Challenging and Refractory FIP Cases

Feline infectious peritonitis (FIP) is an immune-mediated systemic vasculitis and granulomatous inflammatory disease triggered by macrophage-tropic mutant strains of feline coronavirus (FCoV). According to current literature, FIP pathogenesis should be evaluated through the integration of three major axes:

- Viral replication and tissue dissemination,
- Dysregulated immune–inflammatory response (notably neutrophilia with lymphopenia and emergency granulopoiesis),
- Oxidative and nitrosative stress resulting from the collapse of host antioxidant defenses.

In the treatment of FIP, a subset of cats—particularly those diagnosed late or previously treated for FIP—may exhibit inadequate, partial, or transient responses, with disease progression continuing despite virological suppression. This clinical entity is referred to as refractory FIP. Refractory disease does not represent failure of antiviral therapy per se, but rather the clinical expression of irreversible host injury, immune exhaustion, and advanced redox–vascular collapse.

While antiviral agents rapidly suppress the first pathogenic axis, the processes encompassed by the second and third axes—including redox failure, endothelial injury, microthrombosis, and organ dysfunction—may critically limit therapeutic success. Consequently, FIP should no longer be regarded solely as a disease of viral burden, but rather as a disorder of immune dysregulation. Evidence derived from field cases, clinical observations, and experimental studies indicates that, once refractory disease has developed, viral replication is no longer the primary determinant of morbidity, and tissue damage becomes a self-perpetuating process that worsens prognosis.

Pathophysiological Basis of Refractory FIP Syndrome

Irreversible Tissue Injury Prior to Antiviral Initiation

Feline infectious peritonitis (FIP) is frequently diagnosed at an advanced stage, at which point granulomatous lesions, vasculitis, and organ-specific damage (including hepatic degeneration, renal papillary necrosis, and central nervous system granulomas) are already well established. Viral suppression alone cannot reverse the following pathological processes:

- Granuloma-associated parenchymal destruction
- Fibrosis
- Chronic vasculitis and microthrombus formation
- Neuronal loss and glial scarring in neurological FIP

FIP-associated lesions reflect not only viral presence but also chronic immune-mediated tissue injury (Kipar & Meli, 2014). In cats in which antiviral therapy is initiated after critical organ reserve has been lost, the pattern of early clinical improvement followed by deterioration, despite intensified immunosuppression and dose escalation, represents a typical manifestation of the refractory disease state.

Endothelial Dysfunction, Vasculitis, and Microthrombosis

FIP is fundamentally a vascular disease. Histopathological findings frequently demonstrate immune complex–mediated vasculitis, capillary leakage, fibrin deposition, and microthrombus formation (Tasker, 2023; Kipar & Meli, 2014; Boudreaux, 1990). Özbek et al. (2022) reported elevated homocysteine and nitric oxide (NO) levels in cats with FIP, indicating endothelial stress and nitrosative imbalance. Consequently, even when viral RNA replication is effectively suppressed, the downstream consequences of severe microvascular collapse may substantially contribute to the development and persistence of the refractory clinical phenotype.

Immune Exhaustion and Failure of Adaptive Immunity

FIP'li The characteristic neutrophilia (often with a left shift), marked lymphopenia, elevated levels of acute-phase proteins such as serum amyloid A (SAA) and α1-acid glycoprotein (AGP), along with a low albumin/globulin (A/G) ratio secondary to hyperglobulinemia, reflect the core immunopathological mechanisms of feline infectious peritonitis (FIP) (Kipar & Meli, 2014; Hazuchová et al., 2017). Persistent lymphopenia—particularly involving CD4+ and CD8+ T-cell populations—together with cytokine predominance of IFN-γ, IL-6, and TNF-α, is indicative of a macrophage-dominant disease process, as macrophages represent the primary cellular targets of FIP virus (FIPV). **Infected macrophages not only perpetuate inflammation but also actively impair the restoration of adaptive immune responses** (Dewerchin & Nauwynck, 2021; Takano et al., 2007). **Under these conditions, even when antiviral therapy effectively suppresses viral replication, the adaptive immune recovery phase required for resolution of inflammation, immune-mediated clearance of infected macrophages, and regression of granulomatous lesions fails to be engaged.** Clinically, this manifests as transient responsiveness to corticosteroids but persistent antiviral-resistant inflammatory cycles, sustained elevation of acute-phase proteins, ongoing tissue damage, and ultimately the emergence of one of the central components of refractory FIP syndrome. The literature supports that such adaptive immune failure is a defining feature of poor-prognosis forms of FIP (Zwicklbauer et al., 2023; Hartmann, 2020).

Redox Collapse and Oxidative–Nitrosative Injury

Multiple studies have demonstrated that feline infectious peritonitis (FIP) is characterized by severe oxidative stress and depletion of antioxidant capacity at both systemic and tissue levels. Tecles et al. (2015) reported a marked reduction in paraoxonase-1 (PON1) activity and total antioxidant capacity (TAC) in cats with FIP, highlighting these findings as biochemical evidence of antioxidant defense collapse in the disease. Kayar et al. (2015) further showed that even FCoV-seropositive cats without overt clinical FIP exhibit increased malondialdehyde (MDA) levels and total oxidant capacity (TOC), indicating that oxidative burden begins early, well before the onset of clinically apparent disease.

In cases of neurological FIP, elevated levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG)—a marker of oxidative DNA damage—have been detected in cerebrospinal fluid (Başţan et al., 2025). In line with experimental coronavirus encephalitis and neuroinflammation literature, these findings indicate that redox imbalance also develops at the level of the central nervous system (Yamato et al., 2021).

When antioxidant defenses collapse:

- **Activated macrophages generate excessive reactive oxygen species (ROS)**
- **Endothelial cells sustain oxidative injury**
- **Erythrocyte membrane deformation occurs, impairing oxygen transport**
- **Microvascular perfusion deteriorates**
- **A self-perpetuating oxidative feedback loop is established**

Comorbidities

FIP Feline infectious peritonitis (FIP) is fundamentally a severe redox-disruptive disease. The macrophage tropism of FCoV, together with sustained release of IL-1β, IL-6, and TNF-α and increased nitric oxide production, drives excessive generation of reactive oxygen species (ROS) and rapidly depletes host antioxidant defenses, particularly paraoxonase-1 (PON1), total antioxidant capacity (TAC), and the GSH/GSSG redox balance (Tecles et al., 2015; Giordano et al., 2021).

Concurrently, comorbid conditions such as hepatic disease, chronic kidney disease, feline leukemia virus (FeLV) infection, diabetes mellitus, and pancreatitis are themselves characterized by profound mitochondrial dysfunction, lipid peroxidation, increased ROS production, accumulation of advanced glycation end products (AGEs), and glutathione depletion (Ingwersen et al., 2020; O'Brien et al., 2019; Gilor & Graves, 2021; Oppliger et al., 2020). Consequently, in cats in which **FIP coexists with such comorbidities, antioxidant capacity collapses rapidly, and the threshold for systemic inflammation is markedly lowered. Clinically, even when these cats exhibit an initial response to antiviral therapy, they tend to demonstrate partial rather than complete recovery, with easy destabilization, frequent relapses, persistent inappetence, muscle wasting, fluctuating CRP/SAA profiles, and progressive weight loss.** The literature clearly supports that oxidative stress and mitochondrial injury represent a shared pathological denominator between FIP and its comorbid conditions, and that their convergence weakens antiviral responsiveness and narrows the therapeutic window for recovery (Kipar & Meli, 2014; Dewerchin & Nauwynck, 2021).

Determinants of Refractory FIP

1. Pharmacokinetic/Pharmaceutical Determinants and the Dose–Exposure Relationship

Pharmacokinetic and pharmaceutical factors represent one of the dominant contributors to refractory FIP cases. Inadequate initial dosing, inappropriate routes of administration, poor bioavailability, dose loss due to tablet or capsule splitting, or failure to adjust dosing to rapidly changing body weight can all result in subtherapeutic drug exposure, thereby compromising effective viral clearance (Pedersen et al., 2018; Krentz et al., 2021).

Neurological and ocular FIP cases, in particular, require higher exposure thresholds because of pharmacokinetic limitations imposed by the blood–brain barrier (BBB) and blood–ocular barrier, and therefore constitute the slowest-responding subpopulation in clinical practice. Accordingly, data from large clinical cohorts and pharmacokinetic models consistently demonstrate that, in **the vast majority of refractory cases, the primary determinant is not antiviral resistance but insufficient antiviral exposure**. Pharmacokinetic studies have shown that the **BBB reduces CNS penetration of both GS-441524 and remdesivir-derived metabolites by approximately 80–90%** (Dickinson et al., 2020; Pedersen et al., 2019). **In contrast, molnupiravir (EIDD-2801) and its active metabolite β-D-N4-hydroxycytidine (NHC) demonstrate substantially superior CNS penetration due to their low molecular weight** (259 Da) and the fact that NHC is not a P-glycoprotein (P-gp) substrate (Chang et al., 2023). As a result, NHC is not efficiently removed from the CNS via active efflux transporters at the BBB (FitzGerald et al., 2022), conferring a lower risk of transporter-mediated extrusion. Experimental studies in murine, ferret, and SARS-CoV-2 models have demonstrated that NHC achieves cerebrospinal fluid and brain tissue concentrations corresponding to approximately 30–50% of plasma levels (Painter et al., 2021; Zhou et al., 2021). The literature therefore supports that enhanced BBB penetration is one of the principal reasons why molnupiravir is associated with faster clinical responses and improved neurological recovery, particularly in encephalitic and meningoencephalitic forms of FIP.

2. Viral Factors: Spike Fusion and Macrophage Tropism

Minimal amino acid substitutions within the spike protein and the viral replication complex of FIP virus (FIPV) represent small but functionally significant mutations capable of altering key processes such as RNA-dependent RNA polymerase (RdRp) binding, spike-mediated membrane fusion, and macrophage tropism (Brown et al., 2009; Chang et al., 2012; Licitra et al., 2013). **Mutant strains that induce large granulomatous lesions within the intestinal lymph nodes and colonic/mesenteric structures enhance macrophage tropism, thereby promoting more aggressive granulomatous pathology.** These variants are associated with delayed viral clearance, particularly in colonic tissue, mesenteric lymph nodes, and abdominal granulomas (Chang et al., 2012; Brown et al., 2009). Similarly, minor variations within the FCoV/FIPV replicase complex may generate viral variants with reduced susceptibility to RdRp inhibitors such as GS-441524 and remdesivir, as demonstrated in SARS-CoV and murine hepatitis virus (MHV) models (Agostini et al., 2018; Kokic et al., 2021).

3. Host Factors: Hyperglobulinemia, Immune Complexes, and Granulomatous Inflammation

Hyperglobulinemia, a high immune complex burden, and markedly low albumin/globulin (A/G) ratios promote a self-sustaining inflammatory state, even in the presence of effective antiviral suppression. This phenomenon is particularly pronounced in granulomatous and hyperimmune forms of FIP (Kipar & Meli, 2014; Hazuchová et al., 2017). Clinically**, cats presenting with poor baseline condition often exhibit delayed antiviral responses due to multiorgan injury, mitochondrial dysfunction, and endothelial impairment.** Abdominal granulomas, especially those involving the mesenteric lymph nodes and intestinal wall, markedly reduce tissue diffusion of systemically administered drugs because of dense inflammatory architecture and poor vascularization. The fibrous capsule and **high macrophage density within granulomatous lesions further limit antiviral penetration and activity** (Kipar & Meli, 2014). Consequently, **these barrier regions are characterized by low local antiviral exposure, resulting in subtherapeutic tissue drug concentrations despite adequate plasma levels. As a result, viral replication is suppressed more slowly, inflammatory processes persist for longer durations, and the clinical course adopts a slow-responding or refractory phenotype.**

4. Contribution of Lesions Located in Low Tissue-Penetration Sites to Refractory FIP

Refrakter A substantial proportion of refractory or slow-responding FIP cases are associated with lesions located in anatomical sites with inherently limited antiviral tissue penetration. In such regions, therapeutic plasma concentrations may be achieved, yet intratissue drug levels remain insufficient to ensure effective viral suppression. This phenomenon is particularly relevant for lesions within the central nervous system (CNS), intraocular tissues, and large granulomatous masses. In neurological FIP, the blood–brain barrier (BBB), and in ocular FIP, the blood–retinal barrier, severely restrict antiviral diffusion into uveal and neural tissues. Consequently, even when systemic plasma concentrations fall within the therapeutic range, intraocular and CNS antiviral concentrations may fail to reach effective levels (Maggs et al., 2013; Pedersen et al., 2019). Both Pedersen et al. (2019) and Dickinson et al. (2020) have identified these compartments as low-penetration sites for both GS-441524 and remdesivir, highlighting their role in delayed response and refractory disease patterns.

Clinical Phenotypes of Refractory FIP Syndrome

Primary Non-Responders (Non-responsive from Treatment Initiation): These cats exhibit no early signs of clinical improvement following initiation of antiviral therapy. This phenotype is typically driven by severe baseline organ failure, profound redox collapse, pharmacokinetic inadequacy (including impaired absorption, suboptimal dosing, or poor drug quality), severe CNS and/or ocular involvement, and intrinsically low tissue penetration. Such cases represent true refractory disease, in which neither host resilience nor therapeutic intervention is sufficient to overcome the momentum of disease progression.

Late-Stage Multiorgan Refractory Cases: These cases are characterized by progressive azotemia, hyperbilirubinemia, refractory effusions, persistent neurological deficits, and cachexia, despite ongoing antiviral therapy. Importantly, this phenotype reflects host failure rather than antiviral failure, representing an advanced stage in which irreversible systemic damage dominates the clinical course.

Diagnostic Indicators of Refractory Progression in FIP

Hematological and Biochemical Markers

- Persistent A/G ratio < 0.5
- Failure of lymphopenia to show a recovery trend
- Rising bilirubin levels despite virological improvement
- Lack of improvement in ALT/AST levels
- Worsening azotemia
- Persistently elevated SAA and/or AGP levels

These markers collectively indicate ongoing systemic inflammation and vascular injury, despite antiviral intervention.

Clinical Warning Signs

- Sudden clinical deterioration after initial improvement
- Recurrence of fever or anorexia
- Progressive jaundice
- Neurological deterioration
- Cachexia or failure to gain weight
- Respiratory distress (associated with microthrombus formation)

Treatment Strategy in Refractory Cases

In refractory FIP cases, the issue is not failure of antiviral agents per se, but rather the inability of the host to recover once pathological damage exceeds physiological repair capacity. Therefore, contemporary FIP management should be approached as a three-layered therapeutic strategy:

1. **Antiviral therapy → suppresses viral replication**
2. **Redox/antioxidant support → protects tissues from ongoing oxidative damage**
3. **Immune and vascular stabilization → sustains host viability**

If these three components do not function in a coordinated and synergistic manner, the disease course may evolve into a refractory phenotype. In some neurological cases, the disease may transition into a chronic course requiring prolonged antiviral therapy.

1. Inadequate Drug Exposure

- **Insufficient dosing** (e.g., initiation at **8–10 mg/kg**)
- Inconsistent or low bioavailability (improper tablet splitting, absorption impairment)
- **Failure to adjust dose according to changes in body weight**
- **Premature discontinuation of therapy** leading to **silent residual viral replication**

A substantial proportion of refractory or post-treatment recurrent FIP cases are not truly antiviral-resistant. Current literature indicates that, in most of these cases, inadequate drug exposure—including subtherapeutic dosing, inappropriate dosing intervals, incorrect route of administration or poor bioavailability, and early termination of therapy—represents the primary determinant of treatment failure (Pedersen et al., 2018; Krentz et al., 2021).

Neurological and ocular FIP cases, in particular, are pharmacokinetically disadvantaged because therapeutic exposure thresholds are higher than in other organ systems and because central nervous system barriers limit drug penetration (Dickinson et al., 2020; Maggs, 2013). Coggins (2023) reported relapse in 3 of 28 cats treated with remdesivir/GS-441524; these cats subsequently achieved remission following re-treatment at doses of 15–20 mg/kg. Similarly, Jones (2021) and Gokalsing (2024) emphasized an association between low initial dosing or premature treatment cessation and disease relapse. In a large cohort study involving 307 cats, Taylor et al. (2023) reported relapse in 15 cats (45.5%) during treatment and 18 cats (54.5%) after treatment completion, with dosage, route of administration, and treatment duration identified as key contributing factors. Collectively, these findings support the conclusion that the majority of refractory presentations reflect insufficient antiviral exposure rather than true biological resistance.

2. Critical Importance of Early Diagnosis and Treatment

Refractory FIP cases are strongly associated with delayed diagnosis. Early recognition, prompt initiation of antiviral therapy, and close monitoring of the following parameters are therefore essential:

- Complete blood count (CBC), particularly an elevated neutrophil-to-lymphocyte ratio and absolute lymphocyte count
- Albumin/globulin (A/G) ratio
- Redox stress markers, including bilirubin, malondialdehyde (MDA), and SAA/AGP
- Renal and hepatic function parameters

3. Antiviral Dose Escalation Alone Is Insufficient

In true refractory FIP cases, aside from those in which subtherapeutic dosing is corrected and a favorable response is achieved, simply increasing the antiviral dose is insufficient to rescue the patient. At this stage, disease pathology and prognosis are no longer primarily driven by viral replication, but rather by host tissue damage, immune dysregulation, and irreversible organ injury.

4. Redox Modulation and Antioxidant Support

The pronounced oxidative stress and depletion of antioxidant defenses observed in feline infectious peritonitis (FIP) (Tecles et al., 2015; Kayar et al., 2015) establish a self-perpetuating redox cycle that sustains macrophage activation and endothelial dysfunction. At this stage, multiple studies have demonstrated that various phytochemical compounds are capable of disrupting this cycle by activating the three most critical biochemical pathways governing endogenous antioxidant defense and cellular stress responses: the Nrf2/Keap1–ARE, AMPK, and SIRT1 axes (Dai et al., 2019; Dajas, 2012; Lambert et al., 2010; Baur & Sinclair, 2006; Zhao et al., 2018; Marin-Neto et al., 2020).

The Nrf2/Keap1–ARE Axis (Primary Antioxidant Defense Pathway): Nrf2 (nuclear factor erythroid 2–related factor 2) is the principal transcription factor protecting cells against oxidative stress. Under basal conditions, Keap1 sequesters Nrf2 in the cytoplasm and targets it for proteasomal degradation. Upon activation, Nrf2 translocates to the nucleus and binds to antioxidant response elements (AREs) within DNA, inducing the transcription of key antioxidant and cytoprotective enzymes, including heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and enzymes involved in glutathione (GSH) synthesis. Activation of this axis enables cells to repair oxidative damage and reduce reactive oxygen species (ROS) accumulation. In high-ROS conditions such as FIP, the Nrf2 pathway becomes functionally suppressed. Phytochemicals can reactivate Nrf2 signaling, thereby contributing to the recovery of the vulnerable host. Curcumin has been shown, in both in vitro and in vivo models, to enhance nuclear translocation of Nrf2, leading to increased expression of HO-1, NQO1, SOD, and GPx (Dai et al., 2019; Yang et al., 2017). Quercetin similarly strengthens Nrf2 activation, reducing levels of the lipid peroxidation marker malondialdehyde (MDA) while augmenting antioxidant enzyme capacity (Dajas, 2012). Epigallocatechin gallate (EGCG) induces SOD, GPx, and CAT through Nrf2 signaling, thereby restoring redox balance by limiting ROS accumulation (Lambert et al., 2010).

The AMPK Axis (Energy-Sensing Anti-inflammatory Pathway): AMP-activated protein kinase (AMPK) is the cell's most critical metabolic energy sensor. Under conditions of energy depletion or cellular stress, AMPK activation suppresses inflammation, enhances fatty acid oxidation, reduces ROS generation, and secondarily activates Nrf2 signaling. In FIP, macrophages remain locked in a hypermetabolic, proinflammatory M1 phenotype; AMPK activation can promote a shift toward the anti-inflammatory M2 phenotype.

Phytochemicals such as berberine, curcumin, and resveratrol are potent AMPK activators. Berberine, in particular, has been shown to attenuate both inflammation and oxidative stress in macrophages by activating the AMPK–Nrf2 signaling interface (Marin-Neto et al., 2020). Additionally, curcumin and quercetin have been reported to increase glucocorticoid receptor expression, thereby potentiating the anti-inflammatory efficacy of low-dose prednisolone (Kang, Cha & Kim, 2015).

The SIRT1 Axis (Mitochondrial and Anti-aging / Anti-inflammatory Pathway): SIRT1 Sirtuin 1 (SIRT1) is an NAD^+-dependent deacetylase with critical regulatory roles in mitochondrial biogenesis, inflammation control, and DNA repair. Upon SIRT1 activation:

- Nrf2 signaling is enhanced
- NF-κB activity is suppressed, resulting in reduced TNF-α and IL-6 production
- Mitochondrial function improves
- Cellular stress tolerance increases

Activation of the SIRT1 axis supports mitochondrial integrity and stabilizes inflammation in the fragile, redox-compromised host. Resveratrol is among the most potent natural activators of SIRT1; by engaging the SIRT1–Nrf2 signaling axis, it suppresses oxidative stress, inflammation, and mitochondrial dysfunction (Baur & Sinclair, 2006; Zhao et al., 2018).

When considered collectively, these mechanisms indicate that **phytochemical compounds such as curcumin, quercetin, resveratrol, EGCG, and berberine mitigate the severe oxidative burden observed in FIP and restore antioxidant defense capacity, thereby contributing to suppression of the inflammatory cascade, preservation of endothelial integrity, and maintenance of cellular metabolic homeostasis.**

5. Adjunctive / Supportive Therapy

Refrakter F Refractory FIP Syndrome does not represent mere failure of antiviral agents, but rather a clinical state in which pathological injury exceeds the host's physiological repair capacity, encompassing:

- Irreversible tissue damage,
- Host redox collapse,
- Microvascular dysfunction,
- Immune exhaustion.

Recognition of this entity as a distinct clinical condition is essential for prognostic assessment, therapeutic decision-making, and effective communication with caregivers. Moreover, understanding the redox–vascular–immune axis in refractory FIP underscores that, beyond antiviral therapy, supportive strategies aimed at preserving or restoring host resilience are critical determinants of survival and treatment success.

Key supportive interventions may include:

- Antiplatelet and/or endothelial support strategies
- Early use of low-dose corticosteroids, when indicated
- Appetite stimulation in cases of inappetence (e.g., mirtazapine, metoclopramide)
- Correction of dehydration
- Adequate pain control
- Antibiotic therapy for documented or suspected secondary bacterial infections

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