Modulation of the Immune Response During FIP Therapy

Macrophage Tropism and the Course of the Immune Response

- While feline coronavirus (FCoV) is a virus capable of replicating within intestinal epithelial cells, mutated strains acquire macrophage/monocyte tropism. This shift in virus–macrophage affinity forms the basis of systemic dissemination.
- The dry form is characterized predominantly by granuloma formation, whereas the wet form is marked by widespread vasculitis and protein-rich effusion. The principal determinant of this clinical course is an inadequate cellular (Th1/CMI) response accompanied by an exaggerated or misdirected humoral (Th2) response (Paltrinieri, 1998; Kipar, 2005).

Th1/Th2 Balance and the Cellular Immune Response (CMI)

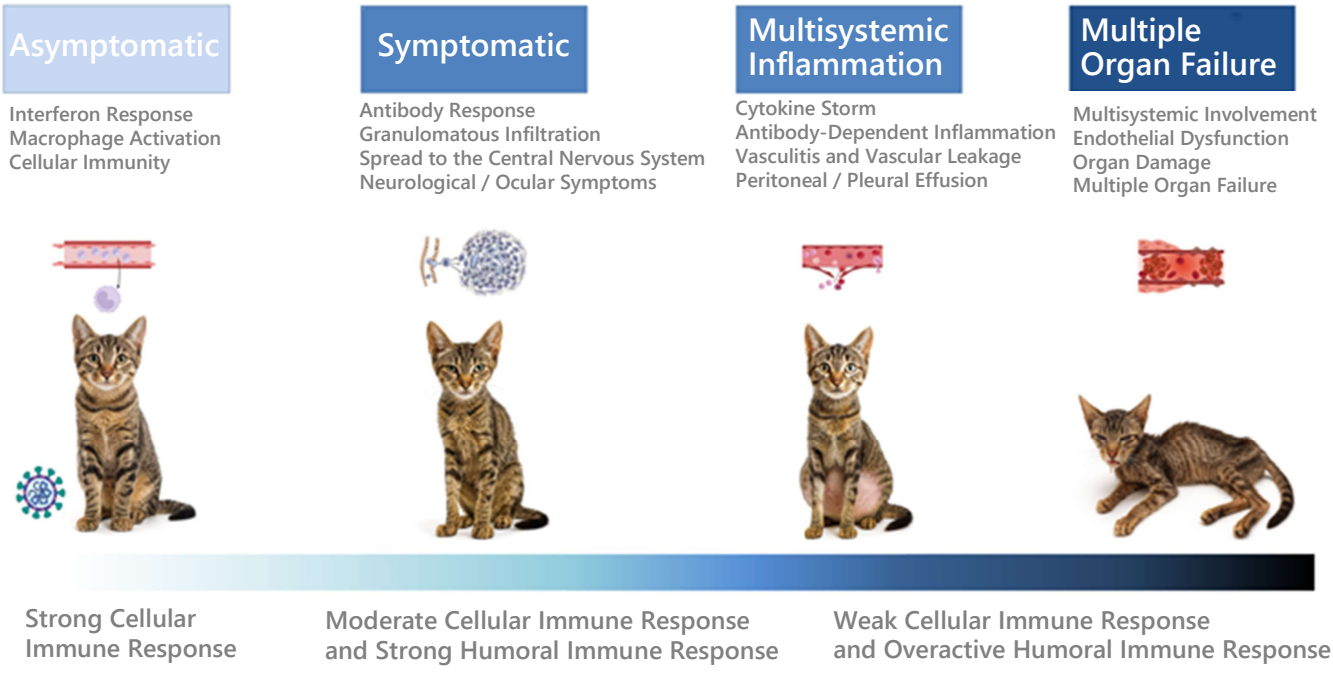
- Protective immunity develops when the Th1-mediated cellular response predominates, whereas a Th2-biased humoral response contributes to disease progression (Kipar and Meli, 2014; Pedersen, 2019). Th1-dominant cellular mediated immunity (CMI) is characterized by IFN-γ–mediated macrophage activation, enhanced phagocytic capacity, and strengthened antigen presentation, all of which are essential for viral control.
- However, numerous studies have shown that in cats that develop FIP, IFN-γ production is insufficient and the TNF-α/IFN-γ ratio is dysregulated (Kiss et al., 2004; Kiss et al., 2016).
- FIP lesions contain both B/plasma cells and $CD4^+$/$CD8^+$ T cells; this "mixed" infiltrate indicates that CMI is present but inadequate, while the Th2/B-cell response becomes dominant (Berg et al., 2005).
- In mesenteric lymph nodes and affected organs, levels of IL-1β, IL-6, TNF-α, type I/II interferons, and various chemokines are elevated. The cytokine profile within tissues activates multiple inflammatory pathways (Malbon et al., 2019).

Interferon Axis (Particularly IFN-γ)

- IFN-γ is the principal modulator of the cellular immune response (CMI) during FCoV infection; however, in cats that develop FIP, a "high TNF-α / low IFN-γ" profile is observed (Tasker, 2023; Foley et al., 2003).
- IFN-γ–positive cells are present within granulomatous foci in tissues and lesions, indicating localized macrophage activation, yet this response is insufficient to achieve complete viral clearance (Berg et al., 2005; Rossi et al., 2011).

Humoral Response, IgG Dynamics, and Antibody-Dependent Enhancement (ADE)

- Seronegative cats typically become seropositive within approximately 7–28 days after FCoV infection (Addie et al., 2009; Tasker et al., 2023).
- The initial antibody response is generally IgM followed by IgG. Although antibody titers are often higher in cats with FIP, high titers do not guarantee protection (Tasker, 2023; Foley et al., 1997).
- The IgG antibody response is robust in FIP. Particularly in the effusive form, low A/G ratio, hyperglobulinemia, and evidence of immune complexes reflect the exaggerated nature of the humoral response (Takano et al., 2008; Hohdatsu et al., 1998).
- Strong antibody responses can trigger antibody-dependent enhancement (ADE): especially antibodies against the spike (S) protein bind to Fc receptors on macrophages, facilitating viral entry into these cells (Hohdatsu et al., 1998; Takano et al., 2008). This non-neutralizing antibody response, when misdirected, plays a disease-enhancing role in FIP progression (Hohdatsu et al., 1998).

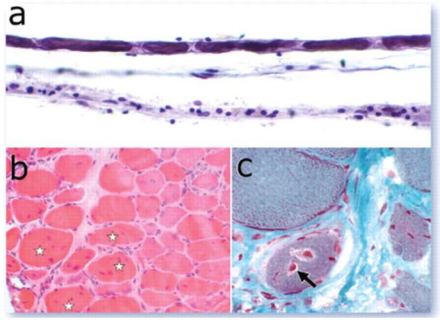


Stage / Substage	Immune Response	Clinical Intervention
Pre-symptomatic / Early Immune Activation	Th1-dominant	Short-Term Antiviral Prophylaxis, Clinical Monitoring of Response, and Immune Enhancement
Subclinical Onset	Th1-dominant	Antiviral Treatment, Clinical Monitoring of Response, Immune Enhancement
Early Systemic (Mild)	Th1-active	Antiviral Treatment + Secondary Infection Control
Early Systemic (Moderate)	Th1-to-Th2 transition	Antiviral Treatment + Corticosteroid-Mediated Immune Regulation + Secondary Infection Control
Advanced Systemic (Without Neurological/Ocular Involvement)	Th2-dominant	Antiviral Treatment + Corticosteroid-Mediated Immune Regulation + Secondary Infection Control + Supportive Therapy
Advanced Systemic (With Neurological/Ocular Involvement)	Th2-dominant, with localized immune escape	
Advanced Systemic (Effusive)	Th2-dominant, ADE	
Terminal (With Partial Response Potential)	T-cell anergy	High-Dose Antiviral Treatment Anti-inflammatory Therapy Secondary Infection Control Supportive Care
Terminal (Non-responsive / Palliative)	T-cell anergy	

- First days of infection: Viral replication and dissemination begin, originating from the intestinal epithelium.
- Weeks 1–3: Seroconversion (increase in IgG).
- If the cellular immune response (CMI) is sufficient, a subclinical infection or carrier state may develop (Dry FIP). As viral replication continues, the infection progresses and CMI becomes inadequate (Dry FIP → Neurological/Ocular Signs).
- If CMI is insufficient, an exaggerated humoral response and immune complex formation trigger the pathological process (Wet FIP → Effusion).
- Disease stage: Inflammatory cytokines (IL-1β, IL-6, TNF-α, type I & II interferons) and chemokines increase within lesions; therefore, immunostimulants or IFN supplementation should not be used before inflammation and viral load are reduced (preferably throughout the treatment period).
- Routine, long-term systemic corticosteroid use is not recommended, as it may mask antiviral efficacy and hinder infection control (Hartmann et al., 2008).

Glucocorticoid-Mediated Immune Modulation

- Prednisolone binds to the glucocorticoid receptor, leading to suppression of inflammation-associated transcription factors such as NF-κB, reduced leukocyte migration, decreased vascular permeability and capillary dilation, mitigation of effusions, and stabilization of clinical status (Puckett et al., 2025).
- In cases of severe effusion, immune-mediated hemolytic anemia (Goto, 2025), or marked neurological signs associated with edema or intracranial hypertension (Murphy, 2024), short-term administration at 1–2 mg/kg/day may be used concurrently with antiviral therapy under close monitoring. Once clinical improvement is observed, tapering should be initiated promptly and gradually (Tasker et al., 2023).
- In ocular FIP/uveitis, a potent topical glucocorticoid (e.g., prednisolone acetate ophthalmic drops) may be used—with regular monitoring of intraocular pressure—while gradually tapering the topical therapy in parallel with antiviral treatment (Ishida, 2004).
- Combination of systemic glucocorticoids with agents such as polyprenyl immunostimulant or recombinant feline interferon-ω is discouraged, as shorter survival times have been reported with such regimens.



The image demonstrates marked mononuclear infiltration around the axon and degeneration of the myelin sheath (a), as well as myofibrillar invasion and endomysial lymphocyte accumulation within the nerve tissue (asterisked areas) (b). Following immunomodulation, a regenerative response is evident in the tissue (c) (Volk et al., 2011). After immunomodulatory treatment, a regenerative zone has formed on a background of fibrosis, the degree of infiltration has decreased, and pre-degenerative fibers (arrow) show evidence of renewal.

In FIP, short-term immunomodulation temporarily suppresses excessive immune responses and thereby limits tissue damage; as the inflammatory cell burden decreases with antiviral therapy, regenerative endothelial changes and areas of fibrous repair develop. If immunomodulation is omitted or introduced too late (resulting in a pattern similar to a–b), granulomatous necrosis and increased vascular permeability may become permanent.

Phytochemical Immune Modulation

- In FIP, the combined use of phytotherapeutic compounds with low-dose prednisolone provides a physiologic synergy capable of achieving immunoregulatory effects comparable to higher-dose corticosteroids, while avoiding their adverse effects.
- Disease progression in FIP is characterized by NF-κB–mediated production of proinflammatory cytokines, particularly increased TNF-α and IL-6 (Pedersen, 2019; Kipar & Meli, 2014). At this stage, curcumin, apigenin, and resveratrol suppress NF-κB signaling, thereby controlling the early steps of the inflammatory cascade (Chainani-Wu, 2003; Shukla & Gupta, 2010; Baur & Sinclair, 2006).
- In the granulomatous form of FIP, macrophages remaining in the M1 phenotype perpetuate tissue injury; berberine and curcumin promote a shift toward the anti-inflammatory M2 phenotype by activating the AMPK–Nrf2 axis (Lao et al., 2006; Marin-Neto et al., 2020).

- Additionally, the Th2-skewed response that contributes to chronicity can be redirected toward a Th1 cytokine profile through the actions of EGCG and β-glucans from Ganoderma lucidum (Reishi), thereby enhancing IFN-γ production and strengthening antiviral cellular immunity (Lambert et al., 2010; Boh et al., 2007).
- In the effusive form of FIP, increased capillary permeability is mitigated by the endothelial barrier–protective effects of curcumin and quercetin (Dajas, 2012; Chainani-Wu, 2003). Furthermore, resveratrol and berberine activate the Nrf2/SIRT1 pathways, preventing oxidative stress–induced cellular injury (Baur & Sinclair, 2006; Marin-Neto et al., 2020). Curcumin and quercetin have also been shown to enhance glucocorticoid receptor expression, thereby potentiating the anti-inflammatory effects of prednisolone (Kang, Cha, & Kim, 2015).

References

Addie, D. D., Toth, S., Murray, G. D., & Jarrett, O. (2009). *Feline coronavirus infection. Veterinary Record, 164*(22), 651–652.

Addie, D. D., Jarrett, O., Hartmann, K., Lutz, H., Paltrinieri, S., Pennisi, M. G., Lloret, A., Ferrer, L., Tasker, S., Hofmann-Lehmann, R., & ABCD Europe. (2024). *Guidelines for diagnosis and monitoring of feline infectious peritonitis (FIP).* European Advisory Board on Cat Diseases (ABCD).

Baur, J. A., & Sinclair, D. A. (2006). Therapeutic potential of resveratrol: The in vivo evidence. *Nature Reviews Drug Discovery, 5*(6), 493–506.

Berg, A. L., Ekman, K., Belák, S., & Berg, M. (2005). Cellular composition and interferon-γ expression of the inflammatory exudates in feline infectious peritonitis. *Veterinary Microbiology, 111*(1–2), 15–23.

Boh, B., Berovič, M., Zhang, J., & Lin, Z.-B. (2007). Ganoderma lucidum and its pharmaceutically active compounds. *Biotechnology Annual Review, 13*, 265–301.

Chainani-Wu, N. (2003). Safety and anti-inflammatory activity of curcumin: A component of turmeric (*Curcuma longa*). *Journal of Alternative and Complementary Medicine, 9*(1), 161–168.

Dajas, F. (2012). Life or death: Neuroprotective and anticancer effects of quercetin. *Journal of Ethnopharmacology, 143*(2), 383–396.

Foley, J. E., Rand, C., Leutenegger, C., & Pedersen, N. C. (2003). Inflammation and changes in cytokine levels in neurologic feline infectious peritonitis. *Journal of Veterinary Internal Medicine, 17*(4), 538–546.

Goto, Y., Takahashi, K., Hayashi, T., Koyama, H., & Ishida, T. (2025). Feline immune-mediated hemolytic anemia secondary to infectious disease: Diagnostic and therapeutic considerations. *Journal of Feline Medicine and Surgery, 27*(1), 55–63.

Hohdatsu, T., Yamada, M., Tominaga, R., Makino, K., Kida, K., & Koyama, H. (1998). Antibody-dependent enhancement of feline infectious peritonitis virus infection in feline alveolar macrophages and human monocyte cell line U937 by serum of cats experimentally or naturally infected with feline coronavirus. *Journal of Veterinary Medical Science, 60*(1), 49–55.

Ishida, T., Shibanai, A., Tanaka, S., Uchida, K., & Mochizuki, M. (2004). Therapeutic effect of recombinant feline interferon-ω in cats with ocular feline infectious peritonitis. *Journal of Veterinary Medical Science, 66*(8), 877–881.

Kang, J. S., Cha, H. J., & Kim, S. H. (2015). Curcumin-induced glucocorticoid receptor expression enhances anti-inflammatory potential through p38 MAPK inhibition. *International Immunopharmacology, 28*(1), 520–529.

Kipar, A., & Meli, M. L. (2014). Feline infectious peritonitis: Still an enigma? *Veterinary Pathology, 51*(2), 505–526.

Kipar, A., May, H., Menger, S., Weber, M., Leukert, W., Reinacher, M., & Schöniger, S. (2005). Morphologic features and development of granulomatous vasculitis in feline infectious peritonitis. *Veterinary Pathology, 42*(3), 321–330.

Kiss, I., Kecskeméti, S., & Madarasz, E. (2004). Preliminary findings suggest immunity against feline infectious peritonitis is associated with high TNF-α/low IFN-γ responses. *Journal of Feline Medicine and Surgery, 6*(S1), 1–8.

Lambert, J. D., Sang, S., Yang, C. S., & Huang, M.-T. (2010). Safety of green-tea catechins in humans: A systematic review. *Food and Chemical Toxicology, 48*(1), 129–136.

Lao, C. D., Ruffin, M. T., Normolle, D., Heath, D. D., Murray, S. I., Bailey, J. M., Boggs, M. E., Crowell, J., Rock, C. L., & Kelloff, G. J. (2006). Dose escalation of a curcuminoid formulation. *BMC Complementary and Alternative Medicine, 6*(1), 10.

Malbon, A., Hecht, W., & Galyon, G. (2019). Feline infectious peritonitis as a systemic inflammatory disease: Cytokine profiling in tissues. *Journal of Comparative Pathology, 170*, 115–125.

Marin-Neto, J. A., Carvalho, B. A., Dantas, R. P., Ribeiro, A. L. P., & Ferreira, R. C. (2020). Pharmacological properties of berberine: Mechanisms and therapeutic perspectives. *Pharmacological Research, 155*, 104741.

Moyadee, W., Sunpongsri, S., Choowongkomon, K., Roytrakul, S., Rattanasrisomporn, A., Tansakul, N., & Rattanasrisomporn, J. (2024). Feline infectious peritonitis: A comprehensive evaluation of clinical manifestations, laboratory diagnosis, and therapeutic approaches. *Journal of Advanced Veterinary and Animal Research, 11*(1), 19–26.

Murphy, C., Finlay, R., Williams, D., Green, M., & Hartmann, K. (2024). Neurological manifestations and therapeutic outcomes in feline infectious peritonitis: A retrospective analysis. *Viruses, 16*(3), 462.

Paltrinieri, S., Cammarata, M. P., Cammarata, G., & Comazzi, S. (1998). Some aspects of humoral and cellular immunity in naturally occurring feline coronavirus infection and feline infectious peritonitis. *Veterinary Immunology and Immunopathology, 65*(2–4), 205–220.

Pedersen, N. C. (2019). An update on feline infectious peritonitis: Diagnostics and therapeutics. *Journal of Feline Medicine and Surgery, 21*(10), 1026–1038.

Puckett, Y., Patel, P., & Bokhari, A. A. (2025, April 26). *Prednisone.* In *StatPearls.* StatPearls Publishing.

Takano, T., Kawakami, C., Yamada, S., Satoh, R., & Hohdatsu, T. (2008). Antibody-dependent enhancement occurs upon re-infection with the identical serotype virus in feline infectious peritonitis virus infection. *Journal of Veterinary Medical Science, 70*(12), 1315–1321.

Tasker, S., Addie, D. D., Belák, S., Boucraut-Baralon, C., Egberink, H., Frymus, T., Gruffydd-Jones, T., Hosie, M. J., Lloret, A., Lutz, H., Marsilio, F., Pennisi, M.