Effusion fluid analysis: specific effusions

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Introduction

Effusions are abnormal fluid accumulations in the peritoneal, pleural, or pericardial cavities. Many effusions are formed by passive transudation secondary to changes in hydrostatic and/or oncotic pressure (transudates) or by active exudation secondary to inflammation (exudates). Classifying an effusion as a transudate or exudate is useful to guide further diagnostics, and, in some cases, a specific diagnosis can be made (e.g. if infectious agents are visualised microscopically). However, some effusions are not accurately classified using the traditional fluid classification criteria of total protein concentration and total nucleated cell count (TNCC). Instead, these specific effusions have unique features that are used to recognise them. Being able to distinguish specific effusions from non-specific transudates and exudates is an important step in reaching a correct diagnosis in affected patients.

What effusion types are considered unique?

These include haemorrhagic effusions, lymphocyte-rich (including chylous) effusions, bile peritonitis, uroperitoneum, and neoplastic effusions. Although transudative and exudative processes may contribute to the formation of these effusions, other more specific pathomechanisms play a role in these cases.

Haemorrhagic effusions

Haemorrhagic effusions may occur in any cavity but are most common in the pericardial sac. When the fluid haematocrit is >3%, haemorrhage is a likely component of the effusion. In true haemorrhagic effusions, the haematocrit is usually similar to or slightly lower than the blood haematocrit. Cytologically, haemorrhagic effusions are characterised by macrophages phagocytosing erythrocytes (acute haemorrhage) and/or containing intracytoplasmic haemosiderin and/or haematoidin (chronic haemorrhage of ≥ 72 hours). Haemosiderin and haematoidin are both products of haemoglobin breakdown. Platelets are not typically seen in haemorrhagic effusions and, if present, usually indicate (concurrent) iatrogenic blood contamination during sampling. Possible causes of haemorrhagic effusions are listed in Table 1. Most pericardial effusions (90%) are haemorrhagic, and in most cases (92.3%), pericardial fluid cytology is not diagnostically useful even when a mass is identified with echocardiography. The diagnostic utility (i.e. the ability to reach an aetiological diagnosis) of pericardial fluid cytology increases when the fluid haematocrit is <10%.

Table 1: Disorders/conditions associated with haemorrhagic effusions

Disorder/condition	Comments
Blunt trauma	e.g. motor vehicle accident/MVA
Penetrating trauma	e.g. stab or gunshot wound
Malignant neoplasia	Commonly haemangiosarcoma
Haematoma	e.g. spleen
Organ torsion or necrosis	e.g. liver, spleen, lung lobe
Coagulopathies	e.g. rodenticide toxicosis
Hepatic rupture secondary to amyloidosis	Usually in predisposed breeds, e.g. Siamese cat, Shar-Pei dog
Parasitic migration	e.g. *Spirocerca lupi*, heartworm
Pulmonary fat embolism	Cats
Iatrogenic	Procedure complication, e.g. post-operative, uncommonly fine needle aspiration
Inadvertent aspiration of a blood-rich organ	Not a true haemorrhagic effusion, e.g. spleen, liver
Idiopathic	Common in pericardial effusions

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Lymphocyte-rich effusions

These effusions are characterised by a predominance of lymphocytes. They occur most often in cats and dogs and occasionally in other species (e.g. horses, cattle). Three types of lymphocyte-rich effusions are recognised: chylous effusions, non-chylous lymphocyte-rich effusions, and neoplastic effusions secondary to lymphoma. The lymphocyte size is the most important feature that differentiates neoplastic from non-neoplastic effusions. Effusions secondary to lymphoma have predominately intermediate or large lymphocytes (formerly lymphoblasts). In dogs, the lymphocyte size is assessed by comparing the cell's nucleus to a nearby erythrocyte or neutrophil. In other species, only the neutrophil is used. For size guidelines, please refer to Table 2.

Table 2: Size guidelines for identifying small, intermediate, and large lymphocytes

Lymphocyte size	Dogs only	All species
Small	Nucleus is 1 – 1.5x erythrocytes	Nucleus is smaller than a neutrophil
Intermediate	Nucleus is 1.5 – 2x erythrocytes	Nucleus is the same size as a neutrophil
Large	Nucleus is >2x erythrocytes	Nucleus is larger than a neutrophil

Other features such as increased mitotic figures, atypical nuclear shapes, prominent nucleoli, and a TNCC >10 000 cells/µL will also support a diagnosis of lymphoma. If the lymphocytes are mostly small in size with dark condensed nuclei, the effusion may be chylous or non-chylous. Non-neoplastic small lymphocytes predominate in these effusions, which arise from lymphatic damage/rupture, increased lymphatic hydrostatic pressure or stasis, and/or increased lymphatic permeability. As chyle is inflammatory, increased neutrophils and macrophages may be seen in longstanding effusions. The presence of triglycerides differentiates chylous and non-chylous effusions. Chylous effusions are milky, white, and opaque due to the presence of chylomicrons, triglyceride-rich lipoproteins synthesised in the enterocytes from absorbed dietary fat.

A chylous effusion is diagnosed when the fluid triglyceride concentration is >1.13 mmol/L. Non-chylous effusions are not chylomicron-rich and thus do not appear milky and have a triglyceride concentration <1.13 mmol/L. Possible causes of chylous and non-chylous effusions are listed in Table 3. Pericardial lymphocyte-rich effusions are rare.

Table 3: Disorders/conditions associated with chylous and non-chylous effusions

Cavity affected	Disorder/condition
Chylothorax	Thoracic duct or cranial vena cava obstruction (e.g. thrombosis)
	Lung lobe torsion
	Mediastinal infection
	Heartworm disease
	Diaphragmatic hernia
	Mediastinal masses (e.g. thymoma, granulomas)
	Chronic coughing or vomiting
Chyloabdomen/peritoneum	Feline infectious peritonitis
	Steatitis (e.g. secondary to pancreatitis)
	Congenital lymphatic abnormalities
	Colonic torsion (horses)
	Intraabdominal adhesions (horses)
Chylothorax or chyloabdomen	Trauma with damage/rupture of lymphatic vessels
	Neoplasia (e.g. lymphoma)
	Cardiovascular disease
	Lymphangiectasia
	Idiopathic (common)

Bile peritonitis

Rupture, necrosis, or leakage of the gall bladder and/or common bile duct causes bile to enter the peritoneal cavity. As bile is highly irritating, inflammation occurs rapidly, resulting in fluid accumulation and an influx of neutrophils and macrophages. Macroscopically, the fluid may have a yellow, brown, or green colour. Cytologically, neutrophils predominate and yellow, green, and dark blue bile may be seen in the background or phagocytosed by macrophages. More often, a mucinous blue-grey amorphous material or "white bile" produced by the biliary and gall bladder epithelium is present in the background or within macrophages. Possible causes of bile peritonitis include gastric dilatation and volvulus, cholelithiasis, biliary tract neoplasia, mucocoele rupture, cholangitis/cholecystitis, and trauma (e.g. MVA). Iatrogenic leakage from cholecystocentesis (<2% complication rate) or surgery is uncommon. In rare cases, bilothorax may occur, usually in association with a diaphragmatic tear. If bile peritonitis is suspected, the fluid bilirubin concentration may be measured. Although hyperbilirubinaemia is typical

in these cases, the fluid bilirubin concentration remains higher than the serum bilirubin, confirming bile peritonitis. Usually, the fluid: serum bilirubin ratio is >2:1. In rare cases, hyperbilirubinaemia may not be present. If bile peritonitis is still suspected, then the serum and fluid bile acid concentrations may be compared.

Uroperitoneum

Uroperitoneum, or uroabdomen, is caused by rupture, necrosis, or injury to the renal pelvis, ureters, bladder, or urethra, resulting in leakage of urine. Possible causes include blunt abdominal trauma (e.g. MVA), iatrogenic rupture due to aggressive catheterisation and bladder palpation or expression, urinary tract obstruction (e.g. urolithiasis), neoplasia, and postoperative leakage. In foals, periparturient trauma or congenital defects may also cause uroperitoneum. Rare cases of concurrent urothorax have also been described. As with bile, urine is an irritant and eventually results in inflammation. Initially, the urine dilutes the leukocytes and proteins and, in (per)acute uroperitoneum, poorly cellular and low protein urine may be mistaken for a low protein transudate. Later on, the TNCC will increase (usually > 5000 cells/µL), but the protein concentration may remain low (< 20 g/L). Such a discrepancy is uncommon, and in these cases, uroperitoneum should be suspected. Cytologically, neutrophils predominate and may appear degenerate due to the effects of the urine. If there is a concurrent urinary tract infection, then bacteria may also be seen (i.e. septic uroperitoneum). In horses, the uroperitoneum may be recognised by the presence of calcium carbonate crystals in the fluid. To confirm a diagnosis of uroperitoneum, the fluid and serum creatinine concentrations should be compared. Although both fluid urea and creatinine are increased, the smaller urea molecules equilibrate with the blood faster than the larger creatinine molecules. For this reason, the fluid: serum creatinine ratio is the test of choice – a ratio >2:1 is diagnostic for uroperitoneum in dogs, cats, and horses. In a recent study, researchers found that a lower ratio of ≥1.25:1 combined with a fluid creatinine concentration of ≥186 µmol/L is also diagnostic for uroperitoneum in dogs. However, these cut-offs may exclude some longstanding cases where the creatinine has also equilibrated with the blood. In these cases, diagnostic imaging and clinical chemistry are necessary. Typically post-renal azotaemia, hyponatraemia, hypochloraemia, and hyperkalaemia are expected. The fluid: serum potassium ratio may also be determined – a ratio of >1.4:1 is expected with uroperitoneum. However, this is not specific to uroperitoneum as other conditions, such as gastric perforation, may also increase the fluid potassium concentration.

Neoplastic effusions

Neoplasia may cause effusions through transudation, exudation, haemorrhage, and/or disruption of the lymphatics. Thus, the cellularity and protein concentration of these effusions is variable and not helpful for ruling in or out neoplasia. A diagnosis of "neoplastic effusion" can be made when exfoliated neoplastic cells are visualised on fluid cytology. This is especially common with carcinomas, round cell tumours, especially lymphoma, and mesothelioma. The presence of atypical cells showing frequent criteria of malignancy such as multinucleation, marked anisokaryosis, large prominent nucleoli, and atypical mitoses should increase the suspicion of neoplasia. Neoplastic effusions should be diagnosed with caution by inexperienced cytologists, as reactive mesothelial cells or macrophages may be confused for neoplastic cells. If neoplasia is suspected, consultation with a veterinary clinical pathologist is recommended.

Conclusions

Specific effusions such as haemorrhagic, lymphocyte-rich, bilious, uroperitoneum, and neoplastic effusions show unique features that differentiate them from non-specific transudates and exudates. Recognising these features is essential for accurate fluid classification and, in many cases, can lead to a definitive diagnosis.

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QUESTION 1

Classically, bile peritonitis is characterised by:
a. Evidence of gall bladder or bile duct leakage or rupture
b. Hyperbilirubinaemia
c. Fluid: serum bilirubin ratio of >2:1
d. Cytological evidence of bile (e.g. white bile, bilirubin crystals)
e. All of the above

QUESTION 2

How is a chronic haemorrhagic effusion identified:
a. Fluid haematocrit is >3%
b. Macrophages phagocytosing erythrocytes
c. Haemosiderin in the macrophages
d. Macroscopically bloody effusion fluid
e. All of the above

QUESTION 3

Which clinical chemistry abnormality is not expected with uroperitoneum?
a. Increased serum urea concentration
b. Hyperkalaemia
c. Increased serum creatinine concentration
d. Hypernatraemia
e. Hypochloraemia

QUESTION 4

You are presented with a cat that has a pleural effusion. After thoracocentesis, you see that the fluid is opaque with a milky/white colour, what do you do next?
a. Measure the fluid TNCC and protein and perform fluid cytology
b. Euthanise the patient due to a poor prognosis
c. Measure the fluid triglyceride concentration
d. Perform advanced diagnostic imaging of the thorax (e.g. echocardiography, CT)
e. Treat the patient with a chest drain and antibiotics

QUESTION 5

Neoplastic effusions secondary to lymphoma have the following features:
a. Lymphocytes that are the size of 1 – 1.5x erythrocytes
b. Triglyceride concentrations <1.13 mmol/L
c. Large multinucleated cells
d. Variable TNCC and protein concentrations
e. None of the above

QUESTION 6

You perform an abdominocentesis on a dog with a peritoneal effusion. The total nucleated cell count is 6370 cells/µL and the protein concentration is <25 g/L. What differential diagnosis is unlikely?
a. Low protein transudate
b. Neoplastic effusion
c. Uroperitoneum
d. Exudate
e. Non-chylous lymphocyte rich effusion

QUESTION 7

Bile peritonitis is not caused by:
a. Cholelithiasis
b. Diaphragmatic hernia or tear
c. Neoplasia
d. Rupture of a mucocoele rupture
e. Motor vehicle accident

QUESTION 8

Which is statement is true regarding lymphocyte-rich effusions in general:
a. They are common in horses
b. They may be neoplastic or non-neoplastic
c. They are identified by a triglyceride concentration of >1.13 mmol/L
d. Intermediate and large lymphocytes are expected
e. The fluid will have a TNCC of >10 000 cells/µL

QUESTION 9

A newborn foal is presented to you with lethargy and acute abdominal distension. You suspect uroperitoneum. What finding is diagnostic for uroperitoneum?
a. Calcium carbonate crystals on microscopy
b. Fluid: serum creatinine ratio of 1.3:1
c. Fluid creatinine concentration of 203 µmol/L
d. TNCC of 5630 cells/uL and a protein concentration of 18 g/L
e. All of the above

QUESTION 10

Pericardial effusions:
a. Are often haemorrhagic
b. Are commonly idiopathic
c. Fluid cytology is often non-diagnostic
d. Are rarely lymphocyte-rich
e. All of the above

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