Identifying the cause of a fever of unknown origin (FUO) in dogs is a considerable diagnostic challenge. The diagnostic workup can be frustrating for veterinarians and clients, especially when it fails to reach a final diagnosis after extensive testing. Fortunately, most causes of FUO can be found or treated successfully. Below is some of the most recent information about up-and-coming diagnostic techniques that may be valuable in diagnosing FUO in dogs in the future.

Fever-Inducing Drugs and Toxins
Although any medication has the potential to cause fever in dogs, the following medications are known to do so:
- Albuterol
- Amphotericin
- Antihistamines
- Atropine
- Barbiturates
- Bleomycin
- Cimetidine
- Colchicine
- Heavy metals
- Nitrofurantoin
- Penicillins
- Procainamide
- Salicylates (high dosages)
- Sulfadiazine
- Tetracyclines

Diagnostic Tests
Frequently, diagnostic clues are not readily apparent on physical examination, so repeated detailed physical examinations are essential (by multiple clinicians if possible).

Blood Cultures
Development of a new DNA isolation kit that can eliminate background human DNA known to cause cross-reactions and inhibit polymerase chain reaction (PCR) has enabled the use of new PCR technology in human medicine for the rapid detection and identification of bacteria and fungi (Candida spp). In one study, all of the positive blood cultures that were later judged to be contaminated had negative results on PCR. Out of 83 negative blood culture samples, six showed a positive PCR result. This technique, when available for dogs, may be a supplemental tool to blood culture in dogs with FUO, especially those that are seriously ill or are infected with slow-growing pathogens.

Synovial Cultures
A recently developed PCR-based test for rapid detection and classification of bacteria from human septic arthritis patients is also available. This test is reliable for the diagnosis of septic arthritis in humans and has improved speed and accuracy compared with other PCR-based tests. The results are promising, and such tests could be very valuable in canine FUO patients if they become available.

C-Reactive Protein and Erythrocyte Sedimentation Rate
C-reactive protein (CRP) is an acute-phase protein that is commonly measured in human patients and is becoming more commonly measured in dogs. Serum CRP is a nonspecific inflammatory marker that may aid in the diagnosis of FUO or other infectious/inflammatory conditions by indicating the presence and extent (local versus generalized, neurologic versus arthritic) of inflammation.
the CRP concentration did not increase in dogs with intervertebral disk protrusion, leading the authors to conclude that it might be useful in differentiating arthritis from spinal or brain diseases in dogs with lameness. In the same study, CRP was found to be markedly elevated in many diseases with inflammation and tissue damage, especially neoplastic and immune-mediated diseases.

In human medicine, the erythrocyte sedimentation rate (ESR) is often monitored along with CRP. The amount of fibrinogen in the blood directly correlates with the ESR. The ESR is helpful in the specific diagnosis and monitoring of a few conditions in humans, such as temporal arteritis, polymyalgia rheumatica, and rheumatoid arthritis. It may also help predict relapse in human patients with Hodgkin's disease. According to one report, infection is the leading cause of a markedly elevated ESR, followed by collagen vascular disease and metastatic malignant tumors.

CRP measurement in dogs is becoming more important and is known to provide diagnostic information about the presence of inflammatory lesions and infectious and immune-mediated diseases as well as response to treatment. Fibrinogen levels were reported to be markedly elevated in canine patients with immune-mediated conditions in the 1998 retrospective study by Dunn and Dunn. Unfortunately, CRP was not measured. The role of these acute-phase proteins (fibrinogen and CRP) is still being investigated, but they may help in diagnosing and localizing lesions in dogs with FUO.

Advanced Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) should be used to help delineate conditions found via other techniques or when the diagnosis remains uncertain. In humans with FUO, nuclear scintigraphy with gallium 67, technetium (Tc) 99m, or indium-labeled leukocytes is commonly used for detecting inflammatory conditions and neoplastic lesions that are frequently underdiagnosed by CT scans. Nuclear scintigraphy is being used more frequently in veterinary medicine, and there are reports of its use in dogs and cats for evaluation of thyroid diseases, lymphatic vasculature, gastric emptying, glomerular filtration rate, portosystemic shunts, reverse patent ductus arteriosus, and pancreatitis. It may also be a valuable tool in investigating FUO through the use of radiolabeled leukocytes or antibiotics to detect sources of occult inflammation or infection (abscesses).

One of the newest imaging modalities being used in investigation of human FUO is called image fusion or coregistration. It combines positron emission tomography (PET; a type of nuclear imaging) and CT, allowing one continuous body scan that simultaneously captures PET images of tiny changes in the body’s metabolism caused by abnormal cells (infection or neoplasia) and CT images of abnormal tissue. One nonspecific tracer of increased glucose metabolism that is commonly used with PET is called 18F-fluorodeoxyglucose (FDG), which accumulates in neoplastic and activated inflammatory cells. The increased glycolytic activity of these cells causes increased 18F-FDG uptake at the site of inflammation and infection. Essentially, coregistration detects small lesions or tumors with PET and precisely locates them with CT. The human medical literature states that PET has a high negative predictive value in ruling out inflammatory causes of fever. One study showed that it was especially helpful when the CRP and ESR were both elevated. Absence of areas of increased uptake with PET/CT may rule out infection in humans.

Three case reports on the use of PET/CT in dogs demonstrate that this imaging technique could play an important role in diagnostic imaging in veterinary medicine. Also, a recent report attempts to establish baseline normal levels for thoracic and abdominal organ uptake of a radiotracer in healthy dogs. One of the problems with interpreting some of the more advanced imaging techniques is obtaining proof that the documented abnormality is the cause of the fever. PET/CT seems promising as a noninvasive diagnostic technique, but because of its limited availability in humans and, therefore, small animals, it is too early to tell.
Fever of Unknown Origin in Dogs

References