific signs associated with the fever. Although these horses can be very frustrating to manage, in the majority of cases, the fever is caused by a common disease with an unusual presentation, and thus, following a logical approach can lead to a diagnosis. In a series of 63 cases of FUO[1], infection was the cause in 43%, neoplasia in 22%, immune-mediated disease in 6.5% and miscellaneous disease in 19%. In this series, the diagnosis of FUO was based on (1) illness of at least 3 weeks duration associated with non-specific signs; (2) body temperature greater than 38.6°C on several occasions; (3) no clear diagnosis after initial haematology and biochemical testing. Infectious diseases identified included endocarditis, peritonitis, abdominal abscesses, cholangitis, pyelonephritis and cellulitis. The most commonly identified neoplasm was lymphoma. Immune-mediated disease was uncommonly diagnosed, which differs from similar studies in humans and small animals. Whether this is because of a truly lower incidence, or because of our relatively limited ability to diagnose immune-mediated conditions in horses is unknown. Despite extensive diagnostic tests, the cause remained unclear in almost 10% of horses.

Approach to a horse with a fever



Suggested samples for investigation of a fever

1. Non-specific signs eg lethargy, anorexia, weight loss

Sample	**Test**	**Evaluation/interpretation**
EDTA blood	Haematology	Leucopaenia suggests acute demand. Often seen with GI disease. (may be response to endotoxaemia rather than infection) Leucocytosis more common in chronic conditions such as Strangles or R equi. Lymphopaenia may be seen with viral infections or as part of 'stress' response
Serum/plasma	Biochemistry Acute phase proteins	May identify organ (s) affected SAA increases rapidly and decreased rapidly. Fibrinogen has more delayed response and resolution. Cannot differentiate between inflammation and infection. Iron levels may be more sensitive

	Coggins (EIA)	If history/geographic location are suggestive

2. Signs localized to respiratory tract

Cough, nasal discharge, lymphadenopathy, abnormal auscultation etc

Sample/procedure	**Test**	**Evaluation/ interpretation**
Endoscopy	URT and LRT	To identify possible sites of infection and guide further sampling eg if obvious drainage from guttural pouches, investigate this area rather than LRT
Tracheal fluid	Cytology, culture	A percutaneous sample is recommended. Obtaining the sample through the scope makes culture results difficult to interpret, as nasopharyngeal contamination is likely – organisms likely to cause LRT infection are typically normal inhabitants of the nasopharynx. Positive culture without cytologic evidence of infection (ie neutrophils) is likely a contaminant
Nasopharyngeal swab, guttural pouch lavage	Culture, PCR	To identify S equi infection/carriers
Nasopharyngeal swab, whole blood, serum	Virus isolation, PCR, antibody titre	For identification of respiratory viruses such as EHV and EI.
Ultrasound	Thorax	Evaluation of pleural cavity and pleural surface – abnormalities overlying aerated lung will not be identified
Radiographs	Thorax	Portable machines can be used for foals, otherwise typically restricted to referral hospitals.
Pleural fluid	Cytology, cell count, protein, culture	Submit if fluid identified on ultrasound evaluation

3. Signs localized to gastrointestinal tract

Colic, diarrhoea, oedema, weight loss, increased liver enzyme activity etc

Sample/procedure	Test	Evaluation/interpretation
Rectal exam		To identify masses/faecal consistency etc. Look for parasites on rectal sleeve
Peritoneal fluid	Cytology, cell count, protein concentration and culture	Changes can be seen with non-infectious lesions such as intestinal strangulation. Marked increased in cell count and protein are more consistent with bacterial peritonitis. Culture may be negative – does not rule out bacterial infection
Ultrasound	Abdomen	To identify masses/abscesses; evaluate solid structures eg liver; evaluate colon contents – fluidy contents may suggest colitis, even if diarrhoea absent. Increased intestinal wall thickness may suggest enteritis/IBD/neoplasia. In weanlings, Lawsonia intracellularis results in thickened SI wall.
Liver biopsy	Histology, culture	Changes may be suggestive of aetiology eg cholangiohepatitis, but are often non-specific. Neutrophilic infiltration may be more suggestive of bacterial cause. Culture recommended, but often unrewarding
Faeces	Culture, faecal egg count, toxin assay	Selective culture for Salmonella – require at least 3 samples. Egg count may be negative with cyathostominosis. Toxin assay for Clostridium perfringens and C difficile, if horse has diarrhoea (especially if history of antibiotic administration)
Serum	S equi ELISA	Especially if intra-abdominal abscess identified (metastatic S equi)

4. Signs localized to central nervous system

Mentation changes, ataxia, paresis, hyperaesthesia , cranial nerve abnormalitiesetc

Sample/procedure	Test	Evaluation/interpretation
CSF	Cytology, cell count, protein concentration, culture	Increases in cell count and protein are non specific for inflammation (viral/bacterial/parasitic). A neutrophilia, or marked increased in cell count and protein would be more consistent with bacterial infection. Culture often unrewarding.
Serum	Antibody levels	EHV levels. (see also respiratory) Depending on geographic location, may test for WNV etc

Radiographs	Cervical spine, head	Evaluation for possible osteomyelitis that could extend to CNS
MRI/CT		For evaluation of intracranial masses

5. Signs localized to the musculoskeletal sytem

Lameness, limb swelling, joint swelling etc

Adult horses with localized synovial structure sepsis will not typically have a fever

Sample/procedure	**Test**	**Evaluation/interpretation**
Synovial fluid analysis	Cell count, protein concentration, cytology, culture	Increases in cell count greater than 20,000/µl and protein greater than 40g/l suggest sepsis. Neutrophilic (>80%) cytology suggests bacterial infection. Culture often unrewarding
Radiographs	Of affected limb/joint	To determine bony involvement/osteomyelitis. If acute infection, bony changes may not have yet occurred
Ultrasound	Of affected area	Can be used to assist with identifying sites for sampling culture eg with cellulitis may be identify fluid pocket to aspirate
Blood	PCR/Serology Cytology	Anaplasma, Borrelia

6. Signs localized to cardiovascular system

Murmur, arrhythmia, signs of cardiac failure

Sample/procedure	**Test**	**Evaluation/interpretation**
Blood	Culture	Multiple samples required to detect bacteraemia.
Ultrasound	Echocardiography Vascular scan	In particular, looking for evidence of valve leaflet thickening (endocarditis),myocardial abnormalities (myocarditis) and pericardial effusion If palpable abnormality of eg jugular vein

Further reading

1. Mair TS, Taylor FGR and Pinsent PJN. (1989) Fever of unknown origin in the horse: a review of 63 cases. *Equine vet J* **21**;260-263

2. Hines MT. Changes in body temperature. In: Equine Internal Medicine. Eds Reed SM, Bayly WM and Sellon DC. 2nd edition, 2004. Elsevier. Pp 148-155