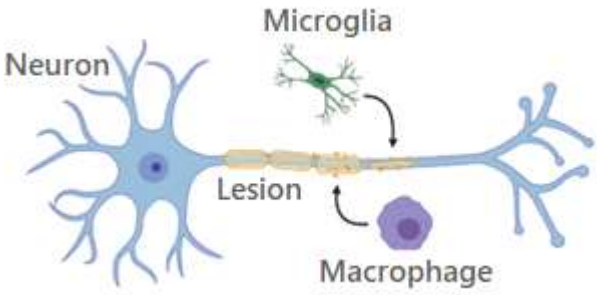
Clinical Response and Remission in Neurological FIP

Monocyte–Macrophage Tropism and Dissemination to the Central Nervous System

Feline infectious peritonitis (FIP) develops when mutated FCoV acquires macrophage tropism. This shift results in the recruitment of monocytes into systemic circulation and their localization within the vascular system. The mutant FCoV variant that progresses to FIP gains efficient replicative capacity within monocytes and is subsequently transported by these cells to the brain and neural tissues (Kipar and Meli, 2010). Neuro-FIP is typically observed as an advanced stage of the "dry form" of FIP.



Neuroinflammation

The elevation of cytokines such as IL-6, TNF-α, IL-1β, and CXCL10 disrupts the integrity of the blood–brain barrier, thereby triggering the neuroinflammatory cascade observed in FIP. This process facilitates the entry of both immune cells and viral particles into the nervous system (Dickinson, 2020; Cataldi et al., 2020). Consequently, infection and inflammation reinforce one another, forming a self-perpetuating cycle of neuroinflammation. The localization of FIPV antigen predominantly within the cytoplasm of macrophages supports the role of these cells as the primary reservoir during disease progression (Rissi, 2018; Wang et al., 2018). In the central nervous system, the simultaneous presence of meningoencephalitis, vasculitis, and pyogranulomatous inflammation distinguishes the neurological form of the disease from other systemic variants (Kipar and Meli, 2014; Wang et al., 2018).

Clinical Findings

Neurological FIP manifests in two clinical forms: primary neurological FIP and secondary neurological FIP.

1) **Primary neurological FIP:** In these cats, neurological signs are the most prominent initial findings, often accompanied by inappetence, weight loss, and lethargy. Fever may be present or may go unnoticed. Approximately half of the cats with primary neurological FIP also exhibit lesions in organs outside the central nervous system; their hematologic values resemble those seen in systemic FIP. In contrast, cats presenting solely with neurological signs frequently have normal CBC and biochemical profiles. Early signs may be subtle and easily overlooked (Pedersen, 2019).

   Early clinical indicators include wall- or floor-licking behavior, muscle fasciculations, anisocoria, and behavioral changes. Initially, cats become reluctant to jump onto elevated surfaces. As the disease progresses, coordination deficits and hindlimb weakness develop, and a plantigrade stance becomes evident. In advanced cases, cognitive abnormalities, seizures, and vestibular dysfunction may emerge (Timmann et al., 2008). These manifestations may occasionally be associated with peripheral nerve root involvement or inflammatory conditions resembling polyradiculoneuritis (Hartmann, 2005; Foley et al., 2008).

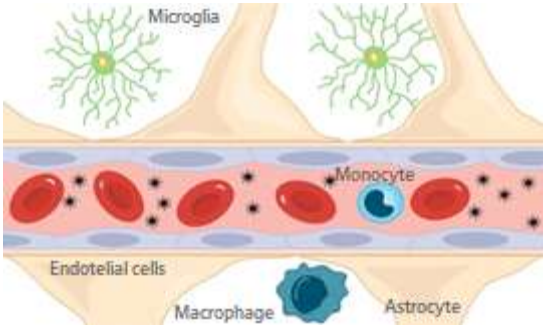
2) **Secondary neurological FIP:** In secondary neurological FIP, cats first display systemic signs of FIP, and central nervous system involvement becomes apparent later as motor dysfunction develops. This form frequently arises during or after antiviral therapy and represents the most common cause of relapse. Relapses typically occur 1–4 weeks after the completion of treatment. Spinal cord involvement is often overlooked, although more than 50% of inflammatory spinal diseases are attributable to FIP. Spinal involvement may result in urinary or fecal incontinence, hindlimb or tail paralysis. Compared with brain involvement, this form carries a higher likelihood of leaving permanent neurological deficits.

Neurological Recovery and Immunomodulation

In neurological FIP cases, achieving complete clearance of intracellular viral persistence and residual inflammatory lesions requires a minimum of 12 weeks (≈ 84 days) of antiviral therapy (Renner et al., 2025; Felten et al., 2025; Murphy et al., 2024). Several studies have shown that higher dosing and ≥12-week treatment regimens are often necessary in neurological and ocular cases; otherwise, the risk of relapse increases significantly (Coggins et al., 2023; Pedersen, 2019).

For effective control of inflammation during treatment, limited-duration corticosteroid therapy and the use of anti-inflammatory agents throughout the antiviral course contribute to improved recovery and immunomodulation. In cases presenting with severe neurological symptoms, short-term prednisolone at approximately 1 mg/kg/day is recommended during the early antiviral phase to manage edema, intracranial pressure, and inflammation (Tasker, 2023). Volk et al. (2011) demonstrated that, prior to immunomodulatory therapy, affected nerve fibers exhibited demyelination and marked mononuclear infiltration, whereas regenerative changes became evident following treatment. Thus, the transition from the granulomatous phase to the regenerative phase is accelerated through immunomodulatory intervention.

Antiviral Treatment Duration and Residual Lesions



Even after completion of antiviral therapy, granulomatous infiltrates and residual viral antigen may persist within tissues for weeks (Pedersen, 2019). This persistence forms the basis of relapse. The long lifespan of tissue-resident macrophages and microglial cells renders them viral reservoirs (Jenkins and Hume, 2014; Ajami et al., 2007). The ability of these cells to remain viable for months contributes to the inadequacy of short treatment protocols in the neurological form of FIP.

Clinical studies have reported partial resistance or suboptimal response to GS-441524, indicating that higher doses and treatment extension can rescue refractory cases. de Witt Curtius et al. (2025) documented neurological relapse occurring 17 days after a 42-day GS-441524 regimen; however, stable remission was achieved following a second 84-day treatment course. In neurological FIP, GS-441524 protocols lasting 84–100 days have been associated with durable remission, and premature or shortened treatment may negate this advantage (Pedersen

and Jacque, 2021). In a study evaluating molnupiravir as a rescue therapy in cats that relapsed after treatment with GS-441524 (and in some cases GC376), the primary causes of relapse were identified as inadequate dosing and insufficient treatment duration (Roy et al., 2022). Yoshida et al. (2025) reported that in molnupiravir-treated cats, SAA normalized early whereas AGP normalized later, and neurological cases exhibited delayed clinical improvement ranging from 15 to 77 days. These findings suggest that ongoing FIPV replication within host macrophages and long-lived microglial infections may lead to disease reactivation if antiviral pressure is withdrawn prematurely.

Recent pathology studies have demonstrated that, despite antiviral therapy, granulomatous infiltrates and residual viral antigen can persist within tissues for several weeks (the immunopathologic residue phase), providing a biological explanation for relapse and residual neurological deficits (de Witt Curtius et al., 2025). Consequently, treatment duration must be planned with consideration of microglial turnover kinetics (Pedersen and Jacque, 2021).

References:

Ajami, B., Bennett, J. L., Krieger, C., Tetzlaff, W., & Rossi, F. M. V. (2007). Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. *Nature Neuroscience, 10*(12), 1538–1543.

Cataldi, M., Pignataro, G., & Taglialatela, M. (2020). Neurobiology of coronaviruses: Potential relevance for COVID-19. *Neurobiology of Disease, 143*, 105007.

Coggins, S. J., Norris, J. M., Malik, R., Govendir, M., Hall, E. J., Kimble, B., Thompson, M. F., & colleagues. (2023). Outcomes of treatment of cats with feline infectious peritonitis using parenterally administered remdesivir, with or without transition to orally administered GS-441524. Journal of Veterinary Internal Medicine, 37(5), 1876–1880.

de Witt Curtius, C., Rodary, M., Hofmann-Lehmann, R., Spiri, A. M., & Meli, M. L. (2025). Navigating neurological re-emergence in feline infectious peritonitis: Challenges and insights from GS-441524 and remdesivir treatment. *JFMS Open Reports, 11*(2), 20551169251360625.

Dickinson, P. J. (2020). Coronavirus infection of the central nervous system: Animal models in the time of COVID-19. *Frontiers in Veterinary Science, 7*, 584673.

Foley, J. E., Leutenegger, C. M., & Pedersen, N. C. (2008). Diagnostic features of clinical neurologic feline infectious peritonitis and utility of MRI and CSF analysis for diagnosis. *Journal of Feline Medicine and Surgery, 10*(5), 409–418.

Hartmann, K. (2005). Feline infectious peritonitis. *Veterinary Clinics of North America: Small Animal Practice, 35*(1), 39–79.

Jenkins, S. J., & Hume, D. A. (2014). Homeostasis and turnover of monocytes and tissue macrophages. *Nature Reviews Immunology, 14*(12), 749–759.

Kipar, A., & Meli, M. L. (2010). Pathogenesis of feline infectious peritonitis: New insights into tissue tropism and host response. *Veterinary Pathology, 47*(2), 321–337.

Kipar, A., & Meli, M. L. (2014). Feline infectious peritonitis: Still an enigma? *The Veterinary Journal, 201*(2), 123–132.

Rissi, D. R. (2018). A retrospective study of the neuropathology and diagnosis of naturally occurring feline infectious peritonitis. *Journal of Veterinary Diagnostic Investigation, 30*(3), 392–399.

Pedersen, N. C., & Jacque, N. (2021, November 3). Alternative treatments for cats with FIP and natural or acquired resistance to GS-441524. Journal of Feline Medicine and Surgery Open Reports, 7(2), 20551169211058233.

Roy, M., Jacque, N., Novicoff, W., Li, E., Negash, R., & Evans, S. J. M. (2022). Unlicensed molnupiravir is an effective rescue treatment following failure of unlicensed GS-441524-like therapy for cats with suspected feline infectious peritonitis. Pathogens, 11(10), 1209.

Tasker, S. (2023). *Guidelines for diagnosis and monitoring of feline infectious peritonitis*. European Advisory Board on Cat Diseases (ABCD). https://www.abcdcatsvets.org/fip-guidelines

Timmann, D., Cizinauskas, S., Tomek, A., & Doherr, M. G. (2008). Retrospective analysis of seizures associated with feline infectious peritonitis in cats. *Journal of Feline Medicine and Surgery, 10*(1), 9–15.

Volk, H. A., Matiasek, L. A., & Feliu-Pascual, A. L. (2011). Neuromuscular disorders in the cat: Clinical approach to weakness. *Journal of Feline Medicine and Surgery, 13*(7), 531–544.

Wang, H., Hirabayashi, M., Chambers, J. K., Uchida, K., & Nakayama, H. (2018). Immunohistochemical studies on meningoencephalitis in feline infectious peritonitis. *Journal of Veterinary Medical Science, 80*(12), 1813–1817.

Yoshida, M., Sato, K., & Tanaka, T. (2025). Clinical improvement course of cats with FIP treated with molnupiravir. *Canadian Veterinary Journal, 66*(5), 546–554.