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Pyrrolizidine Alkaloid Poisoning in Horses

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Introduction

Pyrrolizidine alkaloid (PA) containing plants primarily cause hepatotoxicity and liver failure in horses but may also cause respiratory disease (equine Jaagsiekte) depending on the plants implicated. The three PA containing plant families involved with poisoning in horses include

- *Asteraceae* (*Senecio* spp, tansy ragwort).
- *Tobaceae* (*Crotalaria* spp, rattlebox).
- *Boraginaceae* (*Heliotropum, Amsinckia, Trichodesma* and *Echium* spp).

Many, but not all, pyrrolizidine alkaloid containing plants are unpalatable and so are frequently avoided. However, the risk for toxicity increases when there is little other or alternative feed, where dead PA-containing plants contaminate hay or silage or when feed grains such as wheat or sorghum are contaminated by seeds of PA-containing plants harvested with them. It is also important to remember that PA has a cumulative effect, so repeated ingestion of small amounts over several seasons may eventually result in toxicity. This accumulation of PA may happen over months to years depending on the species and amount of plant eaten. In addition, a single toxic dose of PAs taken in over one or a few days may take months to produce visible disease. This can make it very hard to identify the source of the poisoning, as the offending plants often die and disappear from the pasture before the animal becomes ill.

Pathophysiology

PA's are absorbed from the gastrointestinal tract, after which they undergo metabolism by any cells with adequate cytochrome P450 activity capable of metabolising PA. In addition to hepatocytes in the liver, which is the leading site of bioactivation of PA, proximal convoluted renal tubules and pulmonary club cells (previously termed Clara cells), can also generate highly chemically reactive pyrrolic metabolites that cause local organ injury. Small amounts of these toxic metabolites may enter the milk resulting in toxicity in suckling foals, and rarely they may cross the placenta to damage the foetus. PAs are also regarded as potential carcinogens.

The pyrrolic metabolites of PAs are directly cytotoxic to hepatocytes inducing necrosis and inhibit cell division (by cross-linking DNA), with affected hepatocytes continuing to grow to form enormous hepatocytes (megalocytes). These toxic metabolites also have secondary toxic effects on centrilobular and hepatic veins, with endothelial damage leading to perivascular fibrosis and vascular occlusion. Hepatic encephalopathy is a common consequence of the chronic hepatic pathology induced by PA toxicity in the horse.

There are various theories that have been proposed to explain the pneumotoxic effects of pyrrolizidine alkaloids in equines, including spill-over of toxic pyrroles following hepatic metabolism and extrahepatic metabolic activation of PA by pulmonary club cells. In many instances of "jaagsiekte", pulmonary pathology is severe yet hepatic pathology mild, suggesting that in equines, biotransformation of certain pyrrolizidine alkaloids occurs in the lung.

Clinical Syndromes

Consistent clinical signs of **primary hepatic PA poisoning** in horses include significant loss of body weight, un-thriftiness, staring coat progressing to emaciation ("Dunsiekte") and death due to hepatic cirrhosis and liver failure (Figure 1). Other common consequences are diarrhoea and tenesmus (excessive straining), dullness and hepatic encephalopathy. Plant species most commonly involved in primary hepatic toxicity of horses are various *Senecio* spp with *Crotolaria* spp rarely involved with primary hepatic toxicity in South Africa.



Figure 1. Horse with "Dunsiekte" with generalised muscle atrophy with ribs and spinous vertebral processes clearly visible. Rump muscle sunken.

Hepatic encephalopathy is usually characterised clinically by a slow, insidious onset of persistent yawning ("dummy syndrome"), constant compulsive walking or galloping "walkabout disease", blindness leading to collisions with objects and traumatic skin lacerations to the face, neck, chest and forelegs. The less commonly encountered signs of acute onset hepatic encephalopathy include head pressing against solid obstacles, muscle tremors and irritability.

Such acutely affected horses can exhibit sudden behavioural changes with excitation and aggression, making them dangerous to handle. The development of jaundice is variable in both acute and chronic hepatic encephalopathy.

The changed behaviour of affected equines is due to chemicals released into the circulation from damaged hepatocytes. Hyperammonemia plays the most crucial role in the pathogenesis of hepatic encephalopathy. In addition, brain-blood barrier disturbances, changes in neurotransmission, neuroinflammation, oxidative stress, GABA-ergic or benzodiazepine pathway abnormalities, manganese neurotoxicity, energetic brain disturbances, and brain blood flow abnormalities are also considered to be involved. Ammonia is metabolised by astrocytes in the CNS, and there are suggestions of a direct toxic effect on astrocytes as being central in the pathogenesis of this condition.

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This disturbance in astrocyte function may lead to neuronal degeneration and necrosis, resulting in the spongiotic lesions in the cerebral cortex and basal ganglia, which characterise the histopathology.

Other less common consequences of primary hepatic PA poisoning include subcutaneous oedema of the chest, belly and legs, photosensitisation, haemolysis with haemoglobinuria, paralysis of the larynx, the tongue or both, and gastric impaction.

In the primary **pneumotoxic form of PA poisoning, "jaagsiekte"** respiratory signs dominate, with concurrent hepatic signs less commonly reported. Crotolariosis equorum "jaagsiekte" is a chronic progressive respiratory disease of horses, donkeys and mules resulting from the ingestion of *Crotolaria* spp plants (usually), with other pyrrolizidine alkaloid containing plants rarely involved. The crotalaria species most frequently associated with poisoning in equines include *C.dura, C.globifera, C.juncea, C. ramosissima, C. monteiroi* and *Crotolaria crispate*. Other pyrrolizidine alkaloid containing plants which have been associated with "jaagsiekte" in horses include *Chromolaena odorata* (trifid weed), *Ageratina adenophora* (crofton weed) and *Trichodesma zeylanicum* (camel bush).

The disease syndrome is characterised by undulating fever (in some but not all), cough, rapid respiration (tachypnoea), laboured breathing (dyspnoea), rales, stridor, tachycardia, subcutaneous and pulmonary emphysema, interstitial proliferative pneumonia and sometimes concurrent hepatic disease. The undulating fever documented in some animals is a key confusing clinical sign, which frequently deflects the investigation prioritising exclusion of infectious agents, with pneumotoxic agents frequently not being considered.

Pathology.

In all forms of PA poisoning, affected horses are frequently in an emaciated condition with body condition scores of 0-1 with "ewe" neck, generalised muscle atrophy, ribs are easily visible, vertebral spinal processes are prominent, and the large muscle masses of the rump are sunken.

Hepatic PA poisoning. A post-mortem examination in typical cases reveals an emaciated carcase with depletion of fat reserves and serous atrophy of fat. The liver is distorted by fibrosis with a cobblestoned appearance and increased consistency (Figure 2).

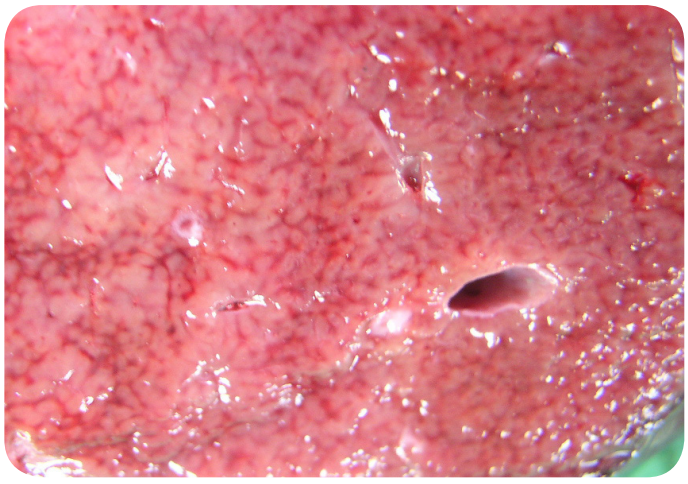


Figure 2. Cut surface of liver exhibiting severe hepatic fibrosis with white discoloured fibrous tissue accentuating lobulation with obliteration of some lobules (hepatic cirrhosis).

There is frequently an excessive volume of fluid in the abdomen (ascites). Histologically the organisation of the liver is highly disrupted by portal and intra-lobular fibrosis (cirrhosis) and sometimes perivascular fibrosis "veno-occlusive disease". There is hepatocyte loss, and some hepatocytes are markedly increased in size (megalocytosis) (Figure 3).

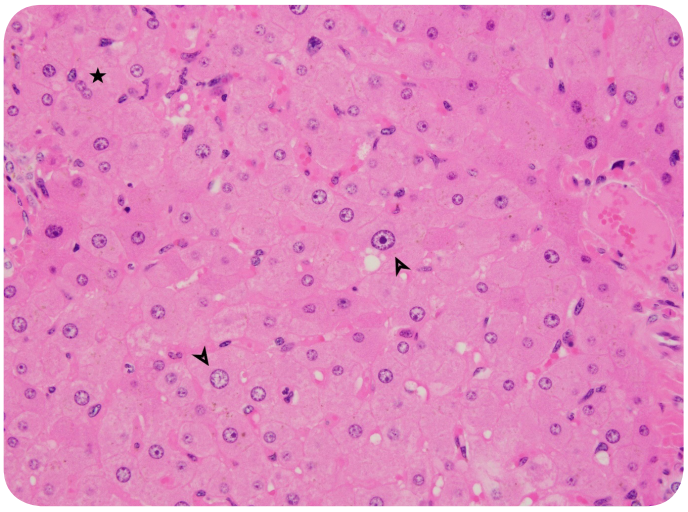


Figure 3. Liver horse exhibiting multiple large hepatocyte megalocytes (arrows) and bi-nucleate hepatocytes (*).

Pulmonary PA poisoning. In cases of 'jaagsiekte' in horses, at post-mortem, the lungs fail to collapse when the chest is opened, and rib impressions are frequently evident on the surface of the lung (Figure 4).

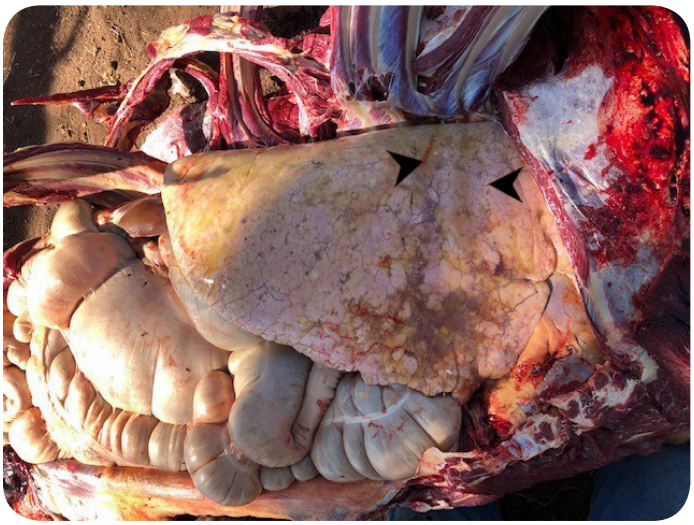


Figure 4. Lung of horse with Jaagsiekte. Lungs have failed to collapse and there are surface rib impressions (arrowheads).

Hydrothorax and hydropericardium are common. There is diffuse consolidation of the lung with scattered reddened zones (atelectasis and congestion), and thickened fluid-filled expansion of interlobular septa which in some instances also contain gas bubbles (interstitial emphysema).

Pulmonary histopathology of bronchial epithelial hyperplasia (particularly that of terminal and respiratory bronchioles with club cell hyperplasia), interstitial fibrosis, alveolar epithelial cell desquamation, bronchial vasculature mural oedema and emphysema are considered diagnostic of "jaagsiekte" (Figure 5 and 6). Hepatic pathology with features consistent with pyrrolizidine alkaloid

hepatopathy (megalocytosis, binucleated hepatocytes, centrilobular necrosis, portal fibrosis), may or may not accompany the pulmonary changes, and when present are frequently mild.

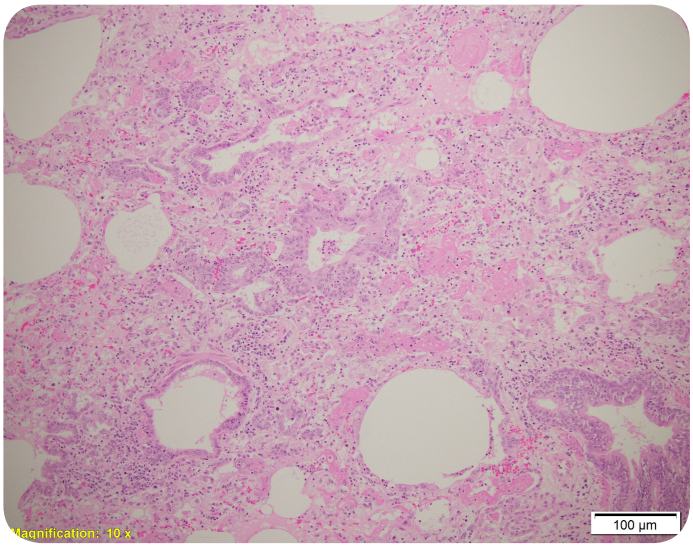


Figure 5. Equine jaagsiekte histopathology exhibiting marked proliferation of respiratory and terminal bronchioles.

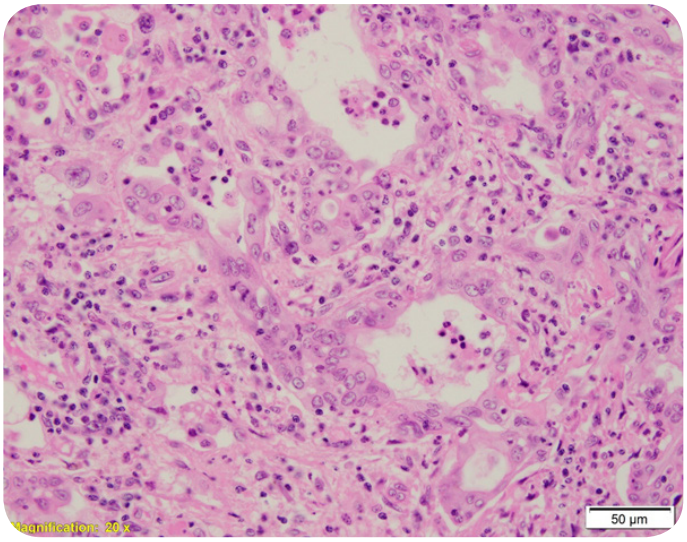


Figure 6. Equine jaagsiekte lung exhibiting proliferating non-ciliated club cells lining respiratory and terminal bronchioles.

Treatment and Control.

There is no effective treatment for PA poisoning in horses. Some affected animals do recover, but usually with significantly impaired hepatic and/or respiratory function due to the varying degrees of chronic hepatic cirrhosis and pulmonary fibrosis. Preventing consumption through removal from affected grazing (if possible), weed control and pasture improvement are the major avenues of control. Herbicide control of weed sources of PAs may be economical in some situations. Screening for toxic weed seeds from feed grains is often effective but can be expensive.

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The SAVA Stress Management Hotline is there to assist members who are experiencing personal problems by offering access to professional counselling/advice.

The hotline can assist with referrals or simply offer much needed emotional support when anxiety, depression, anger, grief, loneliness and fear are at their highest.



The following SAVA members are available on the SAVA stress management hotline. If required, they will refer you to professionals.

Ken Pettey	082 882 7356	ken.pettey@gmail.com
Tod Collins	083 350 1662	tcollins@isat.co.za
Aileen Pypers	072 599 8737	aileen.vet@gmail.com
Willem Schultheiss	082 323 7019	willem.schultheiss@ceva.com
Mike Lowry	084 581 2624	mikelowry@sai.co.za

MULTIPLE-CHOICE QUESTIONS

QUESTION 1

Of the following organ systems which is the MOST COMMON target of pyrrolizidine alkaloid's in equines?
a. Kidney
b. Gastrointestinal tract
c. Liver
d. Spleen
e. Pancreas

QUESTION 2

Which plant species are MOST COMMONLY associated with Jaagsiekte in horses?
a. *Senecio* spp
b. *Crotolaria* spp
c. *Heliotropum* spp
d. *Echium* spp
e. *Amsinckia* spp

QUESTION 3

Which of the following statements regarding pyrrolizidine alkaloid poisoning in horses is FALSE?
a. There is increased risk of toxicity if there is insufficient alternative feed
b. Pyrrolizidine alkaloid's remain toxic in the dried form
c. Repeated intakes of small amounts of toxin over several seasons may result in toxicity
d. Accumulation of pyrrolizidine alkaloids is known to occur
e. A single toxic dose always causes immediate toxicity

QUESTION 4

Which of the following cells CONTAIN sufficient cytochrome P450 enzyme activity to bio-activate pyrrolizidine alkaloids?
a. Pulmonary club (Clara) cells
b. Hepatic sinusoidal Kupfer cells
c. Pulmonary alveolar macrophages
d. Renal glomerular epithelial cells
e. Hepatic bile duct epithelial cells

QUESTION 5

Through WHAT MECHANISM do pyrrolizidine alkaloids induce the formation of hepatocellular megalocytes?
a. Stimulate endoplasmic reticulum proliferation
b. Induce mitochondrial hyperplasia
c. Increase cytoplasmic protein formation
d. Inhibit cell division by cross-linking DNA
e. Induced nuclear apoptosis

QUESTION 6

Which of the following mechanisms are considered the MOST IMPORTANT in development of hepatic encephalopathy?
a. Blood brain barrier disturbances
b. Manganese neurotoxicity
c. Hyperammonemia
d. Neuro-inflammation
e. GABA-ergic pathway abnormalities

QUESTION 7

Which of the following important clinical signs of Jaagsiekte are NOT consistently observed in all cases?
a. Tachypnoea
b. Dyspnoea
c. Rales
d. Stridor
e. Pyrexia

QUESTION 8

From the list below select the MOST COMMON and consistent gross pathological lesion in horses that of died of pyrrolizidine alkaloid poisoning.
a. Icterus
b. Emaciation
c. Anaemia
d. Cyanosis
e. Diffuse splanchnic congestion

QUESTION 9

Of the following liver pathologies which would be MOST likely associated with pyrrolizidine alkaloid poisoning?
a. Hepatic necrosis with decreased liver consistency
b. Irregular cobblestoned hepatic appearance with increased liver consistency
c. Marked cholestasis
d. Thickened and proliferative bile ducts
e. Marked hepatomegaly

QUESTION 10

Which of the following pathologies BEST describe the gross pulmonary pathology of equine Jaagsiekte?
a. Extensive pulmonary haemorrhage
b. Bilateral consolidation of the anterior lobes
c. Extensive pleural fibrosis with adhesions
d. Lungs fail to collapse on opening the thorax with surface rib impressions
e. Multiple pulmonary infarcts

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