Feline infectious peritonitis (FIP) is an infectious disease of cats, predominantly young cats. It occurs when feline enteric coronavirus multiplying in the intestines undergoes a critical mutation which changes its tissue tropism from enterocytes to macrophages. FIP virus moves round the body in macrophages – the ultimate Trojan horse mechanism. This leads to a disseminated infection and the development of a fibrinoid necrotising vasculitis and serositis due to deposition of immune complexes consisting of cat antibodies and FIP viral antigens.

Broadly speaking there are two forms of FIP – effusive (‘wet’) FIP and non-effusive (‘dry’) FIP. The actual disease process can occur in the abdominal cavity, the thoracic cavity, pericardium, the eyes, or the central nervous system. Mix and match combinations of different tissue involvement and dry and wet disease are not unusual.

Until recently, a diagnosis of feline infectious peritonitis (FIP) was by and large a death sentence for a feline patient. But that notion has been turned on its head over the last few years as a result of the pioneering work of Professor Niels C. Pedersen and colleagues at UC Davis.

Omega-interferon (Virbagen) and polyprenyl immunostimulant (PPI) were the first drugs used to treat FIP and both had reasonable efficacy in some patients. Omega interferon was useful in cases of effusive (‘wet’ FIP), often combined with low dose prednisolone according to Ishida’s protocol, whereas PPI, which was pioneered by Prof Al Legendre, was more useful in cases of non-effusive (‘dry’) FIP. In some cases, both drugs were used in concert. The trouble was that both forms of therapy were often expensive especially when both drugs were used, so although patients might improve and have durable clinical remissions while receiving treatment, permanent clinical cures were exceedingly rare. As a result, most vets still considered a diagnosis of FIP to be a death sentence in most cases.

That all changed a few years ago because of the culmination of a life-time of FIP research by Pedersen. Niels is an amazing veterinarian, a North American, with Danish heritage. He grew up on a chicken farm and initially wanted to be a large animal clinician, but with amazing foresight, decided a background in basic science would hold him in good stead in the long term. So, soon after graduation, he travelled to Canberra in the 1960s to the John Curtin School of Medical Research at ANU where he undertook an immunology PhD on kidney transplant rejection with Professor Bede Morris, using sheep as the experimental model to study lymphocyte kinetics.

When Niels returned to UC Davis as clinical faculty, he developed a special focus on infection and immunity. Although he contributed to a huge range of topics in canine and feline internal medicine, FIP was his favourite disease because of its uniqueness and also its complexity. His studies extended from the 1980s, when the focus was initially on diagnosis, virology, and disease pathogenesis, to the present day, with an increasing focus on therapy.

Working with colleagues at Kansas State University, Niels showed that a purpose-designed protease inhibitor GC-376 could prevent and cure experimental FIP in research cats.1,2 However, clinical trials in actual feline patients with naturally-occurring disease in the field were somewhat disappointing for reasons that are not entirely clear. So not easily defeated, he moved onto a different drug known as GS-441524,3,4 a nucleoside analogue being developed by the North American Pharma Gilead. This drug molecule proved to be much more effective than GC-376 for treating FIP, both in experimental infection, and in spontaneous cases in the field. Starting with pharmacokinetic studies, and then dose escalation studies using a wide range of clinical cases, Niels and colleagues determined that the dose required depended on whether or not there was ocular or central nervous system (CNS) involvement.5

Surprisingly, Gilead, the pharmaceutical company which developed GS-441524, has so far shown no interest in developing this molecule as a veterinary treatment for FIP. So, to fill the void for effective FIP therapy worldwide, various research teams in China and eastern Europe started manufacturing GS-441524 and selling it on the black market.

The widespread availability of GS-441524, often of high quality and relatively inexpensive, provided a way for dedicated cat owners to save cats with wet or dry FIP. Inspirations for the work by Samantha Evans a clinical pathologist at Ohio State University suggested a cure rate of possible 80 per cent in the field. Procuring the drug is complicated and fraught with issues, which were circumvented at some level by help from the Facebook collective ‘FIP Warriors’. Unfortunately for Australian cat lovers, the APVMA and Vet Boards eventually twigged to what was happening, and Border Force made it much more difficult to source GS-441524 and safely import it for veterinary use. Indeed, punitive warnings by the regulatory bodies were directed at veterinarians who facilitated the treatment of cats with FIP using GS-441524.

Ironically, the COVID 19 pandemic provided a novel solution to this problem. Gilead had developed remdesivir (GS-7374) as a drug for treating hepatitis C, Ebola, and human Coronavirus disease. Remdesivir is a prodrug of GS-441524, containing an extra chemical group (including a phosphate group) that is supposed to improve intracellular penetration (Figure 2B). Remdesivir (as the product Veklury) was given provisional registration (for a period of two years) by the TGA in July 2020 for treatment of SARS-CoV-2 infections in human COVID-19 patients.
This process of registration would normally have taken several years, but the severity of the COVID pandemic expedited the process by enabling reliance on preliminary clinical trial data. As remdesivir became a licensed human drug, it could be readily used off-label in veterinary applications, such as treatment of FIP in cats and kittens. This has circumvented problems with using GS-441524 - an unlicensed drug purchased on the black market, with the added issues of unproven efficacy, unknown purity, and consistency of product over time. Having said this, many people believe GS-441524 may actually be the superior drug, having several advantages including the ability to dose orally rather than parenterally.

BOVA Australia, an animal compounding pharmacy, has managed to secure reliable supplies of remdesivir to formulate and fill into vials suitable for treating cats. Studies in Australia have determined the shelf-life after reconstitution to be in excess of 7 days and confirmed efficacy in vitro against Coronavirus using tissue culture. Drug analytic purity is now regularly checked by HPLC. For the past 5 months, Australian veterinarians in every state have been using it for the treatment of clinical cases of FIP. Some of these cases have been new diagnoses, while others were cats that had already improved using black-market-sourced GS-441524 that had subsequently become unavailable. There has been a mixture of effusive and non-effusive cases, including some cats with ocular involvement (uveitis) and others with multifocal CNS disease. Based on approximately 100 cats treated between October 2020 and April 2021, remdesivir is proving to be highly effective at managing FIP infections. It is slightly easier to administer subcutaneously and seems a little less painful during injection than its active metabolite (GS-441524) with which it appears to be roughly equipotent.

The molecular weight of remdesivir is 603 g/mol, while the molecular weight of GS-441524 is 291 g/mol. At first glance, this might suggest that cats being treated with remdesivir require twice the dose of cats receiving GS-441524, but this does not account for the improved intracellular penetration of remdesivir compared to GS-441524. The suggested dose rate for remdesivir in human patients with COVID19 is a 200 mg loading dose intravenously (IV), followed by 100 mg IV daily. For a 70 kg human patient, this represents a daily dose of 1.3 mg/kg, so considering normal allometric scaling a dose of 5-10 mg/kg daily for a cat sounds in the right ballpark.

Remdesivir is provided by BOVA as a 100 mg vial which is reconstituted with 9 mL of sterile water for injection to give a 10 mg/mL solution (10 mL per vial after reconstitution). It is important to use water for injection and not sterile saline to avoid making the solution excessively hypertonic.

Currently, Australia is the only country where remdesivir is readily available via prescription for veterinary use via BOVA Australia. However, veterinarians in India, South Africa, and some parts of Europe, have also started accessing the drug using human supplies.

Recently, almost all veterinary cases of FIP are being treated with remdesivir therapy. If you see an effusion – tap it – as fluid is the best diagnostic sample. If you can see a granuloma in an organ, or if large lymph nodes are evident – do an FNA, make a smear, stain with RapidDiff and look for pyrogranulomatous inflammation in the absence of visible infectious agents (Figure 6).

Effusive disease is obviously much easier to diagnose as ascitic, pericardial or pleural fluid provides a convenient sample which can be examined cytologically and via fluid analysis and then subjected to immunofluorescence (IFA) for FIP antigen or reverse transcriptase PCR to detect FIP nucleic acid. IFA is performed at VPDMS, B14, University of Sydney (easily arranged through Vettomics, QML, ASAP, VetPath, Gribbles or IDEXX). Dry FIP is more problematic, as it usually requires a fine needle aspirate biopsy of pyrogranulomatous lesions in the liver, kidney, or abdominal lymph nodes. Occasionally, wet FIP cases can paradoxically have fluid specimens which are negative on IFA and/or PCR testing, yet the patient still likely has FIP as reflected by a favourable response to remdesivir therapy.
Treatment

We have been treating cats with FIP using remdesivir since October 2020, and our protocols are constantly evolving with experience. We try to avoid being too prescriptive in our recommendations, as our suspicion is that there is not a single protocol which suits all patients, and every case has unique considerations, including the size of the patient, whether the cat is still ‘happy’ and eating adequately, or is depressed and dehydrated. A key consideration is the emotional and financial strain, so a new element of the owner’s feature to mention is that the drug seems very safe, even in sick cats and kittens.

Receive consent, and the owner needs to make a commitment to a costly treatment course that spans a period of 3 months. For most clients, this represents an emotional and financial strain, and so cheaper options may work better for certain clients and in certain circumstances. Our view is that in many cases money is better spent on the antiviral therapy rather than on extensive monitoring.

Figure 7: Marked thickening of the iliacocolic region of a cat with so-called ‘focal FIP’, usually a form of non-effusive FIP. Photo supplied by Penny Tisdall.

One approach in newly diagnosed cats with severe disease, is to hospitalise the cat for the first 3–4 days of therapy while remdesivir is given intravenously (IV), effectively as a loading dose. Patients begin their treatment with remdesivir while they are receiving IV fluid therapy (use 2.4 mL/kg/hr; Hartmann’s solution or PlasmaLyte on the first day, and subsequently 0.45% NaCl and 2.5% dextrose containing 20 mmol KCl/L).

On day 1 of hospitalisation, remdesivir is administered at a high dose intravenously (10 mg/kg diluted to 10 mL with saline and given SLOWLY over 20–30 minutes or longer manually or using a syringe driver; in human patients it is given over 2 hours) to provide a loading dose to fill up the volume of distribution for the drug. This achieves rapid antiviral efficacy. Note that many cats can appear somewhat depressed for a few hours after the IV infusion of remdesivir, especially if it is given quickly. In human patients, remdesivir may cause inflammation-related reactions, including low blood pressure, nausea, vomiting, sweating, or shivering.

The benefit of starting therapy intravenously is that dehydration, if present, is corrected; you have IV access in case you need to administer other drugs (such as anticonvulsants). Importantly, once the IV catheter is secure, daily injections of remdesivir do not cause any pain or discomfort.

Cats with FIP treated with remdesivir typically improve markedly over the first 2.5 days during preliminary IV therapy. We have observed, however, that effusive cases and especially those that have presented with pleural effusion prior to treatment should be monitored closely, as the combination of the antiviral effect of the drug and greater than maintenance delivery of crystalloids can result in transient worsening of pleural effusion. This necessitates draining twice daily using a 19-gauge butterfly needle and a 3-way stop-cock (ideally using ultrasound guidance to find the best window for needle insertion). These ‘secondary’ pleural effusions can be fatal if not detected early and seem to occur in about 1 in 10 effusive cases treated with remdesivir. A further problem occasionally seen at this time is the development of neurological signs, including seizures. Our view is that this is not a drug effect per se, but rather the unmasking of subclinical CNS FIP. Such cats need careful observation, while the development of seizures mandates the use of anticonvulsant medication, such as midazolam (0.3 mg/kg IV) or alfaxan or propofol IV to effect, followed by levetiracetam (Keppra) (10–20 mg/kg PO every 8 hours). Phenobarbitone is a reliable anticonvulsant, however it has the propensity to increase the metabolism of many drugs, and until we better understand the pharmacokinetics and metabolism of remdesivir, it is probably safer to use levetiracetam in this setting. Some clinicians also administer dexamethasone or prednisolone as a one-off treatment to help settle down the CNS inflammation.

Although we generally advocate preliminary IV therapy, FIP patients that are still ‘happy’ and still eating well do not require high dose IV therapy at the outset and can instead be started with subcutaneous injections at 5-10 mg/kg/day, with the dose depending on whether they do not have anorexia or CNS disease. This, of course, is far less expensive as the cats or kittens do not need an infusion pump and kept in hospital; so, for clients who have financial constraints, this might be preferable way to begin therapy. One should be flexible, because preevis is the mother of invention. Some clever colleagues, like Jim Eucild, have developed a hybrid approach where kittens receive subcutaneous fluids as a bolus daily and remdesivir is injected into the fluid ‘lump’.

Subsequently, cats are given ONGOING subcutaneous injections of remdesivir, usually at a lower dose. For routine FIP cases – we generally have used 5-6 mg/kg once daily (SID) as remdesivir is thought to be roughly equivalent to GS-441524 in vivo (Niels Pedersen, personal communication). If there is prominent ocular involvement, we recommend 8 mg/kg SID by subcutaneous injection (SC4) and cats with neuro-logical FIP with CNS signs are given 10 mg/kg SID SC5. As well, cats with severe uveitis should be given topical corticosteroids (Pred Forte or Maxidex) for 2-3 days (no longer!) and atropine eye ointment. In a few atypical patients, interestingly, both Ragdoll cats, it was necessary to increase the dose of remdesivir to 15 mg/kg once a day to have the desired effect.

It is important that owners are counselled properly on how to optimally administer daily injections. Cats will find the injection less painful if the remdesivir solution is warmed, allowed to come to room temperature rather than be injected when cold from the fridge. Furthermore, teaching them simple tasks such as washing hands before and after injecting the cat (i.e., use a different needle to the one used to withdraw the drug from the vial) and using 22 or 23-gauge needles, will make the injections more tolerable. Alternately, veterinarians might prepare a full weeks’ worth of injections for the owner, to make things simple and sterile, in a box to be kept in the fridge, with a new syringe to be used every day.

In cats that continue to find the SC injections painful, we have used gabapentin orally (50 to 100 mg) and/or transmucosal or SC buprenorphine administered 30-60 min prior to the injection for sedation/anesthesia. The area to be injected can also be clipped so that topical EMLA cream can be applied 30 minutes prior to injection. In exceptional cases, we have placed a new cephalic catheter every 4-5 days to allow owners to give IV therapy rather than SC injections.

In situations when owners cannot afford a full course of therapy, or where injections are deemed to be too painful, we have used mefloquine (Larumin; 62.5 mg (1/4 tablet in a gelatin capsule) with food 2-3 times a week for an aver-age sized cat; obtained from a specialised com-pounder or a local pharmacy) after preliminary remdesivir therapy. Mefloquine has been shown to have an antiviral effect by Phillip McDonagh, Jacqui Norris, Merran Govendir and their colleagues at the Sydney School of Veterinary Science.7 This probably occurs by mefloquine usurping biochemical antiviral mechanisms usually utilised by FIP virus, a mechanism that has recently been shown also for the antiepilepsy drug clonazepam,8 and several other drugs in the pipeline.

The main advantage of remdesivir therapy for FIP is that the product we are using is subjected to quality assurance. It is only a matter of writing a prescription with the client’s name and address, the name of the patient and the dose to be administered, and BOVA can usually compound and provide vials to any veterinarian in Australia within 24-48 hours.

Currently, the cost of a 100 mg vial is $250 plus GST and postage ($280 typically at the practice), although it is possible that in time the cost will come down because of economies of scale. Of course, buying multiple vials at one time reduces postage and handling fees. We believe most owners will feel much more comfortable obtaining a product from a well-known Australian company, rather than sending money overseas and hoping that black-market drugs of unknown quantity will make it to Australia safely without being seized by customs.

Veterinarians wishing to explore this option, or with general questions about FIP case management, can e-mail Drs Richard Malik (richard.malik@sydney.edu.au), David Hughes (concordvets@concordvets.com.au), Gretta Howard (drgretta@gmail.com), Professor Jacqui Norris (jacqui.norris@sydney.edu.au), or Dr Sally Coggins (dr.sallyc@gmail.com) for advice in relation to diagnosis or therapy. Many Australian veterinarians, including the authors, have developed considerable expertise in the management of these cases. For example, Andrew Spammer in Adelaide has treated in 19 years over 10 cases with excellent results; the authors, can only practices and many internal medicine specialists have managed cases with both GS-441524 (historically) and more recently.
remdesivir, and so for vets who are hesitant in treating their own cases, they have the option of referral.

Clinicians that have accepted FIP case referrals from general practitioners include but are not limited to: QLD Rhet Marshall, Marcus Gunew, Alison Jukes, Rachel Korman; NSW Katherine Briscoe, Michael Linton, Randolph Baral, Melissa Catt; VIC - Carolyn O’Brien, Keshuan Chow, Amy Lingard; WA/Martine Van Boeijen and Murdoch University Veterinary Teaching Hospital; TAS Moira van Dorschard. All these clinicians (and likely more we are not aware of) are happy to accept cases for diagnostic work-up and therapy.

Sally Coggins, working with Lara Boland, Associate Professor Mary Thompson and Professor Jacqui Norris at Sydney School of Veterinary Science will be interested in treating cases with comprehensive diagnosis and monitoring provided gratis. This will form part of Sally’s PhD program, so you will be helping her progress her studies by referring cases. As a result of these studies, hopefully we will develop a better idea of how quickly the cats respond and exactly when therapy can be safely discontinued. Owners will still need to purchase remdesivir for therapy. This group also has an interest in treating cases with interferon-omega and therapy.

Most FIP cases do very well with GS-441524 or remdesivir therapy. Niels Pedersen has written a wonderfully comprehensive treatment document which he published on the Veterinary Information Network (VIN). It’s well worth a read – make sure you have a cup of coffee to keep you focussed! The article is pure gold. Some recommendations are provided on how to monitor cats during therapy. One of us (Malik) is not very protocol driven, so for him the key things to monitor are appetite, attitude, level of activity and changes on body weight and condition over time. Many clinicians (including Hugh & Howard) like to monitor haematology and serum biochemistry every month to ensure that all measurable abnormalities are improving, although this can be stressful for the patient and add to the cost of therapy. A compromise is to collect a few drops of blood to monitor PCV, total plasma protein (TPP) using refractometry and the colour of plasma – in that way one can determine is anaemia is improving, icterus is resolving and whether the reduction on gamma globulin concentrations is resulting in a lower TPP. Do not be concerned by transient increases in globulin concentrations during early therapy; when high protein effusions are absorbed, lots of extra immunoglobulins are dumped into the patient’s plasma. This can be common even up to week 8 of treatment but resolves by week 12. Remdesivir has the potential to cause kidney and liver toxicity, so keep an eye on the ALP, ALT, creatinine and SDMA, so be prepared to dose adjust or discontinue therapy should nephrotoxicity or hepatotoxicity occur.

What about the kitten with multifocal CNS disease, where CNS FIP is the most likely cause of the clinical signs? The traditional approach is serology (to try to exclude cryptococcosis and toxoplasmosis), a good dietary history and trial of thiamine to rule out thiamine deficiency, then MRI scans (Figure 10) and a CSF tap for fluid analysis and multiplex neuroPCR analysis. This approach is very expensive and there is also a finite risk from the anaesthesia and especially CSF collection. We have found that 3–5 days of IV or SC remdesivir therapy can be used as a cost-effective therapeutic trial in cats with likely CNS FIP and is a cost-effective alternative to the full diagnostic work-up which might cost $5–5,000, or more.

Likewise, if the choice is an exploratory laparotomy, biopsy of abnormal tissues, histology, and immunohistochemistry for FIP antigen to diagnose dry intraabdominal FIP before a 3–5-day trial of remdesivir, the latter might be considered to be better option in terms of both welfare and reduced cost. In most cats with non-effusive disease or nose dry intraabdominal FIP, trial of remdesivir, the latter might be considered to be better option in terms of both welfare and reduced cost. In most cats with non-effusive disease or nose dry intraabdominal FIP, trial of remdesivir might be considered. Note ependymitis and ventricular dilatation, especially around the 4th ventricle (white arrows). Figure 10: MRI scan from a cat with CNS FIP. Notice ependymitis and ventricular dilatation, especially around the 4th ventricle (white arrows).

Conclusions
In the past, a diagnosis of FIP was an intellectual exercise, so we could end a cat or kitten’s misery with the certainty of an accurate diagnosis. There is no unambiguous response to therapy, because of Niels Pedersen life-time studies of FIP, we are in a position to successfully treat perhaps 80 per cent of cats with FIP, if the client has sufficient finances. In too early to say how many of these will later recur.

There is a huge learning curve to the diagnosis and management of cases, but with effort, a good GP vet should be able to work with a diligent owner towards obtaining a clinical cure. The most important thing is to not place too many obstacles in the way of a committed owner, and to support them through the 12-week marathon treatment course, by helping them find the best way to medicate their patient. This might involve a sedative/analgesic regimen to help make the cat more tractable and prevent discomfort, having the client bring their cat to the clinic daily for remdesivir injections, managing hiccups along the way such as seizures and providing a payment plan that will let the treatment be affordable for a committed client.

Finally, the impact of COVID-19 on coronavirus research has been profound, and there are several very promising drugs in development that work on most coronaviruses. It is highly likely that some of these will be useful for treating FIP in cats, and some of these drugs can be given orally rather than parenterally. Interestingly we are aware of GS-441524-like drugs available in China and eastern Europe as a cost-effective capsule or tablet6 that is suitable for use in some cats with FIP – which might make therapy easier for many owners in the future.

References


Figure 11: Two cat with dry FIP after successful therapy. As a keen young vet told me by e-mail not so long ago – “this is why I did vet science!” The Devon Rex is called Skimbleshanks (the Railway cat) and is owned by Rose Jackson, a veterinary nurse. The Oriental cat “Milo” was treated by Jessica Green at VetHQ Darlinghurst