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# Fever of unknown origin in the horse with a case report example

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Fever of unknown origin (FUO) is a syndrome characterised by prolonged, unexplained fever, associated with non-specific signs of illness such as lethargy, inappetence and weight loss[10]. FUO can be a frustrating, diagnostic challenge to the equine practitioner. History taking, along with a thorough clinical examination and systematic approach to a diagnostic work-up are vital. Even then, up to 10% of cases can remain undiagnosed[10]. Causes of FUO can include infection, neoplasia and immune-mediated disease[10]. In intensive care units in human hospitals, fever incidence ranges from 23-70% and is related to infection in approximately half of these cases[7].

Fever is a host defence mechanism that has been preserved within the animal kingdom. It is a physiological part of the acute phase response to infection or inflammation. It has a complex pathogenesis, with neuronal and humoral mechanisms being involved in the induction of fever[16]. FUO in the horse has been classified as meeting the following criteria[10]:

- Illness of at least three weeks duration associated with non-specific signs
- Core body temperature of at least 38.6° C (101.5° F) on several occasions
- No clear diagnosis after an initial full blood-count and serum biochemical profile.

Infection is the most common cause and can account for up to 43% of cases[10]. Thus, the investigation of FUO requires a systematic approach, with emphasis placed on the consideration of infectious causes.

**The FUO Work up**

Once it has been established that the horse has a genuine fever (non-febrile hyperthermia may come from anhidrosis, heat exhaustion, malignant hyperthermia, exercise, drugs and toxins), then a diagnostic plan should be put in place.

**Full history and signalment**

Certain causes of fever may be more common in certain populations, e.g. neonatal septicaemia, *R. equi* respiratory infections in 1-6 month old foals, and respiratory tract infections in young horses. Exposure to *S. equi* ssp. *equi* should alert the practitioner to the possibility of internal abscessation. Recent epidemiological knowledge of the local geographical locations should also be considered (especially in South Africa with regard to West Nile Virus, Equine Encephalitis Virus and African Horse Sickness Virus).

Documentation and recording of temperature fluctuations can also provide further information. Intermittent fevers are most often associated with infectious causes, especially viral infections.[14] Although not exclusive to infectious causes, intermittent fevers demonstrate a recurring increase in temperature, interspersed with periods of normal temperature. Remittent temperatures tend to have a diurnal variation that is exaggerated, without a return to a normal temperature in between, or a cyclic pattern where pyrexia remains for several days at a time. This is a common finding with Equine Infectious Anaemia. Sustained fevers occur when the temperature remains permanently elevated.

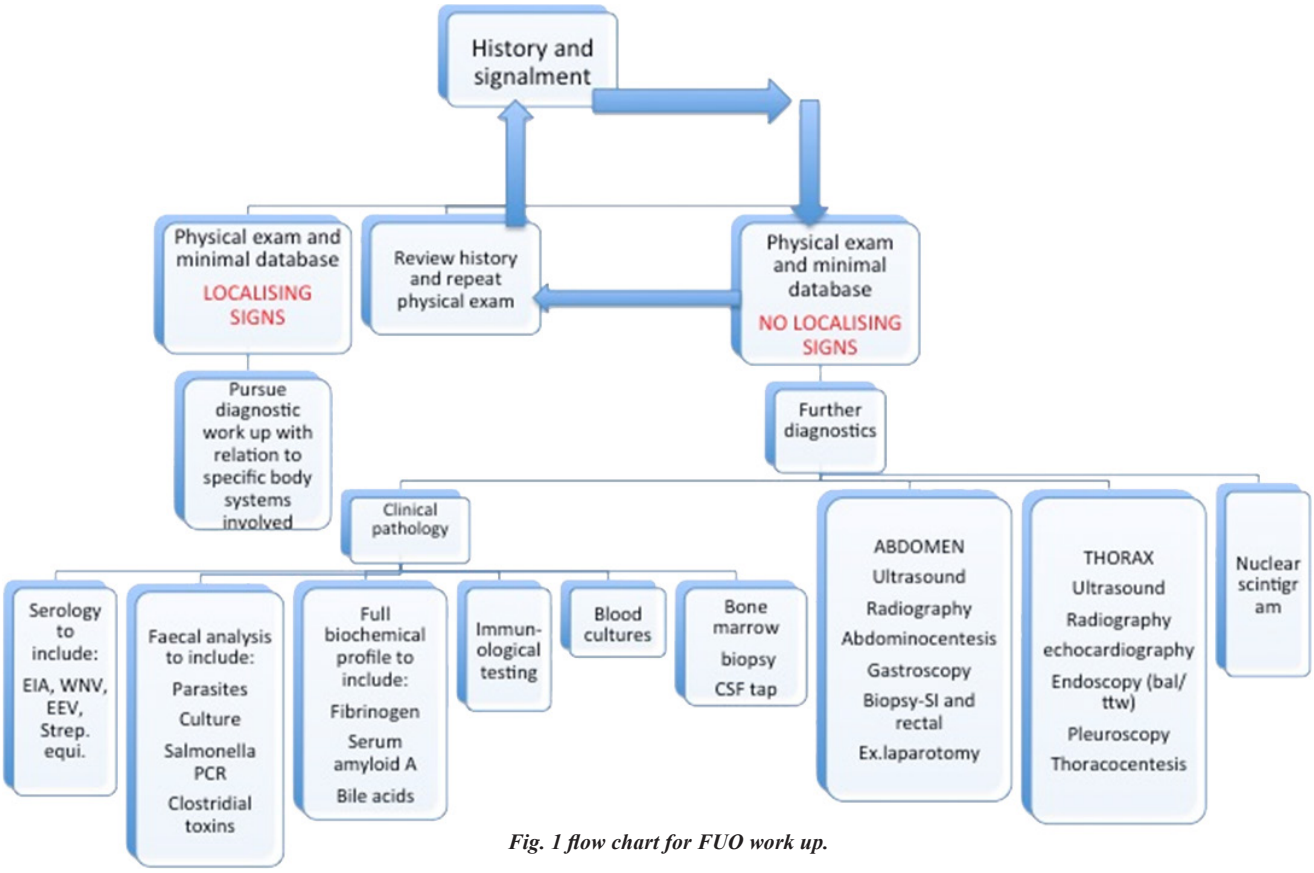


*Fig. 1 flow chart for FUO work up.*

**Physical Examination**

This should be thorough and include auscultation of the thorax with and without a re-breathing bag. A rectal examination and a full neurological examination should also be performed. Often in FUO cases, clinical signs can be few and far between and not elude to which bodily systems are involved. Repeat reviews of the history and repeat physical examinations are often required.

**Clinical Pathology**

A complete blood count and serum biochemical profile should be obtained. A blood smear should be examined for haemoparasites although parasitaemia is often below detectable levels. Urinalysis should be performed. Chronic infection and/or inflammation are often reflected by hyperfibrinogenaemia, hyperglobulinaemia, anaemia and thrombocytosis. Serum electrophoresis can further analyse globulins. If there are persistent abnormalities in circulating cell populations then a bone marrow biopsy may be warranted.

Serological evaluation including EIA, *Strep. equi* sspp. e*qui,* piroplasmosis, and Lymes disease should be considered.

Faecal analysis should include assessment for parasites. If clinical/laboratory signs suggest gastrointestinal protein loss, melaena and/or diarrhoea then faecal culture, clostridial toxin assessment, corona virus assessment, *Salmonella* PCR, rectal biopsies and absorption tests should be considered.

Blood cultures are most useful in neonates but can be useful especially in adult cases of bacterial endocarditis[13]. It is best to try to sample during an episode of pyrexia and when the horse has not received antimicrobials for 48 hours. Taking several samples over an hour period may also increase the chances of a positive culture[16].

Respiratory pathology is commonly involved in FUO. Nasopharyngeal swabs, guttural pouch lavage, bronchoalveolar lavage and transtracheal wash samples can be submitted for laboratory testing. Thoracocentesis can occasionally reveal abnormalities even if there is no dramatic increase in free pleural fluid. Abdominocentesis can be performed to yield peritoneal fluid. Not all neoplastic lesions will be shedding cells into the abdominal cavity so do not rule out neoplasia if cytological analysis is within normal limits[23].

**Diagnostic imaging**

Abdominal and thoracic ultrasonography should be performed and are fairly high yield diagnostic tests. Echocardiography is the best way to identify vegetative endocarditis lesions[13]. Radiography of the abdomen and thorax can also be performed. Nuclear imaging using labelled white blood cells may also be considered in the investigation of FUO [5,15].

**Surgical investigation**

If all other results fail to elude to a diagnosis, then surgical intervention in the form of an exploratory laparotomy could be considered.

This needs serious consideration due to the invasiveness of the procedure combined with the fact that if the horse under investigation is suffering from pyrexia then they are going to be at an increased risk for anaesthesia.

The following case report highlights the thorough and systematic approach required for horses presenting with FUO.

***History***

A 6-year-old Dutch Warmblood chestnut gelding was examined following a period of anorexia, pyrexia, lethargy and weight loss of 4 weeks' duration. The gelding had received 30mg/kg of combined trimethoprim and sulphadiazine, and 2.2 mg/kg phenylbutazone *per os* bid for 7 days with initial transient improvement followed by recurrence of clinical signs.

***Clinical examination***

The horse was in poor bodily condition, weak, markedly depressed and pyrexic (39.4°C). Physical findings were tachycardia (heart rate 58 beats/min) and respiratory rate 12 breaths/min. Mucous membranes were pink and moist with a capillary refill time of less than 2.5s. Borborygmi were reduced on auscultation of all 4 quadrants of the abdomen. No abnormalities were detected upon transrectal examination.

***Laboratory findings***

Initial laboratory findings revealed mild anaemia, leucocytosis, neutrophilia, hyperglobulinaemia, hyperfibrinogenaemia and increased concentration of serum amyloid A (SAA, **Table 1**). The other serum biochemical values were within normal limits. Peritoneal fluid had a mildly increased nucleated cell count (6.9 x $10^9$/l) and protein content (32 g/l). Cytopathology was suggestive of a non-septic reactive peritoneal response. However, cytological analysis of a tracheal aspirate and urine analysis were unremarkable.

| Days following admission | Red blood cell count (x $10^{12}$/l | Packed cell volume (%) | White blood cell count (x $10^9$/l) | Segmented neutrophils (%) | Lymphocytes (%) | Monocytes (%) | Total protein (g/l) | Albumin (g/l) | Globulin (g/l) | Plasma fibrinogen (g/l) | Serum amyloid A (mg/l) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 5.4 | 23 | 9.45 | 82 | 13 | 5 | 80 | 27 | 53 | 9.8 | 419 |
| 6 | 5.29 | 22 | 8.13 | 73 | 23 | 4 | 82 | 24 | 58 | 9.2 | 288 |
| 9 | 5.8 | 25 | 6.71 | 68 | 27 | 4 | 83 | 25 | 58 | 8.4 | 44 |
| 11 | 5.95 | 25 | 6.05 | 64 | 31 | 4 | 85 | 26 | 59 | 9 | 0 |
| 35 | 6.09 | 27 | 6.04 | 68 | 28 | 4 | 76 | 26 | 50 | 3.9 | 0 |
| 60 | 7.28 | 34 | 4.99 | 43 | 48 | 5 | 61 | 33 | 28 | 2.3 | 1.6 |

***Table 1: Laboratory data from Case 1***

***Diagnostic imaging***

Thoracic radiography, ultrasonography and gastroscopy revealed no abnormalities. Transcutaneous abdominal ultrasonography (3.0–5.0 MHz sector transducers, Vivid 3)[1], revealed a hypoechoic, non-encapsulated mass with a central hyperechoic region within the cranial dorsomedial region of the spleen measuring up to 20 cm diameter (**Fig 1a**).

The site was such that it was considered unfeasible to evaluate with laparoscopy and potentially harmful to perform a transcutaneous aspirate. Examination of the remainder of the abdominal viscera revealed no further abnormalities.

***Differential diagnosis***

Differential diagnoses included splenic abscessation, traumatic haematoma formation, splenic neoplasia or splenic granuloma.

***Treatment***

Gentamycin (6.6 mg/kg iv q24h) and procaine penicillin (9 mg/kg im bid) were administered for 11 days, together with iv poly-ionic fluid therapy (Hartmanns

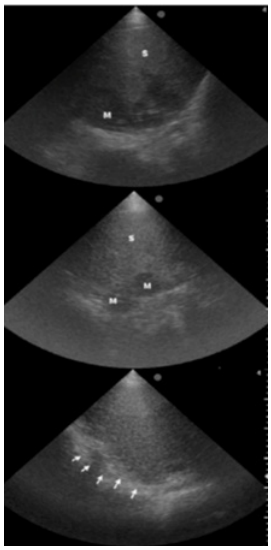

*Fig 1: Ultrasonograms from a horse with splenic abscessation of unknown aetiology obtained from the left cranioventral abdomen. a) Upon admission, the spleen (S) contained a non-encapsulated mass (M) with areas of variable echogenicity. b) 11 days following admission the mass considerably reduced in size. c) 10 weeks following admission the mass had resolved but the caudo-lateral edge of the spleen was slightly irregular suggesting a swelling in that region (arrows).*

at approximately 50 ml/kg/day) for the first 2 days. Throughout this time the gelding's appetite and demeanour improved and there was no further pyrexia. Ultrasonographic examination of the abdomen was performed every other day. This revealed an initial increase in the size of the mass which then became more defined and encapsulated. During this time, with the exception of the hyperglobulinaemia, the haematological parameters improved, although anaemia was still evident (**Table 1**). Antimicrobial therapy was changed to combined trimethoprim and sulphadiazine (30 mg/kg *per os* bid, respectively), and rifampicin (10 mg/kg *per os* bid). Ultrasonography of the spleen at this time revealed a marked decrease in size of the mass (approximately. 13 cm diameter) (**Fig 1b**). Fourteen days following admission, the gelding was discharged with instructions to continue the oral trimethoprim and sulphadiazine and rifampicin, for a further 8 weeks.

***Follow up***

Repeat examinations were carried out 4 and 8 weeks following discharge. During this time the gelding's appetite and demeanour had markedly improved, rectal temperature remained within normal limits and the horse had gained 30 kg in weight. Transcutaneous ultrasonography of the spleen revealed complete resolution of the hypoechoic mass at 8 weeks post discharge. Slight roughening of the caudolateral edge of the spleen was the only abnormality detected at this time (**Fig 1c**). Haematological data and concentrations of serum and plasma proteins had returned to within normal limits (**Table 1**).

The horse continued to make good clinical progress following completion of the antimicrobial therapy. Three months after treatment the horse had returned to light exercise. Eighteen months after initial presentation, the horse was in full work having completed a full season of hunting twice weekly. Due to the success of the response to medical management and ultrasonographic resolution of the splenic mass following antimicrobial therapy, a diagnosis of splenic abscessation of unknown aetiology was made.

***Discussion***

Splenic abscessation in the horse is rare[20,23]. Transabdominal ultrasonography proved to be highly useful in detecting abnormalities within the spleen by a non-invasive technique. However, it was not possible, based on ultrasonography alone, to differentiate the masses, as neoplastic, granulomatous or abscessation lesions all appear similar[27]. Splenic neoplasms are rare in the horse, but the ultrasonographic appearance of splenic lymphosarcoma has been described previously[11]. Ultrasonography facilitated the location and accessibility of the masses and determined and influenced which further diagnostic techniques were employed. Ultrasonographic evaluation was useful in determining the extent of splenic involvement and whether the site of the lesion would be easily visualised with laparoscopy.

Laparoscopy was not performed due to the position of the masses within the cranial abdomen and size of the horse. Transcutaneous fine needle biopsy was not performed as ultrasonography had revealed that the location would be difficult to access and there was a risk of splenic haemorrhage, intestinal perforation and possibility of perforating an abscess with subsequent peritoneal contamination. Exploratory laparotomy would have been an alternative means of visualising these lesions. Nuclear scintigraphy using radiolabelled white blood cells[5] is an alternative minimally invasive technique to detect splenic lesions. However, this technique is not widely available and is not without human risk. As a non-invasive tool, ultrasound was not only useful in determining the location of the lesions, it was also an accurate, non-invasive technique in monitoring the response to treatment. The aetiology of the abscess was not determined. Possible causes include parasitic arteritis of the gastrosplenic artery and bacterial emboli[4], trauma, haematogenous spread and foreign body penetration[8,22]. Abscessation may also occur with neoplastic lesions although the favourable outcome renders it unlikely in this case.

In this case, long-term antimicrobial therapy was successful. Procaine penicillin and gentamycin were initially selected due to their broad spectrum of activity. However, long-term oral antimicrobial therapy was necessary for ease of administration. Rifampicin is very lipophilic and will penetrate most tissues including abscesses. It is concentrated in macrophages and neutrophils and is most effective at acid pH, so is a good choice for septic foci and granulomatous lesions. Resistance develops quickly, therefore it is used in conjunction with trimethoprim sulphonamides. The horse remained on antimicrobials until the lesion was no longer visible on ultrasonographic examination.

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# MULTIPLE-CHOICE QUESTIONS

## QUESTION 1

**Up to _____ % of cases of fever of unknown origin can remain undiagnosed**

a. 1
b. 10
c. 15
d. 20
e. 25

## QUESTION 2

**Fever of unknown origin has been classified as:**

a. Illness of at least 3 weeks duration
b. Illness with non-specific signs
c. A core body temperature of at least 38.6 C/101.5F
d. No clear diagnosis after an initial full blood count and biochemical profile
e. All of the above combined

## QUESTION 3

**The most common underlying aetiology of fever of unknown origin is:**

a. Neoplasia
b. Infection
c. Immune mediated disease
d. Anhidrosis
e. Malignant hyperthermia

## QUESTION 4

**A temperature remaining permanently elevated is:**

a. Sustained
b. Intermittent
c. Cyclic
d. Remittent
e. Biphasic

## QUESTION 5

**Chronic infection/inflammation are often represented on a full blood count and biochemical profile as:**

a. Anaemia
b. Hyperfibrinogenaemia
c. Thrombocytosis
d. Hyperglobulinaemia
e. All of the above

## QUESTION 6

**Blood cultures should ideally be taken:**

a. First thing in the morning
b. In the late afternoon
c. Once only
d. When on antimicrobials
e. During an episode of pyrexia

## QUESTION 7

**Splenic abscessation in the horse is:**

a. Rare
b. Undocumented
c. A regular finding
d. A common sequela to iv catheterisation
e. The most common site for internal abscessation

## QUESTION 8

**Possible causes of splenic abscessation include:**

a. Trauma
b. Haematogenous spread
c. Bacterial emboli
d. Foreign body penetration
e. All of the above

## QUESTION 9

**The antimicrobial rifampicin is most effective at:**

a. Highly acidic pH (pH < 3)
b. Acidic pH (pH 4-5)
c. Alkaline pH (pH 8-9)
d. Neutral pH (pH 7)
e. Highly alkaline pH (pH >9)

## QUESTION 10

**Rifampicin is concentrated in:**

a. Macrophages and eosinophils
b. Macrophages and neutrophils
c. Neutrophils and eosinophils
d. Monocytes and lymphocytes
e. Neutrophils and lymphocytes

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