Antemortem diagnosis and treatment of toxoplasmosis in two cats on cyclosporin therapy

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Clinical toxoplasmosis was diagnosed antemortem in two cats being treated with therapeutic doses of cyclosporin. The diagnosis was made by detecting tachyzoites on cytological examination of bronchoalveolar lavage fluid from one case and pleural effusion from the other. Despite early diagnosis and aggressive treatment in both cases, only one cat survived. Reactivation of latent Toxoplasma gondii infection secondary to cyclosporin-induced immunosuppression was considered likely in both cases. The presence of respiratory signs in cats treated with cyclosporin should alert clinicians to the possibility of clinical toxoplasmosis. Consideration should be given to determining the serostatus of cats to T gondii prior to use of drugs which are potent inhibitors of cell mediated immunity, such as cyclosporin.

Two cases of feline toxoplasmosis are presented. One 11-year-old male, neutered, domestic shorthair cat was referred with an acute onset of dyspnoea. The cat had been acquired at 12 weeks-of-age and housed entirely indoors with its sibling from that time. Its diet consisted of commercial tinned and dry food only. There was no known access to raw meat or to rodents. The cat had a 9-year history of eosinophilic granulomas affecting the hard palate and upper lip. Oral prednisolone (5 to 20 mg orally once daily) in combination with chlorambucil (1.25 mg orally every 48h) or chlorpheniramine (2 mg orally twice daily) had been administered intermittently, but frequently, during this period. Two months prior to presentation, the cat developed diabetes mellitus, which was managed with glimepiride (2 mg orally once daily) and chromium (100 μg orally once daily). Prednisolone therapy was stopped. Instead, the cat was treated with 3 mg/kg (25 mg) cyclosporin (Atopica®, Novartis Animal Health, Australasia) orally, twice daily for 4 weeks then once daily for 1 week prior to presentation.

At presentation the cat was overweight (8.5 kg) and normothermic (38.6°C). Cardiac auscultation was unremarkable (heart rate 180/minute). Tachypnoea (respiratory rate 48/minute), increased inspiratory and expiratory effort and increased bronchovesicular sounds bilaterally, were noted. Thoracic radiographs revealed a diffuse bronchointerstitial pattern and a small volume, unilateral pleural effusion on the right (Figure 1). Abnormalities on a complete blood count included non-regenerative anaemia (PCV 0.22 L/L, reticulocytes 5 x 10⁹/L; uncorrected 0.1%), lymphopenia (0.2 x 10⁹/L; RR 0.9 to 3.6 x 10⁹/L) and a mild neutropaenia (3.8 x 10⁹/L; RR 6 to 14 x 10⁹/L). A serum biochemical profile revealed hyperglycaemia (20.5 mmol/L; RR 3.5 to 6.7) and mild elevations in AST (118 U/L; RR 1 to 80) and creatinine kinase (414 U/L; RR 0 to 180). Serological tests for cryptococcus antigen (LCAT) and FIV antibody were negative.

Case 1
An 11-year-old male, neutered, domestic shorthair cat was referred with an acute onset of dyspnoea. The cat had been acquired at 12 weeks-of-age and housed entirely indoors with its sibling from that time. Its diet consisted of commercial tinned and dry food only. There was no known access to raw meat or to rodents. The cat had a 9-year history of eosinophilic granulomas affecting the hard palate and upper lip. Oral prednisolone (5 to 20 mg orally once daily) in combination with chlorambucil (1.25 mg orally every 48h) or chlorpheniramine (2 mg orally twice daily) had been administered intermittently, but frequently, during this period. Two months prior to presentation, the cat developed diabetes mellitus, which was managed with glimepiride (2 mg orally once daily) and chromium (100 μg orally once daily). Prednisolone therapy was stopped. Instead, the cat was treated with 3 mg/kg (25 mg) cyclosporin (Atopica®, Novartis Animal Health, Australasia) orally, twice daily for 4 weeks then once daily for 1 week prior to presentation.

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In addition to clindamycin, the cat was treated with trimethoprim sulphonamide 15 mg/kg SC every 12 h, terbutaline 12 mg/kg IM every 12 h, lente insulin 1 to 2 units SC every 12 h and IV crystalloids at maintenance rates. The cat made a partial clinical response to treatment, but was anorectic. At no time during hospitalisation was the cat pyrexic. A gastrostomy tube was placed on day 3. Twelve hours later the cat deteriorated. Positive-pressure ventilation under general anaesthesia was necessary to maintain SpO₂ > 95%. The cat’s prognosis was considered grave and the owners elected euthanasia. Necropsy examination was not permitted.

**Case 2**

A 3.5 kg, 6-year-old, female, spayed Siamese cat was referred with an acute onset of dyspnoea and pyrexia. The cat, acquired as a 6-month-old kitten from a breeder, had been housed entirely indoors since birth. There were no other cats in the household. Its diet consisted of raw beef and lamb and commercial dry food. IMHA was diagnosed 18 months prior to referral. No cause for the IMHA had been identified and serological tests for FIV and FeLV were negative. The cat had been treated with oral doxycycline for 3 weeks in case of haemoplasmosis and with varying doses of oral prednisolone (from 15 mg every 24 h to 5 mg every 48 h). After 8 months of treatment the cat ruptured its right cranial cruciate ligament, which was surgically repaired. Chronic prednisolone administration was considered to have contributed to the ligament rupture and this treatment was stopped. Three weeks later the cat was prescribed cyclosporin for ongoing IMHA, at a dose of 25 mg orally twice daily (6 mg/kg) for 5 consecutive days of each week. After 8 weeks of treatment, the cat developed acute dyspnoea. It was anorectic and lethargic for 4 days prior to presentation to the referring veterinarian, at which time it was found to be pyrexic (39.4°C). Thoracic radiographs showed a large volume, bilateral pleural effusion and the cat was referred. Physical findings at referral included ptyalism, tachypnoea (respiratory rate 100/minute), increased inspiratory effort, heart rate 192 beats/minute and rectal temperature 38.1°C. Ocular examination, including fundoscopy, was unremarkable. One hundred and forty mL of clear, yellow fluid was drained from the left and right pleural cavities by ultrasound-guided thoracocentesis. On echocardiographic examination all cardiac parameters were within reference ranges.

Acute toxoplasmosis was suspected on the basis of history and clinical signs. Therapy was commenced with clindamycin phosphate 25 mg/kg every 12 h IV and IV crystalloids at 1.5 times maintenance rates (12 mL/h). On haematological examination there was left shift [segmented neutrophils 3.1 x 10⁹/L (RR 2 to 13 x 10⁹/L), band neutrophils 0.5 x 10⁹/L (RR 0 to 0.2 x 10⁹/L)] and lymphopenia (0.5 x 10⁹/L, RR 0.9 to 7 x 10⁹/L). The PCV was normal (0.37 L/L). Abnormalities on serum biochemical analyses included low urea (4.9 mmol/L, RR 5 to 14), hypoproteinaemia (56 g/L, RR 61 to 84), hypoalbuminaemia (25 g/L, RR 27 to 38), hyperbilirubinaemia (12 mmol/L, RR 0 to 10) and elevations in AST (2407 IU/L, RR 0 to 65), ALT (1761 IU/L, RR 25 to 90) and creatine kinase (928 IU/L, RR 0 to 360). Urine specific gravity was 1.027. Results of pleural fluid analysis demonstrated a protein content of 35 g/L and a nucleated cell count of >90% non-degenerate neutrophils and <10% large, vacuolated macrophages. Many *Toxoplasma* tachyzoites were present intracellularly and free within the fluid (Figure 3).
On day 2 of hospitalisation the cat was pyrexic (40.1°C) but less dyspnoeic (respiratory rate 56/min). Intravenous clindamycin therapy was continued. Pyrimethamine was added to the treatment regime (3 mg orally twice daily). A further 60 mL of yellow fluid was drained by ultrasound-guided thoracentesis from the right hemithorax. The rate of crystalloid administration was reduced to maintenance. On day 3 of hospitalisation a further 50 mL of clear fluid was drained from the right hemithorax. Serology for *T. gondii* IgM was negative and for IgG was positive at a 1:4096 dilution by IFAT.

On day 4 of hospitalisation the cat developed pitting oedema of the forelimbs. The jugular veins were distended and sinus tachycardia (heart rate 260/min), but no murmur, was auscultated. Echocardiography demonstrated evidence of right-sided congestive heart failure and tricuspid regurgitation (regurgitant jet velocity 1.73 m/s). Right atrial diameter was 19.3 mm. Left atrial and ventricular parameters and aortic and pulmonic blood flow velocities were within reference ranges. Fractional shortening was 40.2%. The endocardium and myocardium were markedly hyper-echoic, consistent with myocarditis. Thoracic radiographs showed an interstitial pattern and a small volume pleural effusion. The cat was anaesthetised and a percutaneous gastrostomy tube was placed. The cat was fed a high calorie diet (Hills a/d) through the gastrostomy tube. Treatment with benazepril 2.5 mg orally once daily and frusemide 5 mg orally twice daily was commenced. The dose of clindamycin was reduced to 12.5 mg/kg every 12 h IV.

On day 7 tachypnoea resolved. The dose of frusemide was reduced to 5 mg orally once daily on day 7 and withdrawn on day 11. Pitting oedema resolved on day 8. The cat became progressively anaemic during hospitalisation and on the day of discharge (day 13) the PCV was 0.21 L/L and the total plasma protein was 70 g/L. The cat’s body weight at discharge was 2.89 kg and the total plasma protein was 72 g/L. The cat’s body weight at discharge was 2.89 kg and the total plasma protein was 72 g/L. On day 27 the pyrimethamine dosage was reduced to 3 mg orally once daily. Therapy with benazepril was stopped. At a recheck examination 6 weeks after presentation the cat was clinically normal with a body weight of 3.6 kg. Haematological examination showed resolution of anaemia (PCV 0.37 L/L, total plasma protein 72 g/L) and examination of the peripheral blood film was unremarkable. Serum biochemistry was unremarkable except for mild elevations in ALP (59 IU/L, RR < 51) and ALT (150 IU/L). Serology was repeated. IgM was negative and the IgG titre remained unchanged at 1:4096. All therapy was ceased. Two years after presentation the cat was well, with no recurrence of IMHA (PCV 0.44 L/L).

### Discussion

Clinical toxoplasmosis in the cats described in this report could have resulted from either primary or reactivated latent infections since the *T. gondii* serostatus of these cats prior to clinical signs was not known. It is interesting that both cats were housed indoors for much or all of their lives. Thus it is reasonable to speculate that exposure to *T. gondii* in Case 1 was through ingestion of raw meat in the diet. No source of exposure was identified in Case 2. Reactivated, fatal disseminated infection can be induced in healthy, experimentally infected cats by administration of extremely high doses of glucocorticoids (10 to 80 mg/kg/day oral prednisone or 10 to 80 mg/kg/week methyl prednisolone acetate IM) but not through therapeutic doses.6,7 Therapeutic doses of cyclosporin have induced fatal toxoplasmosis in cats including three cyclosporin-treated cats following renal transplant surgery and in another cat with atopy.8,9 Reactivated donor or host infection occurred in the cats with renal transplants. In one cat bradyzoite cysts in the renal allograft were the likely source of infection. In the other two cats reactivation of latent host infection following immunosuppression was most likely given that bradyzoite cysts and tachyzoites were present in many organs, but not within renal allografts. Lesions were located in the renal allograft, lungs and liver of the first cat and were widely disseminated in the other two cats.8

Other cases of reactivated toxoplasmosis secondary to immunosuppression include a cat prescribed prednisolone and azathioprine for treatment of inflammatory bowel disease10 and an FIV-positive cat treated with repeated depot megestrol acetate injections and oral prednisolone for allergic dermatitis.11 Primary infection was considered unlikely in the first of these cats since it was fed processed food only. Lesions were confined to the intestinal tract. In the latter case, infection was considered to be reactivated on the basis of detection of bradyzoite cysts in tissues where tachyzoite-induced lesions were subacute, and tightly clustered tachyzoites in a ‘burst pattern’ suggested recent release from a bradyzoite cyst. Pathology was confined to the lungs and brain.11 In the atopic cat with cyclosporin-induced fatal systemic toxoplasmosis, hepatic, pancreatic and lymph node necrosis and pneumonia were found at necropsy. Tachyzoites were detected by immunohistochemistry in liver and lung tissue. This cat was considered to have primary infection rather than reactivated
infection based on the distribution of lesions. However, it is not possible to distinguish primary from reactivated infections on the basis of organ involvement. The lung is considered the primary target in both primary and reactivated infections.5,12,13 Furthermore, in reactivated toxoplasmosis infections may be either focal5,10,14 or widely disseminated.6,8 By contrast, in reactivated toxoplasmosis in humans the primary organ affected is the brain although multi-organ involvement can occur.15 Seropositivity to T. gondii in humans in the United States of America and the United Kingdom is 16 to 40%. In immunocompromised patients, reactivation of latent infection is a much more common mechanism of infection than primary infection.15,16 Given similar or higher levels of seroprevalence in adult immunocompromised cats5–4 the likelihood of reactivation of latent infection in both cats of this report is much higher than acquisition of an acute, primary infection during the period of immunosuppression. The absence of both an IgM titre and a rising IgG titre in Case 2 is supportive of reactivation of latent infection.

CMI is the main mechanism of defence in the control of T. gondii infection and prevents latent infection from becoming reactivated. Cyclosporin is a potent suppressor of CMI. By blocking the transcription of IL-2, early T-cell activation, T-cell proliferation and T-cell cytotoxic activity is greatly reduced.17 A microemulsified formulation of cyclosporin, Atopica® (Novartis Animal Health, Australasia) is registered for use in the treatment of atopic dermatitis in dogs at a dose rate of 3.3 to 6.7 mg/kg orally once daily for 4 weeks, then every 48 h. In humans, it is recommended that the daily dose of cyclosporin be given divided as two equal doses, in spite of the relatively slow elimination of the drug. High peak plasma concentrations of cyclosporin cause renal functional impairment. In dogs, a once daily administration is preferred for treating atopy, because nephrotoxicity is uncommon unless extremely high blood levels are maintained (> 3000 ng/mL).17,18

Although not registered for use in cats, cyclosporin has been used for treating atopy, immune-mediated diseases and to induce immunosuppression in organ-transplant recipients.5,8,18 Using the microemulsion formulation, a starting dose of 0.5 to 2.5 mg/kg orally twice daily, aiming to attain 12 h whole blood trough levels of 250 to 500 ng/mL, has been recommended.17 Trough blood concentrations should be measured 24 to 48 h after initiation of therapy and periodically throughout the course of therapy. The elimination half-life of cyclosporin in cats (9 h) is similar to dogs (8 h) and humans (6 to 10 h), however there is significant interpatient variation in the pharmacokinetics of oral cyclosporin in cats.19 Whole blood levels higher than 1000 ng/mL can cause inappetence,19 and if maintained for several weeks or months, opportunistic infections can occur. A newer strategy of measuring blood cyclosporin concentration in cats 2 h after oral administration (C2) as an approximation of peak plasma drug concentration may be a more accurate protocol for therapeutic drug monitoring.19

Definitive antemortem diagnosis of feline toxoplasmosis is notoriously difficult. In these two cases tachyzoites were identified on cytological examination of BAL fluid (Case 1) or pleural effusion (Case 2). In the largest study of 100 cases of toxoplasmosis confirmed histologically by detection of tachyzoites in tissues collected at autopsy, definitive antemortem diagnosis was made in 4% of cases only – tachyzoites were detected in two tracheal aspirates, in one pleural effusion and in a biopsy specimen from a lymph node.12 In another case, Toxoplasma tachyzoites were detected antemortem in BAL fluid from a cat.20 Neither cat in this report had signs of anterior uveitis on physical examination. Fundoscopy was not performed in Case 1, but may have been useful as an adjunct to diagnosis since both anterior uveitis and chorioretinitis are common in cats with generalised toxoplasmosis.12 Given that the lungs are a major target in both primary and reactivated infection in cats, cytological evaluation of BAL fluid should be considered where clinical suspicion of disseminated toxoplasmosis exists. In an experimental study of cats inoculated with T. gondii tachyzoites, bronchial wash cytology 7 to 14 days post-infection was more sensitive than histopathology in the detection of tachyzoites. Of 15 cats with overt toxoplasmosis tachyzoites were identified in BAL fluid from all cats. However numbers of tachyzoites detected ranged from 2 to 5 per 500 X field to 1 or 2 organisms per slide.21 Clinicians should therefore request diligent scrutiny of BAL fluid by a cytologist if they suspect pulmonary toxoplasmosis or if detection of tachyzoites is difficult.22 In humans, diagnosis is further facilitated by PCR and tissue culture of BAL fluid.23 Serology may be used as an adjunct to diagnosing toxoplasmosis though interpretation is complicated. A positive IgM titre or a 4-fold or greater increase in IgG in paired serum samples taken 2 to 4 weeks apart is generally considered diagnostic of active toxoplasmosis.24 Serological tests available include the Sabin-Feldman dye test, IHA, IFAT, ELISA, LAT and MAT. Of these the LAT is the most sensitive and the IHA is the least sensitive. Utilising acetone and formalin-fixed tachyzoites increases the sensitivity and specificity of the MAT in the detection of acute infections. During acute infections (< 3 months) antibodies to acetone-fixed antigen are elevated, whereas antibodies to formalin fixed antigen may remain high for several years.1 ELISA is able to detect feline IgM, IgG and IgA. ELISA methods are as sensitive as IFA and more sensitive than the LAT.1

In both cases in this report IgG titres were positive. A single positive IgG titre indicates exposure but not active infection. High IgG titres (> 1:30 000) may persist for many years in some cats and merely reflect the presence of T. gondii antigen within tissues. Although a 4-fold or greater increase in IgG in paired serum samples taken 2 to 4 weeks apart suggests acute infection,24 a rising IgG titre was not demonstrated in Case 2. In immunocompromised human patients an increase in IgG titres is frequently absent with reactivated toxoplasmosis as opposed to primary infection.25 If the same is true for cats then the failure to demonstrate rising IgG in Case 2 may be consistent with reactivated infection.

In Case 1 the positive IgM titre was supportive of acute infection, however, positive IgM titres do not always denote active infection. In the majority of cats IgM titres do not persist beyond 12 weeks after acute infection.26 False-positive results can occur in some cats where IgM titres remain high for months to years post-infection. Also, in FIV-positive cats a delayed class shift from IgM to IgG may occur.27–29 Glucocorticoid administration can alter T. gondii-specific antibody responses in cats such that IgG titres may diminish and IgM titres may increase.30 False-negative IgM titres can occur in peracute infections since positive IgM titres do not develop until 2 weeks post-infection in most cats. Also, 10 to
20% of cats never develop IgM titles and cats with FIV-infection may not develop an IgM response. Furthermore, re-infection of cats with *T. gondii* cysts several months after a primary infection does not cause an increase in IgM levels. In Case 2, the IgM titre was negative on both occasions that it was tested (days 3 and 27 post-diagnosis). This is also supportive of reactivated infection, since in immunocompromised human patients with reactivated toxoplasmosis, IgM titre are frequently negative.

Successful treatment of clinical feline toxoplasmosis has rarely been described. Of 100 cases confirmed histologically at necropsy, 17 were treated for suspected toxoplasmosis with a sulphonamide and eight also received pyrimethamine. None of the treated cats survived. In another series of 15 cases of clinical toxoplasmosis (diagnosed by serology, clinical signs and response to treatment or histological confirmation of infection) three cats died or were euthanased. Clinical signs resolved in 4 of 12 cats treated with clindamycin at 25 mg/kg divided twice daily. In the other eight cats, which had anterior uveitis, topical, oral or subconjunctival prednisolone was given concurrently. Of these cats clinical signs persisted or recurred in four cats. Even where definitive diagnosis has been achieved ante-mortem, response to therapy has been poor. Two of three renal transplant patients died despite treatment with parenteral clindamycin (total dose 24 to 30 mg/kg/day). A cat with toxoplasmal pneumonia, treated with trimethoprim-sulfonamide (30 mg/kg orally once daily) and clindamycin 10 mg/kg SC once daily also died.

Treatment of focal toxoplasmal enteritis using sulfadiazine, pyrimethamine, folic acid and clindamycin 12.8 mg/kg orally twice daily was successful in another case.

Successful treatment requires not only effective antimicrobial therapy, but also supportive therapy and monitoring for organ failure. Thoracoencesthesia, nasal oxygen, judicious fluid therapy, therapy for heart failure and gastrostomy tube feeding were essential in successful treatment of Case 2. Cats with acute toxoplasmosis should be monitored for effusions, pneumonia, hepatic failure, pancreatitis, encephalomyelitis and myocarditis. Pleural effusion in Case 2 may have been due to vasculitis associated with circulating immune complexes, since right-heart failure was not present initially.

Strategies to prevent toxoplasmosis, and for early detection, should be implemented in cats being treated with drugs that are potent inhibitors of CMI such as cyclosporin. In seronegative cats, attempts to prevent primary infection should be made during the period of immunosuppression. Raw meat diets should be avoided or only thawed frozen meat should be fed, since freezing meat at -12°C for several days destroys most bradyzoite cysts. Seronegative cats should be housed indoors to prevent exposure to sporulated oocysts or intermediate hosts. Similar recommendations could be made for seropositive cats. Although seropositive cats are generally immune to recurrent primary infection from ingestion of *T. gondii* oocysts, gastrointestinal immunity to *T. gondii* can wane in some cats 6 years post infection. The serostatus of cats to *T. gondii* should be determined prior to and during therapy. It has become routine practice in feline renal transplant surgery to avoid using seropositive donors for seronegative recipients. Furthermore, seropositive feline renal transplant recipients on cyclosporin are currently prescribed life-long daily oral clindamycin therapy for toxoplasmosis prophylaxis (LR Aronson, personal communication). Reactivated latent toxoplasmosis should be considered in the differential diagnosis of seropositive cats that develop lower respiratory tract signs during immunosuppressive therapy. Cytolysis of BAL or pleural effusion may be evident in definitive diagnosis in these cats. In seronegative feline cats where seroconversion occurs, or in seropositive cats where IgM or rising IgG titres occur, effective antimicrobial therapy should be prescribed including clindamycin and pyrimethamine or trimethoprim sulfonamide and pyrimethamine. Cats given oral clindamycin capsules should be given food or water subsequently to prevent oesophageal stricture formation. Great care should be taken when using cyclosporin in cats. Careful patient selection and close monitoring are essential to avoid the potentially fatal consequences of immunosuppresion.

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References
BOOK REVIEW


Since the publication of its first edition in 1975, Ettinger and Feldman's Textbook of Veterinary Internal Medicine has been the classic reference text for veterinary students and practitioners alike. It is particularly unique for its inclusion of detailed pathophysiology as well as diagnosis and treatment. The latest edition is a departure from the original text with the introduction of an online resource to complement the hard copy. This 'E-dition' boasts many great features such as video and audio clips, weekly updates for the next 5 years and direct links from the bibliography to Medline abstracts. It is well worth $90.20 more to have this comprehensive web resource.

The book itself still has two volumes with a similar format to the previous editions. There are 19 sections, divided into 279 chapters (the 5th edition had 184). New inclusions are sections on critical care, blood pressure and procedures (from venipuncture to echocardiography). In general, information has been rearranged and expanded to make a larger number of shorter, more detailed chapters. This is particularly noticeable in the oncology, toxicology and nutrition sections. Completely new chapters include those on NSAIDs, nutraceuticals, constant rate infusions, compassionate care and several feline topics. The addition of Ettinger's own physical examination technique is helpful, particularly for students and new graduates. Algorithms have been re-formatted and standardised throughout the text. The overall result presents detailed information in a logical, clear, user-friendly fashion.

Being a North American textbook, you would not consult Ettinger for information on tick paralysis or brown snake envenomation, for example the USA version of Ixodes would seem to be a whimper compared to its Aussie cousin. However, acknowledging that this is a much-loved text worldwide, an effort has been made to include more authors from countries outside of North America. The 6th edition also contains expanded information on tropical diseases, zoonoses and public health.

A bibliography is no longer included in the hard copy. While text is still marked for references, to find these one must go to the CD-ROM or online version. This makes for less bulky books, but may prove quite inconvenient. It also greatly reduces the value in purchasing the book alone.

On the other hand, the CD-ROM/online bibliography boasts direct links to abstracts of the relevant articles via Medline. This is a fantastic feature for those who are writing articles or studying for membership or specialist exams.

The E-dition comprises of a CD-ROM containing the entire text and a linked website. It is very important to check its compatibility with your software and internet access.

The website also has the full text of the book along with many extras. These include colour photos throughout the text and in the image library. There are some beautiful video images of endoscopy, angiography, ultrasound and other procedures. Audio is also included occasionally. A great feature for those preparing presentations or making study notes is that any of these images can be downloaded directly (within the realms of copyright, of course).

Other features include a drug formulary and links to related websites such as WIS. Authors regularly present case studies in 'Grand Rounds', helping users to hone problem-solving skills. Client handouts can be downloaded and customised; most are very well written for this audience, but a few contain too much detail and scientific language.

One of the best features is that information is updated weekly for the next 5 years. These updates are marked in the text, and also presented in a separate section. This textbook will be up-to-date and relevant for much longer than conventional texts.

The website is easy to use. The entire site can be searched for a chosen topic, advanced search options are available, and previous searches can be saved. Pages can be 'book-marked' and there is a facility for making notes while reading the text. Images can be transferred to the 'light-box' for later viewing or downloading. These features should satisfy those who are internet savvy while maintaining simplicity for those of us who are not.

The Textbook of Veterinary Internal Medicine E-dition is an innovative combination of the classic and the new, offering far more than conventional textbooks. Updated weekly for 5 years, offering images, sounds, rounds and article abstracts, it is worth the extra $90 to purchase the E-dition as well as the hard-copy 6th Edition. With this latest edition, the Ettinger's text has reaffirmed its reputation as the 'gold standard' of internal medicine textbooks.

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