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Liver and Pancreatic Disease Mini Series

Session Three: Sick as a Parrot, Yellow as a Canary - How to Approach Hepatobiliary and Pancreatic Disease

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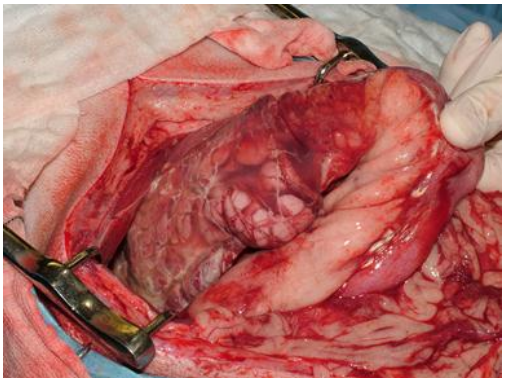

In the last of the three sessions we will look at diseases of the biliary tract and finish by discussing the pancreas and its associated pathology. The anatomy of the gall bladder, biliary and pancreatic tree are intricately connected, which leads to concurrent disease in many cases, especially in cats where the concept of triaditis has become popular in recent years.

The gall bladder is located between the right medial and quadrate lobes and is pear shaped in nature. The gall bladder neck drains into the cystic duct which continues to form the common bile duct. pear-shaped having a wide apical fundus, a body and a neck. The neck drains bile into the cystic duct which continues on to form the common bile duct, after the hepatic duct join. Bile has a complex make up but is formed of cholesterol, bile salts, phospholipid and lecithin. There is marked individual variation in the anatomy of the biliary tree and some changes that can initially seem likely associated with pathology may be normal variation. Examples of this include gall bladder or biliary duct duplication and gall bladder septations.

Cholecystitis

Cholecystitis is inflammation of the gall bladder. Though infectious and parasitic (not in the United Kingdom) causes appear most common, cholecystitis can also occur secondary to cystic or common bile duct obstruction by choleliths, pancreatitis, entrapped sabulous bile material and by local inflammatory and neoplastic processes. Bacterial cholecystitis appears to occur more frequently where conditions predispose to bile stasis (analogous to lower urinary tract infections) such as extrahepatic bile duct obstruction, cholelithiasis and gall bladder mucocoele; immunosuppression may also be a risk factor The English Bull Terrier and the Border Terrier appear to be predisposed breeds, the reasons for this have not been determined.

Clinical sign vary from mild, subtle changes to acute and life-threatening disease. Usually of cranial abdominal pain, fever, vomiting, icterus and anorexia are present. In severe cases signs of systemic inflammatory response syndrome (SIRS), sepsis and shock may be seen, The clinical signs overlap with those of pancreatitis a great deal. Occasional patients may present with signs due to bile peritonitis. The impact and prognosis with this depends on the cause of gall bladder rupture and whether bile is infected. Patients with bacterial cholecystitis which rupture their gall bladder usually have septic peritonitis and an associated high (approx. 50%) mortality rate even with rapid surgical intervention. Assessing total bilirubin in abdominal fluid and comparing with serum values is of help in diagnosing bile peritonitis.

Laboratory findings are usually reveal cholestasis and icterus, possibly with a leucocytosis being present. Diagnosis depends on having a high index of suspicion based on clinical signs, appearance of the gall bladder at ultrasound (which shows thickened of the gall bladder wall, suspended / immobile sediment and sometimes emphysematous change of the gall bladder) coupled with diagnostic cytology and culture of bile. This may be collected percutaneously under ultrasound guidance with care (use the hepatic parenchyma to ‘tamponade’ the gall bladder, remove as much bile as possible, assess for leakage afterwards) or at surgery. Bile is an excellent medium for *in vitro* bacterial growth and it is recommended that bile culture results are always interpreted in light of a concurrent cytological examination. Gram negative enteric aerobes, especially coliforms are most commonly implicated in bacterial cholecystitis and are probably derived from the gastrointestinal tract.

Medical treatment with a systemic antimicrobial based on culture and sensitivity testing is ideal and this should continue for at least 4-6 weeks. Choices of antimicrobials should reflect culture results, should achieve high levels in bile and should reflect that many organisms implicated, even if primarily aerobic may be facultative anaerobes. Potentiated amoxicillin or a fluoroquinolone are usually good choices pending culture with metronidazole or an extended spectrum fluoroquinolone, such as pradofloxacin being suggested to cover anaerobes. Addition of ursodeoxycholic acid may be of benefit if complete bile duct obstruction is not seen. Surgical treatment (cholecystectomy) may be required in non-responsive infections, where multiply resistant organisms are present, in the case of fungal or emphysematous cholecystitis, where bile peritonitis is present or where imminent gall bladder rupture is anticipated. The prognosis for dogs without gall bladder rupture is generally favourable.

Gall bladder mucocoele

Gall bladder mucocoeles were first reported in the veterinary literature in 1995 and describe the accumulation of semi-solid to solid mucinous bile-laden concretions in the bladder accompanied by cytic mucinous hyperplasia of the gall bladder wall. The exact reason for their formation is unknown and many factors are likely implicated in their formation including gall bladder stasis, choleocystitis and localised inflammation. They are seen in some breeds with increased frequency such as Shetland sheepdogs and Cocker spaniels. Their presence in Shetland sheepdogs has been associated with a mutation of the phospholipid flippase gene ABCB4. Endocrine disease, including Hyperadrenocorticism, hypothyroidism and other lipid abnormalities, have been associated with mucocoele formation.

Some mucocoeles are found incidentally however they may also be associated with concurrent pathology such as cholecystitis and extrahepatic biliary duct obstruction (EHBDO). In extreme cases the gall bladder may rupture leading to peritonitis. Around 40% of patients will present jaundiced, with a variety of other non-specific signs reported such as lethargy, reduced appetite and cranial abdominal pain. There are usually fairly easy to identify on ultrasound as the gallbladder will be full and often has a stellate or 'kiwi fruit' type appearance in cross section.

In general treatment is surgical with removal of the gall bladder. This alleviates the risk of rupture and removes the focus of discomfort and pain. Surgery does have risks with peri-operative mortality rates of around 20% reported. With this in mind, medical management might be considered for smaller mucocoeles, using ursodeoxycholic acid and addressing any underlying endocrinopathy or hyperlipidaemia. There are cases of mucocoeles resolving completely with medical management, especially where underlying hypothyroidism is documented. In these cases, the owners must be fully informed of the risks of medical therapy and the gall bladder monitored intermittently with ultrasound to assess progress.

Cholelithiasis

Choleliths may be found within the gallbladder (cholelithiasis) or, cystic or bile ducts (choledocholithiasis). These are made up of concreted bile contents and may be cholesterol, bilirubin or a mixture, and often contain numerous calcium salts. The can also contain bacteria which become trapped within the matrix. The presence of choleliths may be an incidental finding, but if causing obstruction may lead to jaundice and often a great deal of discomfort. There may also act as the focus for chronic infection. Often there calcium content allows them to be diagnosed by radiography; however ultrasound is more useful to document the effects associated with them. Medical therapy revolves around the use of ursodeoxycholic acid, however surgery is often considered as to whether surgical removal is indicated. All surgery of the biliary tract is associated with a relatively high rate of complications, so there needs to be a perceived benefit from their removal. This is generally surgery that is best performed by specialist in soft tissue surgery.

Feline Inflammatory liver disease and triaditis

Vague and frustrating signs such as lethargy and anorexia are common presenting signs in cats presenting in small animal practice and there are a wide number of differential diagnoses to consider. Pancreatic, hepatic and biliary diseases are relatively common causes of these vague signs, although may also result in additional clinical signs such as vomiting or jaundice. Hepatobiliary diseases and pancreatitis often occur together in cats, often also in combination with inflammatory bowel disease (termed 'triaditis'), complicating diagnosis and management.

The close association of these diseases is due to the close anatomical and functional relationship between the major pancreatic duct and common bile duct. Any inflammation/blockage of the distal common bile duct may therefore result in reflux of pancreatic secretions up the pancreatic duct. Vomiting in cats increases the likelihood of pancreaticobiliary reflux compared to dogs, and cats have much higher numbers of bacteria present in the gut, so when reflux occurs a mixed population of bacteria, bile salts and activated pancreatic enzyme enters the pancreatic and biliary ducts.

Inflammatory liver diseases are probably the most common group of hepatic disorders diagnosed in cats in the United Kingdom. Classification is based on histopathological features such as the inflammatory infiltrate (neutrophilic vs lymphocytic) present and the presence of bile duct proliferation and fibrosis. Feline inflammatory liver disease is usually divided into suppurative with predominantly neutrophilic infiltration or non-suppurative with lymphocytic infiltration. The differences in treatment strategies for neutrophilic and lymphocytic inflammation warrant establishing a definitive diagnosis.

Suppurative cholangitis and hepatitis is often associated pancreaticobiliary reflx and as such with pancreatitis and IBD (triaditis), although usually the clinical signs associated with the cholangitis/hepatitis predominate. This form of liver disease tends to occur more commonly in middle-aged to older cats, although can occur at any age. Most cases are presented with acute illness, they are usually jaundiced, pyrexic, anorexic and may have abdominal pain. The most common laboratory abnormalities are elevations in ALT, ALP, GGT, bilirubin and a neutrophilia often with a left shift. Cholelithiasis may occasionally occur and it is unclear whether this is a causative factor, or a consequence of the suppurative cholangitis. Ultrasonography may reveal thickening of the gall bladder wall (>1 mm), distension of the bile duct (> 5 mm) and the presence of sludge or inspissated bile within the gall bladder, and there may be a patchy echogenicity to the liver. Histopathology is necessary for confirming the diagnosis, and samples of liver tissue should also be submitted for bacterial culture and sensitivity. Coagulation times should be assessed prior to taking biopsies and vitamin K treatment administered if coagulation times are prolonged. If biopsies are obtained at laparotomy, the patency of the bile ducts should also be evaluated, and bile aspirated for cytology and culture. Laparotomy or laparoscopy also allows collection of pancreatic and intestinal biopsies to assess for concurrent disease.

Antimicrobial therapy is essential for the treatment of suppurative cholangitis. *E.coli*, and mixed growth including anaerobes is most frequently found, reflecting ascending infection from the intestine. Co-amoxiclav or cephalexin whilst pending culture and sensitivity results, and then adjusts treatment as appropriate. Antibiotic treatment should be maintained for at least 4-6 weeks to reduce the risk of recurrence. Supportive treatment such as intravenous fluid therapy and nutritional support are also usually required. Ursodeoxycholic acid is a choleretic that may have anti-inflammatory, immunomodulatory and antifibrotic properties in addition to increasing the fluidity of biliary and promoting bile flow. Although as yet there is no evidence that it is of benefit, it has been widely used and so is indicated as an additional treatment in inflammatory liver disease, provided there is no evidence of extra-hepatic biliary obstruction. The recommended dose is 10-15mg PO once daily.

S-adenosyl-L-methionine (SAMe) is a nutraceutical agent believed to restore glutathione levels that are reduced in liver disease resulting in oxidative damage. No clinical trials have been performed to confirm potential benefit, but it may be a useful supplement for any cat with liver disease.

Lymphocytic cholangitis occurs most commonly in younger cats with Persians being overrepresented. The aetiology of the disease is unknown, but immune-mediated mechanisms are suspected. In contrast to suppurative inflammatory disease, cats usually bright, with a good appetite; pyrexia is unusual. Significant weight loss can occur and some animals may be polyphagic. Marked jaundice is usually present and a can be accompanied by ascites, as such a major differential is feline infectious peritonitis, as is lymphoma. Hepatomegaly and mild generalised lymphadenopathy is also often present. Laboratory findings are similar to those found with suppurative disease, the main difference being that hyperglobulinaemia is frequently present, neutrophilia is less common and a left-shift would not be expected. If abdominal fluid is present, it is usually proteinaceous with a low cell count. Corticosteroids are the mainstay of treatment for lymphocytic cholangitis. Prednisolone is usually used at a dose of 1-2mg/kg twice daily, with the dose gradually reduced over 6 –12 weeks if good response is seen. Additional treatments that may be beneficial include choleretics, nutritional support and SAMe as described above.

Mixed inflammatory infiltrate can be observed on histopathology of liver biopsies. These cats may have a history of an initial acute illness, followed by gradual loss of condition, inappetance and lethargy. The dilemma with these cases is whether it is antibiotic or corticosteroid treatment that is required. Antimicrobial therapy is usually commenced whilst bacterial culture of liver tissue is pending. If bacterial cultures are positive, a 4-6 week course of antimicrobial is administered, but if there is not complete clinical improvement after 1-2 weeks, an anti-inflammatory dose of prednisolone (0.5-1mg/kg daily) is also initiated. If cultures are negative, anti-inflammatory doses of prednisolone are initiated earlier, and antibiotics continued for 2-3 weeks.

Pancreatitis

Pancreatitis is a common disorder and some breeds (especially miniature schnauzers, CKCS, cocker spaniels, Boxers and collies seem overrepresented). There do not appear to be any sex or age predispositions for pancreatitis. In cats it affects a wide range of breeds although DSH and Siamese are overrepresented in some case series. The cause of pancreatitis in most animals is unknown. Dietary indiscretion is commonly suggested in dog and in a study of risk factors for pancreatitis is given prominence. In some breeds such as miniature schnauzers, idiopathic hyperlipidaemia may contribute to an increased incidence of pancreatitis, though a true cause-and-effect relationship is not well established. In humans mutations in cationic trypsinogen genes and serum protease inhibitor genes increase lifetime risk of pancreatitis. In some breeds, such as the cocker spaniel there is mounting evidence that an immune-mediated aetiology may be present. The effects of drug therapy are again a source of much confusion. More than 50 drugs have been implicated in causing or increasing the risk of pancreatitis in people, and many veterinary drugs list pancreatitis as a potential complication of use. Pancreatitis can occur secondary to other disease processes or at least concurrently with them e.g. diabetes mellitus, hyperadrenocorticism and immune-mediated haemolytic anaemia. In cats, known associations include biliary tract disease, gastrointestinal disease, ischaemia, pancreatic duct obstruction, trauma (accidental or surgical, although hypoperfusion during anaesthesia is probably more important than surgical manipulation itself), organophosphate toxicity, infectious agents (Toxoplasma gondii, liver and pancreatic flukes, FIP, FHV-1, feline parvovirus and virulent calicivirus) and lipodystrophy.

Pancreatitis is thought to result from cellular autodigestion due to premature zymogen activation in pancreatic acinar cells. The exact cause of this premature zymogen activation remains largely unknown since although many experimental models exist using means of premature zymogen activation, exactly how this relates to the *in vivo* situation is unknown. Several mechanisms, both anatomical (such as separation of acinar cells) and physiological (production of zymogens in inactive form, segregation of them from lysosomal enzymes, co-secretion with pancreatic secretory trypsin inhibitor (PSTI) and the widespread 'quenching' affects of plasma protease inhibitors such as alpha-1-proteinase inhibitor and alpha-2-macroglobulin), help limit the 'spread' of pancreatic inflammation and autodigestion. It is only when damage exceeds the capacity of these protective mechanisms that widespread acinar damage and inflammatory and autodigestive responses beyond the pancreas occur.

Once pancreatic proteases have been activated and overwhelm the normal protective mechanisms of the pancreas, they enter the interstitium of the pancreas and the peritoneal cavity. Circulating proteases activate the complement, fibrinogen, coagulation and kinin cascades. PAF (platelet activating factor), NO, free radicals and other cytokines may also play an important role in developmemt of systemic complications. The degree of subsequent damage is regulated by circulating plasma protease inhibitors. Alpha macroglobulins bind proteases which are then cleared by the monocyte-macrophage system. Once the circulating pool of alpha-macroglobulins are depleted rapid development of systemic complications occur.

Diagnosis of pancreatitis is challenging and a number of pancreatic enzyme markers which are commonly employed to attempt diagnosis of pancreatitis including amylase, lipase, trypsin-like immunoreactivity (TLI) and serum pancreatic lipase immunoreactivity (cPLI). Although individually, these tests vary in their sensitivity and specificity, it is quite common to find that evidence is 'accumulated' from performing more than one test, and sometimes in an individual a test of low sensitivity may actually be convincingly abnormal when a theoretically more sensitive test is normal in the same patient.

Pancreatitis commonly causes hyperbilirubinaemia which usually occurs due to a degree of extrahepatic bile duct obstruction, elevations in ALT and ALKP which may be substantial and which may often lead to the erroneous conclusion of a primary liver disease, azotaemia, which may reflect both dehydration due to anorexia, vomiting and diarrhoea, but also the effects of pancreatitis on causing multi-organ dysfunction, hypertriglyceridaemia and hypercholesterolaemia, Hypokalaemia, hypochloraemia, hyponatraemia and hypocalcaemia, especially in cats (30-50%) and has been associated with poorer outcomes, and often a leucocytosis.

Amylase and lipase are very good markers of pancreatitis in man and become raised in experimental models of pancreatitis in dogs their interpretation in the clinical settings is more difficult since not only are they also produced by other tissues (gastric mucosa, hepatic parenchyma) but they accumulate when glomerular filtration rate is reduced. In dogs sensitivity of amylase is reported as 62.1%, specificity 57.1% and for lipase 73.3% with specificity 55.2%. A common recommendation is that results below 3 x the upper limit of the laboratory reference range should be viewed with scepticism as a diagnostic marker of pancreatitis. Amylase and lipase are usually within the reference range in cats with pancreatitis, and in experimental models of feline pancreatitis amylase has been shown to drop to 60-80% below baseline concentrations. Indeed, marked elevations in amylase and lipase are more likely to reflect reduced glomerular filtration than pancreatitis, and are also influenced by glucocorticoids, gastrointestinal disease and peritonitis. Anecdotally, comparison of amylase and lipase in abdominal effusions compared to serum might be of some diagnostic use. Recently DGGR lipase a more pancreatic specific form of lipase has shown promise in the diagnosis of pancreatitis in both dogs and cats.

Canine and feline trypsin-like immunoreactivity(cTLI fTLI) measure combined tryspinogen and trypsin. In experimental models of pancreatitis, TLI levels rapidly increase, but then also decreases rapidly to normal within 3 days of induction due to its short half life. The sensitivity of TLI in dogs is reported as 33-47% and the specificity 65%.

Canine and feline pancreatic lipase immunoreactivity (fPLI / cPLI) available as both a point of care ELISA and a more quantitative monoclonal antibody based immune-assay (Spec cPL) detects lipase that is purely derived from pancreatic acinar cells (as opposed to detecting lipase of other cellular origin as well). The reported sensitivity of this assay in dogs is 64% - 93% and specificity of 78-96.8%.

Trypsin-alpha$_1$-proteinase inhibitor complexes and serum and urinary trypsinogen activation peptide (TAP) concentrations have been evaluated as promising tests for pancreatitis but unfortunately the sensitivity of both seems to be low, limiting their utility. Measurement of lipase levels in abdominal effusion which exceeds the level in the serum is considered supportive of pancreatitis

The pancreas is not normally visible on radiographs but is positioned with the right limb adjacent to the medial surface of the duodenum, the body adjacent to the pyloric region of the stomach and the left limb caudal to the greater curvature of the stomach and maintaining a close relationship with the cranial pole of the left kidney and the mid-portion of the spleen. The principle radiographic abnormalities seen in presence of pancreatitis or pancreatic neoplasia are regional reduction in serosal detail due to peritonitis and regional fluid accumulation and rarely mass-effect caused by marked pancreatic enlargement. Sometimes ileus induced by pancreatitis will be manifested as diffuse small intestinal gaseousness.

In one retrospective study of acute, severe and fatal pancreatitis ultrasonographic abnormalities were found in 23/34 dogs (68%). 20/34 (58.8%) had enlarged irregular pancreases, 16/34 (47%) had peritoneal effusion, 12/34 (35%) had abnormal duodenal corrugation or thickening and 6/34 (17.6%) had evidence of extrahepatic bile duct obstruction. Other reported features include an enlarged hypoechoic pancreas, cavitary lesions such as abscess or pseudocyst, dilated pancreatic duct, swollen hypomotile duodenum, evidence of EHBDO and local accumulation of peritoneal fluid. Findings in cats are very similar.

There have been no retrospective or prospective studies evaluating the efficacy of different treatment regimes in canine of feline pancreatitis. Treatment recommendations are therefore difficult to advise with any degree of certainty and many recommendations are extrapolated from evidence in human pancreatitis, which is usually caused by alcohol abuse or gallstones, so not necessarily a good model for the disease seen in our patients.

Analysis of multiple regression models indicated that dogs >7yrs, spayed females and castrated males, obese dogs, terriers and non-sporting breeds of dog were at increased risk of pancreatitis. Although often cited that pancreatitis is initiated by a fatty meal or dietary indiscretion less than half of the dogs in the study had such a dietary history. Experimentally high fat meal ingestion increases susceptibility to experimentally induced pancreatic injury. Risk factors which may be treatable / avoidable included the presence of concurrent disease (especially diabetes mellitus, hyperadrenocorticism, chronic renal failure, congestive heart failure and autoimmune diseases), the recent use of antibiotics (cephalosporins, penicillins, oxytetracycline and clindamycin), azathioprine or antineoplastic agents (doxorubicin, cisplatin, methotrexate or cyclophosphamide). It seems likely that observation of raises in lipase with dexamethasone administration has helped perpetuate veterinary theories of corticosteroids inducing pancreatitis. In man definite associations for the following drugs and pancreatitis are known: Azathioprine, mercaptopurine, L-asparaginase, (pentamidine, didanosine). Probable associations are reported for frusemide, hydrochlorthiazide, sulphonamides, tetracycline, oestrogens, sulphasalazine. It would seem prudent to discontinue the use of any of these drugs in canine patients with pancreatitis

Fluid therapy should be given to treat severe dehydration, prerenal azotaemia, hypertonic fluid loss due to vomiting, shock, hypotension and systemic inflammatory response syndrome (SIRS). Many patients with pancreatitis will become hypokalaemic due to vomiting and volume expansion with relatively potassium-poor fluid sand potassium monitoring and supplementation where appropriate should be carefully observed. In particular the presence of metabolic acidosis due to dehydration, cellular hypoperfusion and renal failure may falsely elevate serum potassium levels causing overestimation of whole body potassium status. However some patients who are frequently vomiting may become alkalotic and hypochloridaemic. Urine output should be monitored as patients are at risk from acute renal failure, oliguria and iatrogenic overhydration.

In pancreatitis there is marked consumption off plasma protease inhibitors such as α-macroglobulin and α-1 Proteinase inhibitor (AAT) as activated proteases are cleared from the circulation. Saturation of the ability of α-1 macroglobulin to bind circulating proteases results in DIC, shock and contributes to mortality. Administration of plasma may provide additional α-macroglobulin and also albumin which may bind detergents such as free fatty acids and lycolecithin which damage cell membranes. Clinical evidence for efficacy however, in human and animal studies, is lacking.

The use of antimicrobials in acute pancreatitis is highly controversial. In people with acute necrotising pancreatitis and evidence of patchy fluid accumulation within the pancreas on CT, administration of parenteral antibiotics has been shown to decrease mortality due to infected necrotising complications. In dogs the incidence of infected pancreatic necrosis appears rare and perhaps slightly higher in cats (in humans secondary infection is common affecting 40-60% of patients) and the benefits of such measures are unknown. Fluoroquinolones, trimethoprim sulphonamide and second/third generation cephalosporins penetrate well into the canine pancreas and are effective against most pathogens implicated in human infections (usually gram negative aerobic organisms of alimentary origin). In dogs recommendations have included the judicious use of antibiotics in patients with fever or toxic neutrophil morphology or with ultrasonographic evidence of abscessation or cystic cavities.

The practice of withholding food from patients with pancreatitis is of unknown value and is not recommended except in certain circumstances. In many patients who are vomiting continuously in response to food administration, a period of temporary starvation may ameliorate the signs and reduce vomiting-induced fluid and electrolyte disturbances. However, the conventional assumption that feeding orally will further stimulate pancreatic enzyme secretion has been challenged and indeed in experimental models of pancreatitis, secretory

capacity of the organ reduces markedly during initial phases and in particular the response to cholecystokinin (CCK) becomes vastly reduced.

The prolonged withholding of food may negatively impact recovery due to malnutrition, negative nitrogen balance and tissue catabolism and has also been shown to contribute to systemic inflammatory response syndrome and sepsis through breakdown in maintenance of the enteric barrier and translocation of enteric bacteria. Total parenteral nutrition may be considered in patients with pancreatitis but has been shown in human patients to be inferior to enteral nutrition and to increase risk of sepsis and SIRS.

In dogs with pancreatitis, morbidity appears decreased in patients with early nutritional support. This is often best given in the form of supportive nursing care and tempting with food. Sometimes placement of a naso-oesophageal feeding tube temporarily may be all that is needed but in some patients oesophagostomy or PEG placement is needed. In patients not undergoing laparotomy a jejunostomy tube can be placed through a PEG tube by endoscopic manipulation. Nasojejunal tubing appears an attractive alternative in canine patients and the author's early experience with this feeding method is very positive. Oral feeding should be high carbohydrate, high protein, low fat. The optimum composition of jejunostomy feed products and total or partial parenteral nutrition solutions is not known.

In cats, vomiting is less common than in dogs which allows enteral nutrition to be addressed early in the course of treatment. Hepatic lipidosis is common in cats with pancreatitis and is associated with a poorer prognosis. Appropriate, aggressive nutrition is essential to prevent hepatic lipidosis developing or worsening. Attentive nursing and appetite stimulants may tempt cats to eat, but rarely results in consumption of the full caloric requirement. If vomiting is not a major feature, then naso-oesophageal or oesophagostomy tubes can be placed with minimal equipment. In contrast to dogs, obesity and feeding high fat diets have not been associated with pancreatitis in cats. Most recent case series of feline pancreatitis have actually associated the disease with underweight body condition. In addition, since most cats with pancreatitis are inappetant, high calorie palatable diets are usually recommended. Other novel protein or hypoallergenic diets may be required as part of the treatment of any underlying IBD.

Analgesia is required in most cases of canine and feline pancreatitis. Pethidine and buprenorphine are often cited as having benefit over morphine due to reduced spasm of the sphincter of Oddi. However, there is evidence that all opioids do in fact cause a degree of sphincter spasm in humans and the impact of sphincter spasm induced by opiates in the clinical setting of pancreatitis is unknown. The veracity of claims that morphine induces higher sphincter of Oddi pressure than pethidine has been questioned. Generally mild pain can be controlled with buprenorphine, moderate to severe pain with methadone and will often combine this with constant rate infusions of lidocaine in patients with severe visceral pain. Sublingual administration of buprenorphine in cats appears to be very effective where it is absorbed across the buccal mucous membranes. This also has the advantage that owners can administer it at home if required.

There is no known benefit of using antacids in pancreatitis although some suggest this may help reduce gastric discomfort and the amount of bicarbonate the pancreas needs to produce. Rational antiemetic use would include metoclopramide (often used as a constant rate infusion), maripitant or ondansetron. The use of corticosteroids in acute pancreatitis is relatively contraindicated by the low-incidence of immune-mediated pancreatitis in dogs, the lack of proven benefit in human patients with most forms of pancreatitis and the increased morbidity in human patients with existing pancreatitis treated with corticosteroids

The use of pancreatic enzyme supplementation with the aim of suppressing endogenous pancreatic enzyme secretion by negative feedback from an exogenously delivered substrate has theoretical benefit, and despite initial controversy has been shown to decrease enzyme secretion in a number of models. However, its value in acute pancreatitis remains uncertain. In chronic relapsing pancreatitis though, three double-blind trials have demonstrated efficacy in reducing abdominal pain in 75% of human patients with unremitting abdominal pain.

Anecdotally this approach also appears to be effective in some dogs and cats with chronic relapsing pancreatitis

A decision to perform surgery in the presence of pancreatitis needs to be very carefully assessed as in many cases this may lead to a worse prognosis. Recovery from surgical exploration in canine patients with acute fulminant pancreatitis is associated with a high mortality risk. Unfortunately most surgery in this situation is undertaken because a diagnosis has not been made or a wrong diagnosis has been made. Pancreatitis isn't a surgical condition and there are very few situations in which surgery should be considered. These might include: biopsy collection for definitive diagnosis where it is considered possible that pancreatic neoplasia is present, placement of a surgical jejunostomy tube, exploration, lavage and abdominal sepsis management in patients with septic cytology on abdominocentesis of fluid, resection of pancreatic abscess, pseudocyst or necrotic focus

Exocrine pancreatic neoplasia
Primary pancreatic neoplasia in dog and cats is very rare, however it is often suspected due to the nodular appearance that can occur in animals with pancreatitis, which is a lot more commonly documented. Pancreatic adenomas are solitary, capsulated mass lesions that can occur in any location within the pancreas. They generally require no specific treatment but are usually identified after surgical excision of mass by partial pancreatectomy. The most common malignant pancreatic exocrine tumour is the adenocarcinoma. Adenocarcinomas may be identified as the cause of clinical pancreatitis or after effects due to mass-effect and displacement of other abdominal organs. Rarely their presence may lead to destruction of pancreatic beta islet cells causing diabetes mellitus. Laboratory abnormalities are often as those for pancreatitis though in some cases no abnormalities are seen.

Radiography is often unhelpful in identifying the primary neoplasm though pulmonary metastases are common and thoracic films should always be undertaken when neoplasia is suspected. Focal loss of serosal detail due to concurrent pancreatitis may be seen on abdominal films and if focal or diffuse pancreatic enlargement occurs then the spleen may be shifted caudally. The ultrasound appearance may be consistent with a well-demarcated mass but continuation with the pancreas may be difficult to prove and there is considerable overlap between the appearance of pancreatic adenocarcinoma on ultrasound and pancreatitis. Fine needle aspiration cytology can be helpful, although the presence of inflammation does not allow exclusion of tumours as concurrent pancreatitis is very common with neoplasia. Repeated evaluation of the pancreas may be helpful in monitoring the pancreas, with masses associated with pancreatitis resolving over time and those associated with neoplasia progressing. The overall prognosis in dogs with pancreatic adenocarcinoma is extremely poor, euthanasia should be considered in these cases.

Endocrine pancreatic neoplasia
Insulinomas are rare tumours that arise from the beta cells in the pancreatic islets and lead to the excessive, and unregulated, secretion of insulin. The inappropriate release of excessive amounts of insulin, leads to signs of hypoglycaemia. Classic signs are of neurological dysfunction and include collapse, ataxia and seizures, which respond to the administration of glucose. The tumours typically release insulin episodically, with clinical signs being seen intermittently as a result. These are most often associated with prolonged starvation or prolonged periods of exertion. Insulinomas are mostly malignant (around 60%), however even those that appear benign on histopathology behave in a locally aggressive manner, and nearly always metastasis. These are found in the draining lymph nodes and liver in around half of dogs at initial presentation. Insulinomas are typically reported in medium to large breed dogs, with a reported disease predisposition in Boxers, Standard Poodles, Fox terriers and German shepherd dogs. The median age of presentation is around 9 years of age, with a reported range from 3 to 15 years. No apparent sex predisposition is reported and are very rarely reported in cats.

Most animals present due to the intermittent neurological signs as a result of intermittent and excessive release of insulin, leading to neuroglycaemia. The severity of the hypoglycaemic crisis is dependent on the severity of the hypoglycaemia seen, the rate of the blood glucose decline and the duration of the hypoglycaemia.

Signs are often gradual in onset and variable in there progression (over 1-6 months). Usually signs start with hind limb weakness (around 40% of cases) and lethargy, and progress to collapse, ataxia and mental confusion. A complete loss of consciousness is rarely reported, however seizures will occur as the condition progresses. Animals appear to adapt to very low blood glucose levels (1-2mmol/l) and may have no clinical for long periods, with small changes such as exercise or starvation triggering the onset of clinical signs. Clinical examination findings are often unremarkable, although some animals will have increased body condition due to the anabolic growth hormone like effects of insulin.

Traditionally the diagnosis of insulinoma has been based on fore filling the 3 components of Whipple's triad. These are that clinical signs of hypoglycaemia are present, a low blood glucose level can be documented when these signs are present and that the clinical signs seen resolve with the administration of glucose. These criteria were developed in the 1930's to try to distinguish human patients that may have insulinoma and that required surgery, prior to the development of assays for insulin. With the development of reliable insulin assays, the documentation of inappropriate insulin levels is also required to make a definitive diagnosis. Differentials for hypoglycaemia are considered in the table below.

Glucose levels are usually very tightly controlled in the body and numerous hormones are implicated in the control of blood glucose levels. Insulin reduces serum glucose levels allowing glucose to be stored as glycogen within tissues. As such its secretion in the normal animal is inhibited at very low glucose levels. If an insulinoma is suspect, insulin should be measured, but in light of the serum glucose levels and it should only be measured if a low serum (<3mmol/l) glucose level is documented. An elevated insulin level in a hypoglycaemic patient is inappropriate and is consistent with an insulinoma. An insulin level with in the normal range, with a hypoglycaemic patient, is also inappropriate and is suggestive of an insulinoma. A patient with a low insulin level in response to hypoglycaemia is not consistent with an insulinoma. Fructosamine and glycosylated haemoglobin A1c levels have been used to strengthen the clinical suspicion of prolonged periods of hypoglycaemia.

Ultrasound is successful at identify pancreatic masses in around half of dogs with defined insulinoma. A larger mass (>2cm diameter) is more likely to be seen on ultrasound and the sensitivity of ultrasound is greatly affected by the equipment used and the experience of the operator. Ultrasound may give both false positive (due to non-neoplastic pancreatic nodules) and false negative (the mass is not apparent) results. Metastatic changes can also be identified and are seen on ultrasound in around 20% of cases.

CT is used in people due to its increased sensitivity for detecting small pancreatic lesions. Small studies using CT in dogs have been published and it appears better than ultrasound at diagnosing pancreatic masses that have been confirmed at surgery, with around 70% of tumours seen. Metastases are also detected by CT, however due to the higher resolution the chance of false positive results in much greater. The use of dual phase and Positron Emission Tomography (PET-CT) are currently being evaluated.

Symptoms of hypoglycaemia normally resolve quickly with the administration of intravenous glucose or dextrose (1ml/kg of 50% glucose solution diluted 1:2 in 0.9% sodium chloride). This should be given slowly (as tumours retain some degree of responsiveness to insulin levels and rapid boluses of glucose may lead to further release of insulin) and followed with a constant rate infusion (2.5 – 5% glucose in an isotonic crystalloid solution). The infusion can be discontinued when clinical signs abate, usually this is relatively rapid. If there is a failure to respond to glucose alone, then injection of dexamethasone (0.1mg/kg i/v BID), octeride (10-50µg/kg s/c TID) or a glucagon constant rate infusion (5-10ng/kg/min) could be considered. In severe seizures or those that do not respond to glucose diazepam or phenobarbitone loading may need to be considered. Mannitol should be considered if cerebral oedema is suspected.

Where possible surgery should be considered to try to remove as much of the insulin secreting tumour as possible. Medical signs should be controlled as much as possible prior to explorative laparotomy. Studies have shown roughly even distribution of tumours to the left (42%) and right (41%) limbs, with 17% present in the central area around the pancreatic and bile ducts; tumours in this location are not amenable to surgery.

Confirming the presence of an insulinoma should be done visually and by palpation of the pancreas (around 15% of dogs have multiple nodules). The use of intraoperative ultrasound and possibly the injection of new methylene blue can increase the chances of finding the mass. If a mass is not found surgical resection of either the right or left lobe could be considered in the hope of removing the bulk of the tumour. As there will be extensive handing of the pancreas at surgery post-operative pancreatitis is a significant concern and diabetes mellitus is seen in around 10% of patients, in some patients the need for insulin will resolve over time.

In some case of insulinoma frequent feeding of complex carbohydrates, and diets high in protein and fat, may control the clinical signs of hypoglycaemia, the gradual release of post-prandial carbohydrate may decrease the potential for insulin release. Prednisolone should be started is dietary management alone does not control signs and the dose increased as needed (0.5-2mg/kg/day in divided doses). Glucocorticoids increase blood glucose levels by increasing gluconeogenesis, elevating glucose 6-phosphatase activity, decreasing blood glucose uptake into tissues and stimulating glucagon release. Steroids are cheap and effective, but as the tumour progresses signs of iatrogenic hyperadrenocortisicm may limit their use.

Diazoxide is used in patients that stop responding to steroids and acts by inhibiting insulin release, but also by increasing glycogenolysis, gluconeogenesis and inhibiting tissue uptake of glucose. Treatment usually starts at 10mg/kg in divided doses (2-3 times a day) and is titrated up to effect to 50-60mg/kg/day. Around 70% of dogs will respond to treatment with diazoxide, but in comparison to prednisolone is much more expensive. It is generally not recommended but the use of thiazide diuretics (e.g. chlorothiazide 2-4mg/kg/day) may potentiate the effects of diazoxide. Common potential side effects include vomiting and inappetance; other potential adverse effects include bone marrow suppression, sodium retention, diarrhoea, tachycardia, aplastic anaemia, hyperglycaemia and cataract formation.

The long term prognosis for dogs with insulinoma is guarded, due to the likelihood of the development of metastasis and associated clinical signs. Median survival times for dogs undergoing partial pancreatectomy is around a year, with a range of 0 days to 5 years. Reported survival times are longer for dogs treated with surgery initially compared to medical management (MST 381 days c.f. 74 days) used alone. A more recent study has reported better survival times for dogs undergoing surgery (MST 785 days) and much longer survival times is prednisolone was used with signs of hypoglycaemia recurred (1316 days).

Exocrine pancreatic insufficiency

Exocrine pancreatic insufficiency (EPI) is a syndrome resulting in lack of synthesis and / or secretion of pancreatic enzymes, leading to clinical signs of maldigestion. Most commonly EPI is caused by pancreatic acinar atrophy (PAA) but it may also happen secondary to exocrine pancreatic inflammation (pancreatitis).The exocrine pancreas has a huge reserve capacity so approximately 90% of its function has to be lost before signs of EPI develop. PAA has a possibly autosomal recessive mode of inheritance in the German shepherd dog and Eurasian dog. In other dogs and in all cats, the most common cause of EPI is chronic pancreatitis. Pancreatitis will results in destruction of pancreatic endocrine as well as exocrine cells, therefore diabetes mellitus can rarely develop along with EPI in patients with chronic pancreatitis. Very rarely animals may have normal pancreatic enzyme production but have secretions blocked by pathology of the duodenal papillar or pancreatic duct.

The most common presenting sign is weight loss. Diarrhoea is variably present as is steatorrhoea and large voluminous faecal bulk. An increased appetite is frequently reported but is not a consistent finding. The hair coat is frequently dull, especially in cats. Polyuria and polydipsia may be present if the patient is diabetic but sometimes PU/PD is seen in patients with EPI alone for reasons which are poorly understood. Some dogs with EPI appear clinically unwell but most are very bright.

Trypsin like immunoreactivity (TLI) is the gold standard in dogs and cats. Because of the pancreatic reserve capacity, it is possible to see quite low TLI concentrations in clinically normal animals. In a patient with appropriate clinical signs, a TLI result <2.5µg/l confirms a diagnosis of EPI. A result >5.5 µg/l suggests normal exocrine function. A test result between 2.5 and 5.5µg/l may be normal or early / sub-clinical disease. TLI concentrations may be increased by recent feeding; this assay should be repeated after a 12 hour fact if recent feeding is suspected. Measurement of faecal elastase test is possible, but has a high rate of false positives (around 25%). This may be useful in proving disease where obstruction of the duct is suspected.

Powdered forms of pancreatic enzyme supplementation are usually preferred to encapsulated form, although recent studies appear to have demonstrate similar efficacy between different formulations. The suggested starting dose is one teaspoon of powdered (preferable to encapsulated forms) pancreatic extract per 10kg bodyweight in each meal. Once the patient has completely responded, the amount of pancreatic extract can be gradually reduced. Oral bleeding is occasionally reported in dogs receiving pancreatic extract but can often be diminished by more thorough mixing with food or cautious dose reduction. If this develops, a coagulation profile should be checked. If this is normal, then the amount of extract administered should be reduced.

Feeding a low fat diet does not appear to uniformly benefit dogs with EPI, and this diet may lead to a deficiency in fat soluble vitamins (A, D, E, K). It appears that individual animals respond differently to different diets. In general a high quality maintenance diet, avoiding excessive fibre which could interfere with weight gain and absorption of fat soluble vitamins. Approximately 80% of dogs with EPI are deficient in cobalamin, and hypocobalaminemia negatively affects response to treatment. Cobalamin should be measured, and if deficient, supplemented parenterally. A suggested dose regime for dogs is 250-1500 µg SC weekly for six weeks, then every other week for six weeks, then again in four weeks time and rechecking cobalamin concentrations one month later.

If a dog fails to respond to treatment then check that the dose and formulation of enzyme supplement is correct and increase or alter the dosing as needed. Check for concurrent disease for example diabetes or chronic pancreatitis. Evaluate for concurrent gastrointestinal disease. In particular, dogs with EPI can develop a dysregulation of their bacterial flora, so trial therapy with an antibiotic (Metronidazole, oxytetracycline or tylosin) may be beneficial. Altering diet may help. A novel protein / carbohydrate source to exclude sensitivity or a low fat diet may be considered. Supplementation with vitamin E (400-500IU PO q24hrs for 1 month) may be considered. A low gastric pH can destroy much of the ingested pancreatic lipase. Trial therapy with H_2 blockers or proton pump inhibitors may help.