EFFICACY, DOSING, AND DURATION OF ANTIVIRAL THERAPY IN FELINE INFECTIOUS PERITONITIS: A SYSTEMATIC REVIEW PROTOCOL TO SUPPORT ISCAID FIP TREATMENT GUIDELINES

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Rationale

Feline infectious peritonitis (FIP) is a progressive, systemic disease caused by feline coronavirus (FCoV) and characterised by pyogranulomatous inflammation, vasculitis, and variable clinical manifestations. Historically, FIP was considered uniformly fatal, but the emergence of antiviral therapies in recent years has transformed the therapeutic landscape and created an urgent need for rigorous, evidence-based evaluation of available treatment strategies. Despite increasing research interest, published studies remain highly variable in diagnostic criteria, case definitions, treatment protocols, outcome measures, and methodological quality, making interpretation and comparison challenging.

To ensure that the forthcoming treatment guideline addresses the most relevant and clinically meaningful questions, a panel of 16 stakeholders from 10 countries across six continents was formed. Panel members represent a deliberately broad range of perspectives, including general practitioners, specialist clinicians, virologists, cat owners, and breeders. This diverse

group collaboratively drafted, refined, and prioritised the key clinical questions using the PICO (Population, Intervention, Comparator, Outcome) framework.

This systematic review will support the ISCAID (International Society for Companion Animal Infectious Diseases) guideline and will apply the GRADE framework to rate the certainty of evidence and support trustworthy, actionable recommendations.

Objectives

- To compare the efficacy of antiviral therapies for FIP on patient-important outcomes, using GS-441524 as the standard-of-care comparator where applicable.
- To evaluate how dose category (very low to very high, in mg/kg/day) and treatment duration (short vs long) affect efficacy and safety.
- To explore effect modifiers (e.g., FIP form, diagnostic certainty, route and frequency of administration, baseline severity) on response to treatment, as data allow.

REPORTING AND PROTOCOL REGISTRATION

This protocol is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 statement and will be registered with SYREAF.org (https://syreaf.org/protocols/). Important protocol amendments will be reported in the final manuscript.

FUNDING

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ELIGIBILITY

Our inclusion criteria are intentionally liberal due to the scarcity of comparative studies. We will include studies of cats with feline infectious peritonitis (FIP) treated with an antiviral agent in which clinical outcomes are reported. Eligibility is structured according to prespecified PICO questions (participants, interventions, comparators, outcomes) across three domains—substance, dosage, and duration (Table 1).

Population We will include cats of any age and setting (owned or shelter) with feline infectious peritonitis (FIP) of any form, including effusive (wet), non-effusive (dry), ocular, and neurological presentations. Eligible case definitions encompass confirmed FIP (e.g., histopathology with immunohistochemistry, or positive PCR on effusion/CSF/tissue) and probable/presumed FIP based on clinical, laboratory, and imaging criteria as applied by study authors. Cats with co-infections (e.g., FIV/FeLV) and other comorbidities will be included. Diagnostic method and certainty, FIP form, and relevant baseline characteristics (including co-infections/comorbidities) will be extracted and reported transparently in study characteristics, and—where data allow—analyses will be stratified by these factors.

Comparators and controls: Eligible comparators include GS-441524 (both licensed and unlicenced), other antiviral agents, different doses or durations of the same agent, and placebo/no antiviral plus standard care where applicable. Studies using historical or external controls are eligible if comparator selection, time frames, and outcome definitions are clearly described. Single-arm studies without explicit comparators will also be eligible.

Dosage Where possible, GS-441524 doses will be harmonized to total daily mg/kg and categorized as:

- Very low: ≤5 mg/kg/day
- Low: 6–10 mg/kg/day
- Moderate low: 11–13 mg/kg/day
- Standard: 14–16 mg/kg/day
- Moderate high: 17–20 mg/kg/day
- High: 21–24 mg/kg/day
- Very high: ≥25 mg/kg/day

Route and dosing frequency: All administration routes (oral, subcutaneous, intravenous) and dosing frequencies (e.g., once- or twice-daily) are eligible. Route and frequency will be extracted for all studies and treated as prespecified potential effect modifiers in analysis and interpretation.

Study designs: We will include randomized and non-randomized comparative studies, prospective or retrospective cohort studies, and non-comparative single-arm studies reporting outcomes of the specified antivirals in cats with FIP. For non-comparative case series, a

minimum size of 10 cats is required; single-case reports and case series with ≤10 cats will be excluded. No minimum sample size will be applied to comparative designs.

Report characteristics: There will be no restrictions on language or year of publication. Eligible records include peer-reviewed articles, preprints, theses/dissertations, conference abstracts, and other grey literature. Grey literature sources such as owner forums/registries used in FIP might be considered, provided they contain sufficient methodological detail and extractable outcome data, but there is currently no a systematic plan in place. Where necessary, translations will be sought or authors/maintainers contacted for clarification.

Other questions regarding background information, monitoring and other management questions were asked by the panel and will be considered in the guideline but go beyond the scope of this systematic review. These questions can be found in Appendix 2.

Table 1. PICOs included in the systematic review

Population	**Intervention**	**Comparator**	**Outcome**
Domain 1: Substance			
Cats with FIP	Molnupiravir	GS-441524	1) Treatment failure 2) Mortality • Early (<7 days) • Late (>7 days until end of treatment) • Observational period (90 days after treatment) • After observational period 3) Re-emergent • Observational period • After observational period 4) Adverse events 5) Chronic sequela 6) Normalisation of clinical signs
	EIDD-1931	GS-441524	
	Nirmatrelvir/ritonavir (Paxlovid™)	GS-441524	
	GC376	GS-441524	
	Remdesivir	GS-441524	
	Combination antiviral and other drug	GS-441524	
Domain 2: Dosage and administration			
Cats with FIP	Low dose (or any other category) GS-441524	Standard GS-441524	
Cats with FIP	Higher induction dose per os (GS-441424)	No induction	
Cats with FIP (all types)	Parenteral induction (GS and/or remdesivir)	No induction	
	Molnupiravir low dose (<10 mg/kg)	Molnupiravir (10-15 mg/kg)	

Domain 3: Duration of treatment			
Cats with FIP	Short duration (<42 days or other shorter category)	Long duration (84 days)	

INFORMATION RESOURCES AND SEARCH STRATEGY

Medline (via OVID), Web of Science and CAB Abstracts were searched. The initial search was performed December 16, 2024, and was revised January 19, 2026. The search strategy is described in Appendix 1.

DATA MANAGEMENT

Retrieved references were imported into Covidence. De-duplication was performed during importing into Covidence, with further manual de-duplication as required.
Data extraction will be done in Excel.

SELECTION PROCESS

Two reviewers will independently screen titles/abstracts against the prespecified eligiblity criteria (cats with FIP treated with an antiviral and reporting clinical outcomes), following a brief calibration exercise to ensure consistency. Potentially eligible records will undergo independent, duplicate full-text screening; disagreements at either stage will be resolved by discussion or a third reviewer. Reasons for full-text exclusion will be recorded using standardized categories, and selection will be summarized in a PRISMA 2020 flow diagram.

Additionally, we will note studies that assess treatments other than nucleoside antivirals (for example, corticosteroids, polyprenyl immunostimulant, mefloquine and feline interferon-omega). We will screen these and record key details, but they will not be included in our main analyses. The reason for this is to enable potential future use as external/historical comparators (e.g., in network meta-analysis), but they will be excluded from the prespecified PICO syntheses and presented in supplementary tables.

DATA COLLECTION PROCESS

Two reviewers will independently extract data in duplicate using Excel. We conducted a calibration exercise on the first 10 studies to align variable definitions, dose categorization, routes, and outcome time windows. Discrepancies will be resolved by discussion or, if

needed, a third reviewer. We will capture study-, arm-, and outcome-level data. When key details are unclear or missing (e.g., dosage or duration), we will contact authors; if unresolved, assumptions will be documented and derived fields flagged.

DATA ITEMS

- Bibliographic and funding
    - First author, title, year, journal, country of study
    - Funding/source of support
- Study design and conduct
    - Study design (RCT or observational)
    - Retrospective vs prospective
    - Total study duration/follow-up
    - Total number of included cats (overall and per arm, where applicable)
- Population and diagnosis (at baseline; for both intervention and comparator arms in comparative studies)
    - FIP form: effusive/wet, non-effusive/dry, neurological, ophthalmic, or combination
    - Diagnostic approach: immunohistochemistry, PCR (effusion/CSF/tissue), clinical signs/history, or combination
    - Age (median or as reported by authors)
    - Co-interventions/other treatments received (e.g., prednisolone, meloxicam, cobalamin, etc.)
- Intervention: characteristics and treatment
    - Antiviral agent/substance
    - Dosage (mg/kg/day; convert split dosing to total daily dose where possible; contact authors if needed to classify into dose categories)
    - Route of administration (oral, intravenous, subcutaneous, or combination)
    - Duration of antiviral treatment (contact authors if needed to classify into short vs long)
- Intervention: outcomes (use study definitions and time windows; extract numerators/denominators where possible)
    - Early mortality (<7 days from treatment start)

    - Late mortality (>7 days but during treatment)
    - Mortality during observational period (post-treatment follow-up, e.g., to 90 days)
    - Mortality after the observational period
    - All-cause mortality (any time point)
    - Treatment failure
    - Re-emergence/relapse during the observational period
    - Re-emergence/relapse after the observational period
    - Adverse events (overall), with free-text description/type of events
    - Normalization of clinical signs
    - Long-term sequelae (e.g., persistent neurological or ophthalmic signs)
- Comparator (for comparative studies): characteristics and treatment
    - Population characteristics (FIP form, diagnosis method, age—as above)
    - Comparator treatment (antiviral agent/substance or standard care/no antiviral)
    - Dosage (as above; contact authors if needed)
    - Duration (as above)
    - Total number of cats in comparator arm
- Comparator: outcomes (same outcome set and time windows as for the intervention arm)
    - Early, late, observational, and post-observational mortality; all-cause mortality
    - Treatment failure
    - Re-emergence during and after the observational period
    - Adverse events (overall and type)
    - Normalization of clinical signs
    - Long-term sequelae

OUTCOME AND PRIORITIZATION

Following the GRADE guidance, the ISCAID guideline panel first specified all potentially patient-important outcomes, then rated their importance on a 1–9 scale (7–9 = critical; 4–6 = important; 1–3 = of limited importance). Only outcomes rated critical or important will inform recommendations and certainty judgments; outcomes of limited importance (if encountered) will not be prioritized for synthesis.

Critical outcomes

1) Treatment failure
2) Mortality
   - Early: <7 days from treatment start
   - Late: >7 days until end of treatment
   - Observational period: up to 90 days after treatment completion
   - After observational period: >90 days post-treatment
3) Re-emergent disease (relapse)
   - During observational period (≤90 days post-treatment)
   - After observational period (>90 days)
4) Adverse events (overall and by type when available)

Important outcomes

1) Chronic sequelae (e.g., persistent neurological or ophthalmic deficits)
2) Normalization of clinical signs

Where studies use different definitions or time windows, we will map them to these prespecified categories and report any assumptions transparently.

Outcome definitions

An initial Delphi round was conducted with panellists, to clarify key terminology for use in the systematic review. Using an a priori consensus threshold of 80%, all proposed definitions achieved ≥80% agreement in the first round. Accordingly, these definitions were accepted without modification and carried forward into the review.

Primary treatment course: refers to the initial, uninterrupted period of antiviral therapy administered for a diagnosis of FIP, commencing on Day 1 of treatment and continuing until the planned cessation of therapy, regardless of duration or formulation (e.g. remdesivir, GS-441524, or sequential use of both).

Early treatment mortality: death on or before Day 7 of commencing antiviral therapy

Late treatment mortality: death after Day 7 of commencing therapy but before completion of treatment.

Post-treatment mortality: death after completion of the primary antiviral course

Observation period: the 12 weeks (3 months) following completion of the primary antiviral treatment course, regardless of its duration.

Treatment failure: refers to an inadequate or unsustained clinical response occurring during the primary treatment course of antiviral therapy for FIP. Treatment failure includes any of the following occurring before cessation of the primary course:

Partial response: incomplete resolution of referrable clinical signs or persistent clinicopathological abnormalities inconsistent with remission.

Progression of disease: development of new clinical signs or worsening of existing signs attributable to FIP despite ongoing therapy.

Relapse during treatment: recurrence of clinical signs consistent with FIP after an initial period of clinical improvement while still receiving antiviral therapy.

Deterioration following initial improvement: re-emergence or worsening of referrable clinical signs after documented improvement, occurring prior to completion of the planned treatment course.

Treatment failure is distinct from re-emergent FIP, which occurs after cessation of the primary treatment course.

Re-emergent FIP: refers to the recurrence of clinical signs consistent with FIP following cessation of the primary antiviral treatment course.

This term is used in place of "relapse" or "reinfection" because definitive differentiation between these entities requires advanced diagnostic confirmation, including comparative viral genomic sequencing at initial diagnosis and recurrence, and evidence clarifying the potential for viral latency. Such data are rarely available in clinical practice or published studies.

In the absence of confirmatory sequencing or equivalent evidence, it is not possible to reliably determine whether recurrence represents reactivation of the original infection or infection with a new viral strain. Accordingly, the neutral term re-emergent FIP is recommended to ensure accuracy, consistency, and transparency in reporting outcomes.

All mortality outcomes were defined as all-cause mortality, recognising the difficulty in confidently attributing cause of death in cats previously affected by FIP.

RISK OF BIAS IN INDIVIDUAL STUDIES

Two reviewers will independently assess risk of bias with consensus or discussion with. A third-reviewer. For randomized trials we will use RoB 2, and for non-randomized comparative studies we will use ROBINS-I (www.riskofbias.info) Judgements will be made at the outcome level for the main (critical/important) outcomes where feasible.

Non-comparative studies: Given the anticipated volume of single-arm cohorts/case series, we will develop a FIP-specific risk-of-bias tool tailored to non-comparative evidence. Signaling questions will cover:

- Diagnostic certainty (confirmed vs presumed; methods used and thresholds)
- Participant selection (e.g., consecutive vs selective enrollment; inclusion/exclusion clarity)
- Intervention fidelity (antiviral identity and provenance—licensed vs unlicensed GS; dose accuracy; route/frequency; co-interventions)
- Missing data and follow-up completeness (loss to follow-up; handling of withdrawals)
- Outcome measurement (definitions, timing windows, objectivity; consistency across participants)
- Selective reporting (protocol/registry alignment where available) and conflicts of interest/funding Each study will be summarized as low, moderate, or high risk of bias overall for each critical outcome; the full tool and guidance will be provided in a supplement after piloting.

Risk-of-bias judgements will inform the certainty of evidence ratings in GRADE at the outcome level. Where data allow, we will perform sensitivity analyses excluding high-risk studies and explore risk-of-bias categories in subgroup/stratified analyses. Where outcome-level assessment is not possible, study-level judgements will be transparently reported and their implications discussed.

DATA SYNTHESIS

Pairwise meta-analyses will be conducted when at least two studies evaluate the same PICO comparison and outcome using sufficiently comparable outcome definitions, follow-up time points, and clinically similar populations and interventions (including antiviral agent, dose, route, and duration). Clinical and methodological homogeneity will be assessed a priori based on predefined criteria. When pooling is not appropriate due to substantial heterogeneity or insufficient data, findings will be summarized narratively.

For comparative studies, relative treatment effect will be expressed as risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes (e.g., survival, clinical remission, relapse, adverse events). Absolute effects will be calculated where feasible using pooled

baseline risks. Continuous outcomes, if reported (e.g., time to clinical improvement), will be summarized using mean differences (MD) or standardized mean differences (SMD), as appropriate. Random-effects models will be used for all meta-analyses to account for expected clinical and methodological heterogeneity across studies, particularly given anticipated variability in antiviral agent, dose, duration, disease phenotype, and study design. Statistical heterogeneity will be quantified using I^2 statistic.

For single-arm or non-comparative studies, pooled proportions (e.g., overall survival, remission rates, relapse rates, frequency of adverse events) will be calculated using random-effect meta-analysis of proportions with appropriate variance-stabilizing transformations (e.g., logit transformation) where necessary. Exact methods will be used when event counts are small.

Subgroup and Sensitivity Analyses

If data permit, prespecified subgroup analyses will explore potential effect modification by:

- FIP form (effusive, non-effusive, ocular, neurological)
- Diagnostic certainty (confirmed vs probable/presumed)
- Antiviral agent (licensed vs unlicensed GS-441524)
- Route of administration (oral vs parenteral)
- Dose category (Standard vs high dose; predefined thresholds)
- Treatment duration (≤12 weeks vs >12 weeks or as clinically categorized)

Subgroup effects will be interpreted as exploratory unless supported by formal interaction testing.

Sensitivity analyses will include:

- Exclusion of studies at high risk-of-bias
- Exclusion of grey literature or non-peer-reviewed reports
- Exclusion of studies with unclear dosing or duration reporting
- Use of alternative statistical models or effect measures (e.g., odds ratio vs risk ratio)

Certainty of Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be used to assess the certainty of evidence (https://book.gradepro.org). We will primarily assess inconsistency and imprecision using the GRADE approach, focusing on clinically meaningful thresholds agreed by the guideline panel rather than relying on statistical metrics (e.g., I2) for decision-making (Guyatt et al., 2023).

APPENDIX 1 shows the search string

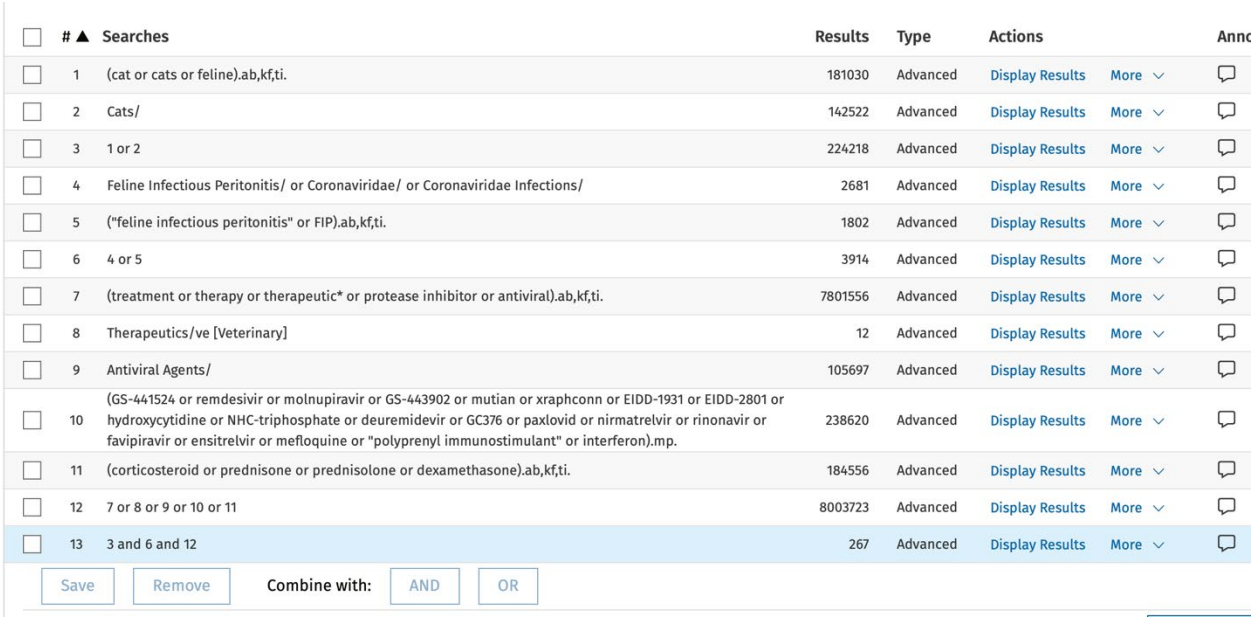
Web of Science

Cat OR Cats OR feline /topic
AND
FIP OR "feline infectious peritonitis" OR "coronavirus" /topic
AND
GS-441524 OR remdesivir OR molnupiravir OR GS-443902 OR mutian OR xraphconn OR EIDD-1931 OR EIDD-2801 OR hydroxycytidine OR NHC-triphosphate OR deuremidevir OR GC376 OR paxlovid OR nirmatrelvir OR rinonavir OR favipiravir OR ensitrelvir OR mefloquine OR immunostimulant OR immunomodulator OR interferon OR antiviral OR treatment OR therapy OR therapeutic OR therapeutics OR "protease inhibitor" OR antiviral OR corticosteroid OR prednisone OR prednisolone OR dexamethasone /topic

CAB

Cat OR Cats OR feline /all fields
AND
FIP OR "feline infectious peritonitis" OR "coronavirus" /abstract
AND
GS-441524 OR remdesivir OR molnupiravir OR GS-443902 OR mutian OR xraphconn OR EIDD-1931 OR EIDD-2801 OR hydroxycytidine OR NHC-triphosphate OR deuremidevir OR GC376 OR paxlovid OR nirmatrelvir OR rinonavir OR favipiravir OR ensitrelvir OR mefloquine OR immunostimulant OR immunomodulator OR interferon OR antiviral OR treatment OR therapy OR therapeutic OR therapeutics OR "protease inhibitor" OR antiviral OR corticosteroid OR prednisone OR prednisolone OR dexamethasone /all fields

Medline via OVID



# ▲	Searches	Results	Type	Actions	Anno
1	(cat or cats or feline).ab,kf,ti.	181030	Advanced	Display Results More	
2	Cats/	142522	Advanced	Display Results More	
3	1 or 2	224218	Advanced	Display Results More	
4	Feline Infectious Peritonitis/ or Coronaviridae/ or Coronaviridae Infections/	2681	Advanced	Display Results More	
5	("feline infectious peritonitis" or FIP).ab,kf,ti.	1802	Advanced	Display Results More	
6	4 or 5	3914	Advanced	Display Results More	
7	(treatment or therapy or therapeutic* or protease inhibitor or antiviral).ab,kf,ti.	7801556	Advanced	Display Results More	
8	Therapeutics/ve [Veterinary]	12	Advanced	Display Results More	
9	Antiviral Agents/	105697	Advanced	Display Results More	
10	(GS-441524 or remdesivir or molnupiravir or GS-443902 or mutian or xraphconn or EIDD-1931 or EIDD-2801 or hydroxycytidine or NHC-triphosphate or deuremidevir or GC376 or paxlovid or nirmatrelvir or rinonavir or favipiravir or ensitrelvir or mefloquine or "polyprenyl immunostimulant" or interferon).mp.	238620	Advanced	Display Results More	
11	(corticosteroid or prednisone or prednisolone or dexamethasone).ab,kf,ti.	184556	Advanced	Display Results More	
12	7 or 8 or 9 or 10 or 11	8003723	Advanced	Display Results More	
13	3 and 6 and 12	267	Advanced	Display Results More	

Save Remove Combine with: AND OR

Appendix 2 shows additional questions that will be considered in the guideline

Monitoring (during and after treatment) and response to treatment
For how long should I monitor bloodworks after treatment?
How and when to transition between different drugs?
When is continued treatment no longer indicated
Should viral loads be monitored during treatment?
Should A:G ratio/APP/SAA be monitored during treatment? And during observational period?
Should therapeutic drug monitoring be performed?
Does therapeutic drug monitoring improve survival rates?
Background questions
When is a treatment trial indicated
Should I vaccinate for FIP?
What are poor prognostic indicators (comorbidities, age)
Most common complications of FIP
Most common comorbidities
What response to treatment can be expected?
Other questions
What alternative therapies can be considered if owner can't afford antivirals?
What to do if uroliths secondary to GS?
How to prevent injections site necrosis?
Should vaccination/spay/neuter be done during antiviral treatment or after?
Should cats in the same household be isolated from cats with FIP?
Should asymptomatic corona positive cats be treated with antivirals?
Should asymptomatic breeding cats be treated with antivirals?

Should coronapositive cats with chronic diarrhoea be treated with antivirals?
Should neutraceuticals be given together with antivirals?

Reference

Guyatt G, Zhao Y, Mayer M, et al. GRADE guidance 36: updates to GRADE's approach to addressing inconsistency. J Clin Epidemiol. 2023;158:70–83. doi:10.1016/j.jclinepi.2023.03.003.