The Shifting Paradigm of Feline Infectious Peritonitis

New Diagnostics and Therapeutics

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KEYWORDS

• Feline infectious peritonitis • Feline coronavirus • GS-441524 • Antiviral therapy • RT-PCR

KEY POINTS

- Feline infectious peritonitis (FIP) is no longer a uniformly fatal disease, and treatment should be offered whenever feasible.
- Antiviral therapy targeting viral replication represents one of the most dramatic therapeutic revolutions in veterinary medicine.
- Reverse transcriptase polymerase chain reaction, when applied to appropriate samples, currently provides the highest level of antemortem diagnostic confidence.
- Clinical phenotypes of FIP differ significantly and require phenotype-specific diagnostic and therapeutic strategies.
- Both diagnostic testing and treatment protocols for FIP continue to evolve rapidly, requiring ongoing engagement with emerging literature.

INTRODUCTION

For decades, feline infectious peritonitis (FIP) has stood as one of the most feared diagnoses in small animal medicine. Despite its relatively high prevalence and unmistakable emotional impact, clinicians historically had little to offer beyond presumptive diagnosis and palliative care. Textbooks and review articles routinely described FIP as *invariably fatal*, reinforcing a sense of therapeutic nihilism that permeated clinical decision-making and client communication. Now we know that such framing is no longer scientifically or ethically justifiable.

The transformation of FIP from an untreatable condition to a disease with high rates of sustained remission represents one of the most remarkable paradigm shifts in veterinary medicine. The introduction of targeted antiviral therapies—initially

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Abbreviations	
FCoV	feline coronavirus
FECV	feline enteric coronavirus
FIP	feline infectious peritonitis
MF-ICC	multiplex fluorescent immunocytochemistry
RT-PCR	reverse transcriptase polymerase chain reaction

experimental and controversial, now increasingly mainstream–has altered prognosis in a manner comparable to landmark developments in human infectious disease medicine. In parallel, advances in diagnostic techniques, particularly molecular methods such as real-time reverse transcriptase polymerase chain reaction (RT-PCR) and refined immunocytochemical assays, have improved the clinician's ability to establish an antemortem diagnosis with confidence.

The shift has been so rapid that clinical practice, regulatory frameworks, and professional culture have struggled to keep pace. As a result, many veterinarians remain uncertain about how aggressively to pursue diagnosis or how confidently to recommend treatment. This article seeks to contextualize current knowledge, address lingering misconceptions, and frame FIP as a disease undergoing a once-in-a-generation transformation in veterinary medicine.

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CONCEPTUAL FRAMEWORK OF DISEASE

Feline Coronavirus and Disease Spectrum

Feline coronavirus (FCoV) infection is widespread in domestic cat populations worldwide, particularly in multi-cat environments. Most infections involve feline enteric coronavirus (FECV), a virus typically confined to the gastrointestinal tract and associated with mild (primarily diarrhea) or subclinical disease. Seroprevalence rates exceeding 80% to 90% are commonly reported in high-density feline populations such as shelters, breeding catteries, and multicat households.[1,2]

FIP does not arise directly from environmental exposure to a distinct pathogenic virus, but rather from *mutation of FECV within an individual host*, resulting in a virulent biotype capable of efficient replication within monocytes and macrophages.[3] This mutation confers the capacity for systemic dissemination and establishes the foundation for subsequent immune-mediated disease. Importantly, FIP is therefore an infectious disease but not a contagious disease in the traditional sense; it represents a unique host-virus interaction rather than simple viral transmission.

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Pathogenesis: Virus, Host, and Immune Dysregulation

The hallmark of FIP pathogenesis is macrophage-associated viral replication coupled with an aberrant immune response.[2,3] Viral mutations (most notably within the spike protein) facilitate entry into monocytes and macrophages, resulting in altered cell tropism and enabling systemic viral dissemination.[4–6] Once dissemination occurs, disease progression is driven less by direct cytopathic viral injury and more by immune-

mediated vasculitis and pyogranulomatous inflammation, which are the histologic hallmarks of FIP lesions.[3,7]

The balance between humoral and cell-mediated immunity plays a critical role in determining clinical phenotype. Cats mounting ineffective or dysregulated cell-mediated immune responses develop progressive systemic disease, whereas partial immune containment is associated with more localized, chronic, or noneffusive manifestations.[2,3] This understanding directly informed the rationale for antiviral therapy: ongoing viral replication is required to sustain immune activation and disease progression, and interruption of viral replication can halt, and in many cases reverse, the inflammatory cascade characteristic of FIP.[8,9]

Clinical Phenotypes of Feline Infectious Peritonitis

FIP is perhaps the most clinically pleomorphic disease known to feline medicine, which in this author's estimation, causes it to be simultaneously underdiagnosed and overdiagnosed in practice. Cases present as a nonbinary spectrum of noneffusive to effusive disease, and either of these forms can have ocular or neurologic involvement.

Effusive (Wet) Feline Infectious Peritonitis

Effusive FIP is characterized by accumulation of protein-rich effusions within one or more body cavities, most commonly the abdomen and less often in the pleural space. Effusions are typically straw-colored, viscous, and high in globulin concentration, with relatively low cellularity and low albumin content (leading to low A:G ratio). Clinical signs frequently include abdominal distension, dyspnea, persistent fever, anorexia, and lethargy.[10,11]

From a diagnostic standpoint, effusive FIP offers the advantage of accessible fluid for analysis and FCoV-specific testing. From a therapeutic perspective, effusive disease is often the most dramatically responsive to antiviral therapy, with rapid clinical improvement observed within days of treatment initiation.[12]

Noneffusive (Dry) Feline Infectious Peritonitis

Noneffusive FIP presents a substantially greater diagnostic challenge. In these cases, granulomatous or pyogranulomatous inflammation develops within organs such as lymph nodes, kidneys, liver, spleen, intestines, and lungs (as well as eyes and central nervous system–see further), without overt effusion. Clinical signs are frequently nonspecific and chronic, including weight loss, intermittent fever, anorexia, and organ-specific dysfunction.[11,12]

Historically, noneffusive FIP was underdiagnosed or diagnosed only at necropsy due to the lack of accessible lesions. For these reasons, noneffusive FIP has historically been thought to comprise a minority of cases (~20%–30%).[13] Advances in imaging, targeted fine-needle aspiration, and molecular diagnostics have improved diagnostic confidence, though false negatives remain more common than in effusive disease.[14] In the author's opinion, the true prevalence of noneffusive FIP is likely considerably higher than historical estimates because it is less likely to be considered as a clinical differential (and therefore tested for less often) and when testing is performed, less likely to appear positive by currently-available diagnostic tests.

Ocular and Neurologic Feline Infectious Peritonitis

Ocular and neurologic manifestations represent some of the most challenging forms of FIP. Ocular disease most commonly presents as anterior uveitis, often accompanied by keratic precipitates, hyphema, aqueous flare, or retinal perivascular changes, while neurologic involvement may include ataxia, seizures, cranial nerve deficits, altered

mentation, or others.[13,14] These phenotypes frequently coexist with noneffusive disease, but can be present along with effusions, and are thought to reflect viral persistence within immune-privileged sites, including the central nervous system and ocular tissues.[3] Both diagnosis and treatment are complicated by reduced drug penetration across the blood–brain and blood–ocular barriers, necessitating modified diagnostic approaches and higher or prolonged antiviral dosing strategies.[15,16]

OBTAINING A DIAGNOSIS

Traditional Clinicopathologic Indicators

Classic laboratory abnormalities associated with FIP include hyperglobulinemia, hypoalbuminemia, decreased albumin-to-globulin ratio (<0.8 is most inclusive, but it is often <0.4), nonregenerative anemia, lymphopenia, hyperbilirubinemia and elevated acute phase proteins (serum amyloid A and alpha-1 acid glycoprotein). These findings remain valuable components of clinical suspicion but lack specificity and cannot be used in isolation for diagnosis.[11,14]

Serologic testing for FCoV antibodies demonstrates exposure but does not distinguish between FECV infection and FIP, and is generally not considered useful. High titers may support suspicion in the appropriate context but should never be interpreted as diagnostic, and importantly, a low titer does not rule out FIP.[14]

Reverse Transcriptase Polymerase Chain Reaction: Central Role and Limitations

RT-PCR for FCoV RNA is perhaps the single most useful test FIP, but it is important to be aware of its limitations. When applied to appropriate sample types it can provide high specificity within the proper clinical context, but sensitivity varies considerably. Effusions yield the highest detection rates, followed by solid organ tissue aspirates. Peripheral blood samples are associated with very low sensitivity, while RT-PCR for FCoV on feces lacks utility entirely due to the very high prevalence of FECV shedding in healthy or non-FIP diseased cats.[17,18] Blood is no longer recommended at all due to the aforementioned low sensitivity combined evidence of poor specificity as well (a recent study showed equal amounts of FCoV RNA in non-FIP cats cohoused with cats with FIP).[17,19] Thus, it should be emphasized that *sample selection is the single most important determinant of RT-PCR utility.* The most appropriate sample types for FCoV RT-PCR are the following.

- Effusion fluid
- Solid tissue aspirates (eg, liver, kidney, spleen, LN, other) with organomegaly or imaging lesions
- Aqueous humor (suspect ocular FIP only)
- Cerebrospinal fluid (suspect neurologic FIP only)

Despite these requirements, RT-PCR currently represents the strongest antemortem diagnostic tool available when appropriately applied. Of note, there are commercially available *FIP mutation* assays, which seek to detect mutations associated with conversion from FECV to FIP virus, but these assays have not demonstrated diagnostic benefit over RT-PCR alone, and are generally not recommended.[20]

Sample selection is the single most important determinant of FCoV RT PCR utility.

Antigen Detection Techniques

Visualization of FCoV antigen inside of macrophages within the characteristic lesions (pyogranulomatous or granulomatous inflammation) has long been considered the

reference (*gold standard*) method for diagnosis of FIP. As an extension, various versions of immunocytochemical or immunofluorescence assays have been used, with variable reports of diagnostic accuracy.[11,14] Newer multiplex fluorescent immunocytochemistry (MF-ICC) assays aim to enhance specificity through simultaneous labeling of viral antigen and macrophage markers, improving interpretive confidence.[21] A recent study by the author and colleagues found that MF-ICC is complementary to other available tests for FIP (including PCR) and can be performed on similar sample types as an adjunctive tool.[22]

The Next Frontier in Feline Infectious Peritonitis: Better Diagnostic Tools

Thanks to the availability of safe and remarkably effective therapeutics, a better *silver bullet* diagnostic tool for FIP is badly needed to avoid missing FIP cases which could benefit from antiviral therapy and mistreatment of non-FIP disease (poor antimicrobial stewardship). An ideal test would be minimally invasive, highly sensitive and specific, affordable, and applicable across all FIP phenotypes. While no such test currently exists, there is great interest in this area, with improvements in RT-PCR assays,[23,24] development of serum biomarkers,[25,26] and application of machine learning models.[27,28] A cell tube block technique on effusion fluid with FCoV IHC has also been piloted recently.[29]

Finally, in recent years, empiric therapy with antiviral drugs has played an increasingly large role in the diagnostic algorithm. Concerns with this technique include that (1) clinical improvement can be coincidental to antiviral therapy, and this practice could promote indiscriminate use of powerful antiviral drugs; and (2) if cats respond sub optimally to antiviral therapy and subsequent definitive diagnostic testing is pursued, ongoing therapy can complicate interpretation of FCoV-specific tests like RT-PCR and antigen detection. Nevertheless, it is the opinion of this author that a *short course* (5–7 days total) of empiric therapy is a valuable and valid addition to the diagnostic toolkit, particularly where finances are limited or available diagnostic tests are inconclusive. This author and colleagues have published a streamlined FIP diagnostic algorithm which incorporates the concept of empiric therapy in **Fig. 1**. Important differential diagnoses and the best discriminating diagnostic tests for each are presented in **Table 1**.

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THERAPEUTICS: THE ANTIVIRAL ERA

Historical Perspective and One Health

Before the antiviral era, treatment of FIP focused largely on immunosuppression, anti-inflammatory therapy, and nonspecific supportive care, including corticosteroids, cytotoxic agents, and various adjunctive therapies aimed at dampening the host immune response.[2,13] While such interventions occasionally resulted in transient clinical improvement, particularly through reduction of inflammatory signs, no treatment reliably altered disease progression or long-term survival, and prognosis remained poor.[3,13] This paradigm shifted with the recognition that active viral replication persists throughout the course of disease and is required to sustain immune activation and lesion development, rendering FIP a rational target for direct-acting antiviral therapy rather than purely immunomodulatory approaches.[8,9] This shift has represented what the author considers the most significant breakthrough in feline medicine this

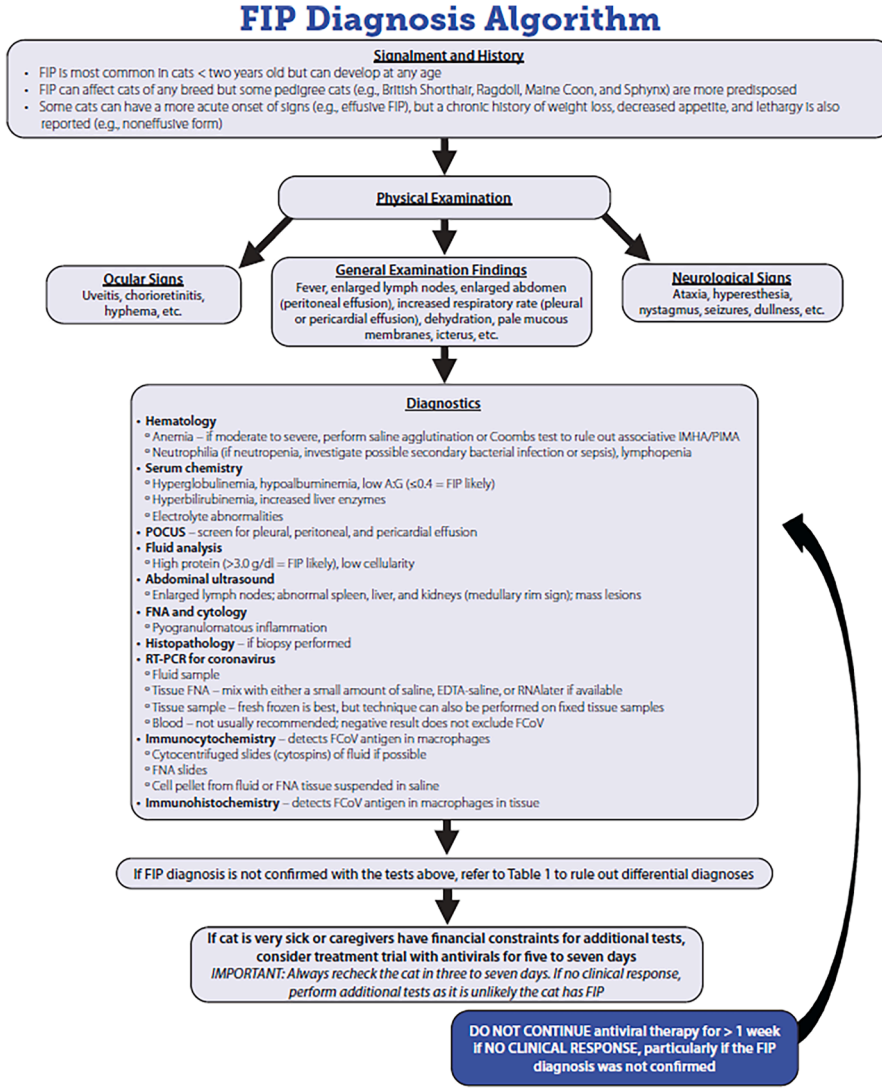


Fig. 1. Algorithm to assist clinicians with FIP diagnosis. (*Image courtesy* This image is the courtesy of Petra Černa, Sally Coggins, and Samantha Evans.)

century. And there are many layers of intrigue to this development, which are summarized by the following 4 main points.

1. Changing an essentially 100% fatal disease into ~85% curable with first-pass therapy using a single drug[30,31] is, by itself, outstanding. Breakthroughs to that magnitude are rare in medicine for any species, and especially for cats.
2. Apart from the occasional use of the acyclovir series in cats with feline herpesvirus infection,[32] this represents the first widespread use of antiviral drugs in veterinary medicine, and certainly the first highly successful antiviral therapy for a fatal viral disease. Thus, this phenomenon has opened the door to the 'antiviral era' in veterinary medicine, and there is great interest in expanding the use of these and other

Table 1
Common differential diagnoses for feline infectious peritonitis and best test(s) to differentiate from feline infectious peritonitis

Common Differential Diagnosis	Primary Specific Clinical Sign Overlapping with Feline Infectious Peritonitis	Best Test(s) to Differentiate from Feline Infectious Peritonitis
Heart Failure	Cavity effusion	Echocardiogram; auscultation with murmur
Pancreatitis	Abdominal effusion	AUS and fPLI
Bacterial sepsis	Cavity effusion	Fluid analysis (very high cell count with neutrophils) and culture*
Neoplasia	Cavity effusion	Fluid analysis with cytology; AUS/TXR (evaluating for primary mass)
Neoplasia	Organomegaly or masses	Cytology; biopsy
Toxoplasmosis	Neuro/ocular changes	IgM and IgG titers
Mycobacteriosis	Fever, lymphadenopathy, respiratory signs, uveitis; multiple masses	Cytology (demonstrating organisms); PCR; mycobacterial culture
Cholangiohepatitis	Fever, vomiting, and jaundice	Liver biopsy
Monoclonal gammopathy (myeloma-related disorder)	Hyperglobulinemia	Serum ($\pm$ urine) protein electrophoresis and immunofixation
Idiopathic uveitis	Uveitis	Negative FCoV PCR on aqueocentesis; no response to antivirals
Epilepsy	Seizures	Negative FCoV PCR on CSF; no response to antivirals
Glomerulonephritis	Renal lesions on imaging, fever, hyperglobulinemia, cavity effusions, and pododermatitis	Renal biopsy
Systemic fungal disease (Cryptococcosis; Histoplasmosis; Blastomycosis; Coccidiomycosis)	Multiple nodules/masses, ocular signs, and fever	Cytology (demonstrating organisms), fungal antigen tests; fungal titers
Inflammatory bowel disease	Vomiting, diarrhea	Intestinal biopsies
Chylothorax	Thoracic effusion	Fluid analysis with paired fluid/serum triglycerides
FeLV/FIV	Cytopenias, fever	Point of care test followed by ELISA or Western Blot (may require serial testing); bone marrow IFA

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Table 1
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Common Differential Diagnosis	Primary Specific Clinical Sign Overlapping with Feline Infectious Peritonitis	Best Test(s) to Differentiate from Feline Infectious Peritonitis
Primary bone marrow disorders (MDS, AML, ALL, and AUL, myelofibrosis, toxic myelosuppression, gelatinous transformation, and other)	Cytopenias, dysplastic morphology changes in peripheral blood	Blood smear path review; Bone marrow aspirate and core biopsy

Guidance for using this table: While FIP is not traditionally considered a diagnosis of exclusion, arriving at a presumptive diagnosis of FIP can certainly be assisted by ruling out common conditions in patients with overlapping clinical signs. If clinically feasible (considering both patient and caregiver factors), attempts should be made to rule out the conditions above prior to starting empiric drug therapy (aka *treatment trial*), unless the diagnosis has been confirmed via FCoV PCR or IHC. Note: Nearly all of these conditions (and FIP) may also present with the nonspecific signs of lethargy, weight loss, and hyporexia/anorexia.

Abbreviations: ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; AUL, acute undifferentiated leukemia; MDS, myelodysplastic syndrome.

antivirals to additional diseases of veterinary importance (such as recently for calicivirus-associated feline chronic gingivostomatitis[33]).

3. The manner in which this phenomenon has developed is incredibly unique, in that the first widespread use of antivirals came through lay owners treating their cats at home outside of veterinary supervision. This is a direct result of scientific publications lauding the success of these drugs in the absence of a commercially available product, causing cat caretakers to turn to unlicensed (*black market*) producers with the help of social media distribution and advice.[34] This may be the first and most prominent example of *citizen medicine* in the veterinary field, but it likely will not be the last.
4. Finally, the development of this therapy occurred in parallel, and mostly coincidentally, with the most globally significant human pandemic of the modern era: coronavirus disease of 2019 (COVID-19), caused by another coronavirus which is susceptible to largely the same antiviral compounds.[35] While it is true that remdesivir (prodrug form of the mainstay antiviral GS-441524 used in cats) was quickly repurposed for human clinical trials,[36] in this author's opinion, the lack of commercial development of these drugs for cats before the COVID-19 pandemic was a devastating missed opportunity for success from a *one health* perspective. It took 6 years from the first publication of GS-441524 success in cats with FIP (2018)[9] before the availability of legally-prescribable compounded GS-441524 in the United States and Canada (2024), and had it been put through the FDA pipeline and commercialized back in 2018, there could have been at least 2 years of additional data, resources, and manufacturing processes developed ahead of the recognition of the human pandemic (2020).

This FIP phenomenon has opened the door to the antiviral era in veterinary medicine, and there is great interest in expanding the use of antivirals to additional diseases of veterinary importance.

This may be the first and most prominent example of citizen medicine in the veterinary field, but it likely will not be the last.

GS-441524: Foundation of Contemporary Therapy

GS-441524 is an adenosine nucleoside analog that inhibits viral RNA-dependent RNA polymerase, effectively halting replication of FIP virus.[9] Clinical trials and real-world case series consistently demonstrate high rates of remission across all major FIP phenotypes (~85% in a recent systematic review)[31] when adequate dosing and treatment duration are employed. It has also been shown to be a safe drug with limited side effects, when used orally at the currently recommended dosages.[30] It is this author's opinion that the safety profile and remarkable efficacy of GS-441524 makes it the most successful antiviral drug ever used in veterinary medicine. GS-441524 therapy is the recommended first-line therapy for FIP, and should be initiated as soon as possible following a presumptive diagnosis of FIP.

GS-441524 is the recommended first-line therapy for FIP; it's safety profile and remarkable efficacy make it the most successful antiviral drug ever used in veterinary medicine.

Practical Dosing Considerations

Although protocols vary slightly among institutions, commonly accepted guidelines include.[30,31]

- Effusive or noneffusive FIP *without* ocular or neurologic signs: 15 mg/kg PO once daily
- Ocular FIP: 15 to 20 mg/kg PO once daily (or split into twice daily dosing)
- Neurologic FIP: 10 mg/kg PO twice daily (for a total of 20 mg/kg/day)

It is important not to decrease less than 15 mg/kg/day PO, necessitating frequent (ideally weekly) body weight measurement. As these cats are often young, growing animals, and they have often been chronically ill for weeks or months ahead of diagnosis, they often gain weight quickly with successful therapy. Thus, this author highly recommends at-home scales are purchased by caregivers to monitor weight change and keep up with a minimum of 15 mg/kg/day GS-441524 therapy.

The dosages earlier are for oral use, and oral therapy is recommended whenever possible. Although many of the early studies on this drug employed subcutaneous injection, that is no longer recommended for the following reasons: 1) oral therapy has been shown by many studies to be highly effective[30]; 2) injectable products are extremely acidic (average 1.30 pH)[37] leading high patient morbidity (painful reactions, open wounds, abscesses, severe ulceration, and others–see **Fig. 2**)[38]; and 3) this author has observed a handful of soft tissue sarcomas strongly suspected to represent injection site sarcomas secondary to 84 days of injected GS-441524 in cats. In cats unable to swallow oral medications because they are severely neurologic or moribund and lack a swallow reflex, the preference (in order) for treatment is as follows: 1) placement of an esophagostomy tube for enteral GS-441524 administration along with nutritional support; 2) administration of remdesivir (see further) IV; 3) administration of compounded GS-441524 (limited availability in North America) at a dosage of 8 mg/kg/day. Once a swallow reflex has returned, cats should be immediately converted to oral GS-441524 therapy.

Treatment duration has typically been a minimum of 84 days (12 weeks), with extension or dose escalation as clinically indicated. Emerging evidence suggests that 42 days (6 weeks) can be equally effective in effusive FIP cases,[39] though at present, this author and colleagues generally still recommend the full 84 days where possible.



Fig. 2. Severe injection site reactions in 2 cats receiving subcutaneous injections of GS-441524. The morbidity of highly acidic (average 1.30 pH) injectable formulations is a primary reason for the recommendation of oral GS-441524 whenever possible. (*Image Courtesy* This image is the courtesy of Nicole Jacque.)

Clinical improvement is often rapid, serving both as therapeutic confirmation and retrospective diagnostic support.

Remdesivir

Remdesivir, the parent prodrug of GS-441524, has demonstrated comparable efficacy, particularly when administered parenterally during induction followed by oral GS-441524.[40] Remdesivir is available in the Unitd States through off-label prescription of the human COVID-19 product (Veklury), but is frequently cost prohibitive (author observation).

Molnupiravir and EIDD-1931

Molnupiravir (also known as EIDD-2801) and its active metabolite EIDD-1931 are nucleoside/nucleotide analogs which exert antiviral effects through lethal mutagenesis. These agents have shown efficacy both as primary therapy[41–44] and as rescue therapy[42,45] in cases of relapse, expanding the therapeutic armamentarium available to clinicians. However, despite their promising efficacy, molnupiravir/EIDD-1931 are considered second-line therapy (less preferred than GS-441524) for the following reasons: (1) the mechanism of action (lethal mutagenesis) has led to concerns regarding viral mutagenesis potentially leading to more virulent or drug-resistant strains of FCoV as has been seen in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[46]; (2) they appear to have a somewhat lower safety profile with increased side effects (vomiting, diarrhea, neutropenia, hyporexia, and cartilage/skin/hair changes),[30,44]; (3) they are teratogenic and unsafe for pregnant women, necessitating gloves and increased caution with young or pregnant animals[30]; and (4) there are potentially slower response times compared with GS-441524.[42] Molnupiravir and EIDD-1931 are often less expensive, however, and this author considers them acceptable alternatives if GS-441524 is unavailable or cost prohibitive, or for cases of relapse and suspected resistance to GS-441524 (though true viral resistance has yet to be documented).

Molnupiravir and EIDD-1931 are considered second-line therapies for FIP.

Protease Inhibitors: GC376 and Nirmatrelvir

GC376, a 3C-like protease inhibitor, was the first drug ever used to cure FIP under both experimental and naturally-acquired conditions.[8,47] It has been undergoing the FDA approval process for many years under license by biotechnology company Anivive Lifesciences; however, this drug is not currently available for legal prescription in North America. From the limited data available, monotherapy with GC376 does not appear to be as effective as GS-441524, as it was shown to reverse FIP in only 7 out of 20 cats with naturally-acquired FIP.[47] Nirmatrelvir (Paxlovid) is another 3C-like protease inhibitor, which has also been successfully used against FCoV in vitro, but the use in cats is currently limited to anecdotal evidence.[16,30] Combination therapy with protease inhibitors alongside nucleoside analogs may enhance efficacy or shorten treatment duration,[48] and is a promising area of further investigation.

DISCUSSION: IMPLICATIONS OF A RAPIDLY EVOLVING LANDSCAPE

The transformation of FIP from a fatal diagnosis to a treatable disease has occurred with unusual speed, outpacing formal consensus statements, regulatory adaptation, and, in many cases, changes in clinician perception. This disconnection between emerging evidence and embedded clinical culture has significant implications for how FIP is approached in everyday practice. This author contends that FIP now represents a *threshold disease*: one in which early recognition and decisive action markedly alter outcome, and in which diagnostic uncertainty should no longer default to therapeutic nihilism. Historically, the absence of effective treatment rendered aggressive diagnostic pursuit ethically ambiguous. In contrast, the availability of safe and effective antivirals has reframed diagnosis as a critical gateway to survival.

One of the most persistent challenges in FIP management remains the absence of a single, universally definitive antemortem test. However, requiring definitive proof of FIP (traditionally through histopathology with IHC) is no longer appropriate in a disease for which delaying treatment may directly worsen prognosis. RT-PCR and immunocytochemistry techniques each carry inherent limitations. False negatives occur, particularly in noneffusive and neurologic/ocular disease. Nevertheless, when these modalities are applied to appropriate samples and interpreted alongside clinical findings, they provide a level of diagnostic confidence sufficient to justify treatment initiation in the majority of cases. In practical terms, this represents a shift from seeking absolute certainty to accepting *clinically actionable probability*, a transition well-recognized in other areas of veterinary and human medicine. Importantly, rapid clinical response to antiviral therapy often provides retrospective support of the diagnosis, but is not definitive proof of FIP.

LEGAL AND REGULATORY LANDSCAPE IN NORTH AMERICA

The regulatory environment surrounding antiviral therapy for FIP has evolved significantly, particularly in North America. The allowance of compounded GS-441524 formulations under FDA enforcement discretion has meaningfully reduced reliance on unregulated products and has greatly restored veterinary oversight to the therapeutic process. Similarly, availability of remdesivir, molnupiravir, and other antivirals through legal pathways has improved therapeutic access and patient outcomes. Nevertheless, the unregulated (*black market*) ecosystem persists in abundance, sometimes threatening patient welfare, owner finances, and trust in veterinary institutions. Moreover, legal access remains variable by region. This author argues that continued advocacy by the veterinary profession is warranted, not only to improve access but also to

ensure quality control, appropriate dosing and wholistic treatment guidance, and pharmacovigilance. There should be particular emphasis on improved veterinary education on this topic and immediate drug access through stocking of legally-sourced antiviral medications in feline practices and urgent care centers across North America and beyond.

ANTIVIRAL STEWARDSHIP AND RESISTANCE

As antiviral therapy becomes more widespread, concerns regarding viral resistance merit consideration. Development of antiviral resistance within FCoV strains has not been conclusively documented to date. Cases that are clinically refractory to GS-441524 or related compounds appears uncommon, particularly when appropriate dosing and treatment duration are maintained. However, lessons from human medicine underscore the importance of stewardship (including appropriate case selection), combination strategies, and adherence to evidence-based protocols. This author strongly supports ongoing investigation into combination antiviral therapy, dose optimization, and treatment shortening strategies—not only as a means to reduce cost and patient morbidity, but to preserve long-term efficacy across populations.

Ongoing investigation into combination antiviral therapy, dose optimization, and treatment shortening strategies are critical not only as a means to reduce cost and patient morbidity, but to preserve long term efficacy across populations.

FUTURE DIRECTIONS

Despite extraordinary advances in recent years, substantial gaps remain in foundational knowledge and practice. Priority areas for future FIP research include.

- Development of a single or small collection of accurate, minimally-invasive, and affordable antemortem diagnostic test(s) which can effectively distinguish FIP from non-FIP disease, and ideally, predict treatment outcome
- Development of standardized monitoring protocols for treatment response and relapse prediction
- Evaluation of combination antiviral regimens and resistance mitigation strategies
- Understanding of barriers to the use of legally-sourced medication and seeking veterinary care for FIP
- Evaluating the potential for immunomodulatory or other effects of these antiviral drugs beyond suppression of viral replication
- Expanding antiviral therapy to other viral diseases of veterinary importance

SUMMARY

Feline infectious peritonitis has undergone one of the most dramatic paradigm shifts in veterinary medicine. Once regarded as an inevitable death sentence, FIP is now a treatable disease with high rates of sustained remission when diagnosed early and treated appropriately. This transformation has been driven by the advent of direct-acting antiviral therapies, most notably GS-441524. While challenges remain, particularly surrounding regulatory access and diagnostic confidence, the current evidence clearly supports a proactive, treatment-oriented approach. As diagnostic and therapeutic strategies continue to evolve, clinicians must remain engaged with emerging data and prepared to reassess long-held assumptions. In doing so, the profession

can ensure that the revolution in FIP management translates into meaningful, life-saving outcomes for feline patients.

As diagnostic and therapeutic strategies for FIP continue to evolve rapidly, clinicians must remain engaged with emerging literature.

CLINICS CARE POINTS

- Treat suspected feline infectious peritonitis (FIP) as a medical emergency rather than a terminal diagnosis.
- Prioritize complete fluid analysis with A:G ratio in effusive cases, and reverse transcriptase polymerase chain reaction (RT-PCR) on tissue aspirates for noneffusive cases.
- Initiate antiviral therapy promptly when clinical suspicion is high, even in the absence of diagnostic certainty.
- For cases lacking positive confirmatory testing (RT-PCR, immunocytochemistry, or histopathology), do not continue antiviral therapy beyond 1 week without observing clinical improvement, since the likelihood of non-FIP disease is high.
- Oral GS-441524 is the recommended first-line therapy for FIP in all cats with a competent swallow reflex; oral molnupiravir and EIDD-1931 are best reserved for second-line therapy.
- Recheck weight at least every 1 to 2 weeks to ensure the dosage of GS-441524 never decreases to less than 15 mg/kg/day.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the authors used Generative AI. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

DISCLOSURE

The author declares no conflicts of interests related to this article.

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