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Journal of
Respiratory Medicine and Research

ISSN 2831-3240

*Review Article*

# Aspects of immunopathology in humans during ssRNA virus infections - what do we know and do we have a foundation for treatment? - A narrative review - Part two.

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**Abstract**

**Background:** The pathophysiological mechanisms underlying single-stranded RNA (ssRNA) virus infections have been investigated extensively and at an accelerated pace in recent years, largely driven by the COVID-19 pandemic. Particular attention has been given to their potential roles in respiratory insufficiency, endothelial dysfunction, thrombosis, and inflammatory responses within the central nervous system.
**Aim:** This narrative review aims to summarize important pathophysiological mechanisms and pathways reported in the literature on respiratory ssRNA virus infections. Key findings are used to explain the outcome of present treatments and to suggest a more immuno-pathological based treatment strategy in these patients.
**Method:** The review is based on studies extracted from an extensive body of literature, encompassing basic research in biochemistry, immunology, virology, and genetics, as well as clinical and therapeutic studies, all indexed in the PubMed database.
**Results:** A species specific human immunological pathway reaction occurs against respiratory ssRNA viral genome antigen. It encompasses by an inferior interferon response limiting the force of the viral defense. A viral independent immunoinflammatory response, with monocytic cell infiltration in the lung ensues and may become severe, characterized by fortifying endothelial activation, a prothrombogenic pathway, and respiratory insufficiency. The pro-inflammatory response has potential ability of becoming chronic, with propagation to the central nervous system, but all responses seem potential treatable from an immune-pathological perspective.
**Conclusion:** The review may serve as a template for treatment and for future studies. It can be concluded that it is essential to have broad immunopathological knowledge when treating and developing strategies for ssRNA virus infections.

**Keywords** : *RNA virus, innate immunity, COVID-19, RSV, Influenza.*

## Aspect of present therapies from immunopathological perspectives

### (a) Antiviral drugs

Autopsy findings from patients who died of COVID-19 show that SARS-CoV-2 is non-cytotoxic and the associated respiratory injury is primarily caused by a concurrent virus-independent immunopathological process [53]. Consequently, antiviral treatment is expected to have limited efficacy, particularly in severely ill patients where the immune response is already activated. This has been demonstrated in several randomized, double-blind, placebo-controlled, multicenter trials, where the antiviral agent remdesivir did not result in significant clinical improvement in patients with moderate to severe COVID-19 [59, 211-213]. One randomized controlled trial (RCT) reported a reduction in time to recovery [214], while a European multicenter RCT found no clinical benefit from remdesivir treatment [215]. The limited or absent effect of remdesivir on all-cause or in-hospital mortality in patients with moderate to severe COVID-19 was later confirmed in the WHO Solidarity trial (including remdesivir and lopinavir) and in a Cochrane review on remdesivir for COVID-19 [60, 216]. These findings support the hypothesis that respiratory injury in COVID-19 is primarily immunologically mediated rather than due to direct viral cytotoxicity.

From a pathophysiologic perspective we assume that antiviral drugs may reduce viral load when administered early during infection, thereby limiting viral replication and mitigating

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**Received:** 05-Nov-2025, Manuscript No. JRMR - 5233**; Editor Assigned:** 07-Nov-2025 **; Reviewed:** 25-Nov-2025, QC No. JRMR - 5233 **; Published:** 03-Dec-2025, **DOI:** 10.52338/jrmr.2025.5233
**Citation:** **Lars Lindberg PhD,MD**. Aspects Of Immunopathology In Humans During Ssrna Virus Infections - What Do We Know And Do We Have A Foundation For Treatment? - A Narrative Review - Part Two. Journal of Respiratory Medicine and Research. 2025 December; 14(1). doi: 10.52338/jrmr.2025.5233.

the subsequent immune response. This was fortified in a meta-analysis on the effect of remdesivir where the authors concluded that a subgroup analysis of hospitalized patients with COVID-19 who did require low or no extra oxygen supplementation had a statistical significant reduced mortality [213]. Early treatment with oral antiviral drugs, such as nirmatrelvir/ritonavir (Paxlovid), in patients with mild to moderate COVID-19 was associated with a reduced risk of all-cause mortality. However, no significant effect was observed on the need for invasive mechanical ventilation, intensive care, or time to recovery in patients under 60 years of age or in vaccinated individuals, as reported in a retrospective cohort study [217]. A Cochrane systematic review concluded that there is very low-certainty evidence supporting an effect of Paxlovid on all-cause mortality, and currently, there is no conclusive evidence to support its use for preventing COVID-19 [218].

Similar findings have been described, when antiviral drugs have been studied in patients with other ssRNA viruses such as, RSV and influenza infections [219, 220].

In summary: The evidence for anti-viral treatment for respiratory ssRNA viruses is conflicting and most studies show no or only a marginal effect on all-cause mortality. Subgroup analyses indicate that there is a small, but statistical significant benefit of anti-viral treatment, if it is used early in patients with mild to moderate disease, thereby reducing the viral load and the following immune response.

**(b) Anti-cytokine treatments**

Infection with respiratory ssRNA viruses promotes an immunologic response characterized by production of various pro-inflammatory cytokines, chemokines, and adhesion molecules. T cells, neutrophils, and monocytes further amplify the inflammatory response through the release of additional pro-inflammatory mediators, as previously described.

Initially, these pro-inflammatory mediators were believed to cause or significantly contribute to multi-organ failure and mortality in COVID-19 patients [221]. The cytokine response to SARS-CoV-2 was characterized as a "cytokine storm," making cytokines a primary target for interventions aimed at reducing mortality [221-223]. However, subsequent findings revealed that the cytokine release was relatively modest. Interleukin-6 (IL-6) levels in COVID-19 patients were 10–200 times lower than those observed in patients with acute respiratory distress syndrome (ARDS) [224]. Conversely, the incidence of vasculitis with microthrombi was nine times higher in COVID-19 than in ARDS, suggesting that T cell-mediated endothelial activation (CD40L/CD40) played a more critical role than the cytokine release [225].

In addition, findings from autopsies and lung biopsies of patients with severe ssRNA virus infections suggest that tissue damage and ARDS-related mortality are primarily mediated by the recruitment and activation of monocytes and macrophages in the lungs, rather than by the presence of elevated pro-inflammatory mediators. These observations are supported by experimental studies, which demonstrated that inhibiting individual inflammatory mediators, or inducing hypocytokinemia in transgenic mice, failed to prevent the development of ARDS or reduce related mortality [226-228].

Several anti-cytokine treatments were recommended during the COVID-19 pandemic and numerous randomized controlled trials (RCTs) were initiated.

**(i) Inhibition of IL-6**

IL-6 levels increase during COVID-19 and have been implicated as a key mediator in the pro-inflammatory cascade. IL-6 exerts its effects through both a pro-inflammatory pathway, via its soluble receptor, and an anti-inflammatory pathway, via its membrane-bound receptor [229].

Tocilizumab, a monoclonal antibody targeting the IL-6 receptor initially demonstrated survival benefits in retrospective studies [230]. It was later recognized that retrospective studies frequently overestimated drug efficacy due to concurrent improvements in standard care over time and may have obscure the clinicians assessment of the drugs. This emphasized the need for blinded RCTs to accurately evaluate treatment effects. However, a randomized controlled trial comparing tocilizumab with standard care in severe COVID-19 was halted due to increased mortality of those treated with tocilizumab: 14 deaths (21%) occurred in the tocilizumab group versus 6 deaths (9%) in the standard care group [231]. Subsequent randomized, double-blind, placebo-controlled trials of tocilizumab in hospitalized COVID-19 patients showed no significant improvement in clinical status or mortality at either 28 or 60 days, even when combined with remdesivir [232-235]. In the large-scale RECOVERY trial, 4116 patients with hypoxia and elevated C-reactive protein levels were randomized to assess tocilizumab's effects. Tocilizumab was associated with reduced 28-day mortality (29%) compared to standard care (35%). However, subgroup analysis revealed that this benefit was limited to patients who also received glucocorticosteroids. In patients treated with tocilizumab alone, mortality was higher (39%) compared to standard care (35%), although the difference was not statistically significant, likely due to a smaller sample size [236]. This raises questions about the true efficacy of tocilizumab, suggesting that the observed mortality reduction may be attributable to corticosteroids rather than IL-6 inhibition alone.

Furthermore, sarilumab, another IL-6 receptor inhibitor, failed to demonstrate significant mortality benefits in a double-blind RCT involving patients with severe or critical COVID-19 [237] . Overall, most RCTs published to date have reported no or limited benefits of IL-6 inhibition with tocilizumab or sarilumab [238-241].

The efficacy of IL-6 inhibitors in COVID-19 remains uncertain and appears to depend on factors such as patient selection, timing of administration, and treatment protocols in the control groups. A consistent and substantial improvement in outcomes from IL-6 inhibition has not been confirmed in systematic reviews or meta-analyses [242].

**(ii) Inhibition of IL-1 and IL18**

Interleukin-1β (IL-1β) and interleukin-18 (IL-18) have been reported to be elevated in some studies of SARS-CoV-2 infection, suggesting an intense inflammatory activation [1, 243]. However, several other studies have found undetectable or normal IL-1β levels (<5 pg/mL), even in patients with severe disease or those who died [43, 46, 170, 244-252].

TLR8 responds to ssRNA viruses in humans by activating nuclear factor κB (NF-κB), a transcription factor for several cytokines including pro-IL-1β, and pro-IL-18 (IL-6, TNF-α, IL-12, IL-10). Pro-IL-1β and pro-IL-18 are inactive precursors that must be cleaved by caspase-1, an enzyme activated within a multiprotein complex known as the inflammasome to generate their active forms, IL-1β and IL-18.

The absence of IL-1β in many patients suggests that pro-IL-1β is not being cleaved or secreted during SARS-CoV-2 infection [43]. Although, inflammasome activation has been demonstrated in SARS-CoV-2-infected cells in vitro and ex vivo, but this process typically requires an additional external stimulus [247]. These findings suggest that while pro-IL-1β is induced, the inflammasome is not activated in vivo. Normal to low IL-1β levels in patients with COVID-19 and multisystem inflammatory syndrome in children (MIS-C) further support the lack of in vivo inflammasome activation [31, 32, 253].

Episodes of elevated IL-1β likely indicate secondary complications such as bacterial infections (pyroptosis) or tissue ischemia from thrombotic infarctions (apoptosis), both of which are known to activate the inflammasome. These complications may explain the cases where IL-1β elevation has been observed. Moreover, the absence of IL-1β activity suggests that neutrophil extracellular traps (NETs), which are linked to inflammasome activation, are unlikely to be a major factor. Additionally, retinoic acid-inducible gene I (RIG-I)-like receptors, which are RNA-sensing molecules involved in inflammasome activation, have been shown to be inhibited by ssRNA viruses such as SARS-CoV-2 and RSV [49, 254].

The lack of therapeutic efficacy in most randomized controlled trials involving IL-1 blockade in COVID-19 patients supports the conclusion that pro-IL-1β is not activated and that IL-1 is not a critical cytokine in SARS-CoV-2 infection (including COVID-19 and MIS-C) in the absence of complications [250, 252, 255].

Conversely, elevated free IL-18 levels in COVID-19 have been associated with an increased risk of macrophage activation syndrome (MAS), severity of illness, and higher mortality [169, 256, 257]. This may result from a caspase-1-independent activation pathway for pro-IL-18, which has been observed in human epithelial cells and macrophages. It explains the discrepancy between IL-1β and IL-18 levels [253, 258]. IL-18 is also known as an interferon-gamma (IFN-γ)-inducing factor and may account for the increased IFN-γ levels reported in COVID-19 and MIS-C [174, 259]. IL-18 stimulates IL-6 and GM-CSF. It also induces the release of an IL-18 binding protein, which controls the levels of the biological active free IL-18. Thereby, it induces a negative-feedback of its pro-inflammatory role [260]. IL-18 inhibition has been shown to effectively reverse IFN-γ-mediated symptoms, such as enterocolitis, rash (via CXCL9 release) [182] and thrombocytopenia—common features of MIS-C [261, 262].

**(iii) Inhibition of tumor necrosis factor-alpha (TNF-α)**

Elevated levels of TNF-α, IL-6 and IL-8, but not IL-1β have been shown to be associated with increased severity and mortality during SARS-CoV-2 infections [263]. The use of monoclonal antibodies inhibiting TNF-α have been investigated and the current evidence remains inconclusive with studies reporting conflicting results. A double-blind, placebo-controlled randomized controlled trial (RCT) found no statistically significant difference in outcomes between COVID-19 patients treated with infliximab and those receiving standard care [264]. However, a systematic review and meta-analysis indicated that early TNF-α inhibition was associated with a lower probability of hospitalization, although the search strategy and methodology was criticized [265, 266].

Combining infliximab with tocilizumab improved survival compared to treatment with tocilizumab and standard care alone in a prospective cohort study [267].

**(iv) Inhibition of INF-γ**

Lung biopsy studies in patients with COVID-19 have demonstrated a robust late IFN-γ activation, which correlates with disease severity, mortality, and the intensity of the inflammatory response [32, 167-169]. IFN-γ regulates the polarization and differentiation of macrophages toward the pro-inflammatory phenotype in the lungs. It is also increased during other ssRNA virus infections such as influenza [268]. Low levels of INF-γ were detected early in neonates, within 7 days after onset of RSV infections [269].

The INF-gamma (IFN-γ) signaling pathway can be inhibited using Janus kinase (JAK1/JAK2) inhibitors such as baricitinib, tofacitinib, and ruxolitinib. These agents possess anti-cytokine properties and can suppress the differentiation of monocytes into macrophages.

All three JAK inhibitors have been evaluated in randomized, placebo-controlled trials, showing beneficial efficacy on mortality and described as one of few proven treatments for patients with COVID-19 [270-273]. Several systematic

reviews and meta-analyses have also demonstrated that JAK inhibition is associated with a reduction in mortality among COVID-19 patients and a moderate- to high-certainty evidence to conclude that JAK inhibition is effective [274-277].

In summary, of the anti-cytokine treatments, inhibition of INF-γ proves to have the most consistent beneficial effect on outcome. Interestingly, it is also the cytokine that regulates the polarization of the recruited macrophages towards a pro-inflammatory direction in the lung.

**(c) Glucocorticosteroids**

Glucocorticosteroids bind to glucocorticoid receptors, which translocate into the cell nucleus and bind to glucocorticoid response elements in the promoter regions of target genes. This interaction leads to upregulation of anti-inflammatory proteins and/or downregulation of pro-inflammatory proteins. Glucocorticosteroids suppress NF-κB–mediated gene induction and limit the expression of several cytokines and chemokines, including IL-1 to IL-6, IL-8, IL-11, IL-13, IL-16, IFN-γ, GM-CSF, TNF-α, RANTES, eotaxin, macrophage inflammatory protein-1α, and monocyte chemoattractant protein-1. They also inhibit the induction of adhesion molecules such as ICAM-1 and VCAM-1 and reduce antibody synthesis [278, 279]

In a randomized, double-blinded controlled study in small children with acute RSV infection glucocorticosteroids treatment with dexamethasone had no effect on the course of the disease [280]. In another randomized, double-blind, placebo-controlled trial no beneficial effects could be detected by glucocorticosteroids treatment with dexamethasone in children with RSV infection needed mechanical ventilation [281].

In a review and meta-analysis evaluating the use of glucocorticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia no statistically significant difference was found between the treated group and control group [282].

In a controlled trial of hospitalized patients with COVID-19, glucocorticosteroid treatment with dexamethasone reduced 28-day all-cause mortality significantly, from 25.7% to 22.9%, with benefit confined only to patients with symptoms in more than 7 days and requiring respiratory support at randomization [283]. In those not receiving invasive mechanical ventilation at randomization the benefit was less and dexamethasone treatment decreased mortality from 22.7 % to 21.7 % (95 % - 0.84–1.03).

In the RECOVERY trial, treatment with the IL-6 inhibitor, tocilizumab, alone was associated with slightly higher mortality compared with patients who received standard care. However, glucocorticosteroids reversed this negative response to an insignificantly reduced mortality [236].

In summary, available data indicate that glucocorticosteroids may provide a small beneficial effect, although it remains unclear whether this benefit arises from a general anti-inflammatory activity or from inhibition of specific pro-inflammatory mediators. It indicates that the pro-inflammatory cells may be a more important target than the mediators they release.

**(d) Inhibition of ANG II**

Angiotensin II potentiates several pro-inflammatory responses and contributes to the polarization of the recruited macrophages to the pro-inflammatory M1 phenotype, one of the cell types responsible for the lung damages during ssRNA infection in the lung [284].

High circulating levels of ANG II have been associated with the severity of lung injury in patients with Influenza A infection, COVID-19, and acute respiratory distress syndrome (ARDS) [20, 24, 25, 147]. Administration of angiotensin-converting enzyme 2 (ACE2), which degrades ANG II, has been linked to reduced lung injury severity in ARDS [285], RSV [19], influenza A [21] and COVID19 [286]. Conditions associated with induction of ACE2 expression in the airways, such as during active smoking or estrogen therapy, have also been associated with a decreased risk of severe and fatal outcomes in patients with SARS-CoV-2 infection [138, 287, 288]. These findings support the role of ANG II in mediating lung injury during respiratory ssRNA viral infections.

Antihypertensive treatments that either inhibit ANG II production through ACE inhibitors or block the AT1R using angiotensin receptor blockers (ARBs) have been associated with improved outcomes in COVID-19 across numerous studies. ARBs, in particular, have been shown to reduce ICU admissions, the need for mechanical ventilation, hospital length of stay (LOS), and mortality, without increasing infection risk [289-303]. These improvements in patients with cardiovascular comorbidities suggest that ANG II and its AT1R play a pathogenic role in COVID-19-associated lung injury, as supported by experimental models [304].

The bioavailability and affinity for the AT1R in the lung may be of importance for ARBs lung protective effects. Telmisartan exhibits the highest distribution volume, lipophilicity, bioavailability, AT1R affinity, and the longest receptor dissociation half-life among tested ARBs. These properties make telmisartan particularly effective in sustaining AT1R inhibition [305-307]. Unlike losartan, telmisartan is not metabolized by cytochrome P450 enzymes, minimizing the risk of drug interactions [306]. Given the short half-life of ANG II (<1 minute) and its rapid internalization upon AT1R binding, sustained receptor blockade is likely beneficial.

Telmisartan significantly reduced 30-day mortality from 23% to 4% in multicenter RCT involving patients with severe COVID-19 [308]. Other ARBs with lower lung bioavailability and receptor affinity have shown more modest protective effects in large population studies of patients with COVID-19

and hypertension [297, 298, 300, 303, 309-311].

Meta-analyses and systematic reviews on the use of ACE inhibitors or ARBs have not consistently demonstrated a reduced risk of all-cause mortality, but an increased risk of acute kidney injury [312-314]. In severely ill patients, ARB use has been associated with decreased arterial blood pressure and increased need for vasopressor support [315]. This effect, often considered adverse, should instead be regarded as an expected pharmacological response in the context of a compensated hypovolemia. Inflammation-induced vascular leakage reduces circulating blood volume in severe COVID-19, and afterload-reducing effects by ARB´s may further lower arterial pressure unless intravascular volume is concurrently expanded using colloids or blood products. ARB´s do not impair cardiac contractility; however, compensating low blood pressure with vasopressors instead of volume resuscitation can compromise cardiac output, oxygen delivery, and renal perfusion, ultimately increasing morbidity [312, 316]. Optimal management involves supporting circulating volume with colloid solutions or blood products rather than crystalloids, which risk exacerbating interstitial fluid overload.

In summary, variability in ARB pharmacodynamics, dose, patient selection, timing of initiating treatment, and concurrent vasopressor use may influence clinical outcomes [316-318]. ARB therapy has not been associated with increased mortality [319]. While several trials have not shown statistically significant differences compared to placebo, often due to small sample sizes, ARBs have consistently demonstrated improvements in disease course.

**(e) Stimulation of PPAR-γ**

Several pharmacological agents enhance PPAR-γ expression, such as certain angiotensin receptor blockers (ARBs) and statins [306, 308, 318, 320-322]. Both have demonstrated protective effects in COVID-19 and promote the polarization of monocyte-derived macrophages toward the anti-inflammatory M2 phenotype. Among ARBs, telmisartan is a notably stronger PPAR-γ activator compared to candesartan, losartan, and other ARBs [306, 318, 323].

Other PPAR-γ agonists, such as melatonin and astaxanthin, have also been shown to be potential therapeutic agents for mitigating the hyper-inflammatory response in SARS-CoV-2 infection, RSV and influenza [185, 186, 324-327].

Notably, melatonin and its metabolites act as ligands for the PPAR-γ nuclear receptors at clinical concentrations. These molecules may exert effects through PPAR-γ activation, offering a mechanistic explanation for the previously observed cytoprotective effects of melatonin [328, 329]. Given their low toxicity, these compounds hold therapeutic promise for immune modulation and inflammatory resolution in ssRNA viral infection and other inflammatory diseases [327, 330, 331].

## Plausible temporal phases of ssRNA viral infections, with aspects of current and future management strategies.

**(a) The acute phase of ssRNA virus infections**

A safe indoors distance from a ssRNA infected individual may require a range of at least 5–7 meters despite an air exchange rate of 10 times per hour and prevention from getting infection for caretakers may require the use of full-face, airtight gas masks. The effectiveness of infection control depends more on well-designed airflow patterns within a room than on the nominal air exchange rate [4].

The clinical course and treatment responses vary widely among individuals, influenced by factors such as pre-existing comorbidities, viral exposure load, genetic background, and ongoing therapies. To date, no treatment has proven curative. An important observation emerging from the COVID-19 pandemic is the significant improvement in standard care over time. This temporal improvement has, in some cases, exceeded the therapeutic impact of experimental treatments, complicating interpretation of retrospective studies [230, 231, 235, 240, 241, 332-335].

Vaccination remains by far the most effective strategy for reducing morbidity and mortality from ssRNA virus infections. Its prophylactic value is well established and irrefutably essential in public health.

When antiviral therapy is considered, it must be administered early in the disease course and targeted at high-risk individuals to effectively limit viral replication and reduce viral load. However, due to the high cost, antiviral drugs are often used as a last resort in severely ill patients—an approach that has proven ineffective in several randomized controlled trials [216]. The observed benefits of vaccination and early antiviral therapy suggest that, while ssRNA viruses may not be intrinsically cytotoxic, uncontrolled viral replication in the absence of inhibitory pathways (such as ACE2) can drive immune activation to life-threatening levels. This highlights the importance of early viral containment.

Findings from autopsies and lung biopsies of patients with severe ssRNA virus infections suggest that tissue damage and ARDS-related mortality are primarily mediated by the recruitment and activation of monocytes and macrophages in the lungs, rather than by the presence of elevated pro-inflammatory mediators. These observations are supported by experimental studies, which demonstrated that inhibiting individual inflammatory mediators, or inducing hypocytokinemia, failed to prevent the development of ARDS or reduce related mortality [226-228]. In contrast, treatments aimed at modulating the polarization and activation of pro-inflammatory monocytes that infiltrate the lung and produce inflammatory mediators have shown more promising results in both experimental models and clinical trials [226, 336].

Hypercytokinemia should be interpreted as a marker of immune cell activation, not as the direct cause of the lung injury. Therapies targeting macrophage activation and polarization, including ANG II inhibition, IFN-γ blockade, and PPAR-γ stimulation (e.g., with ARB or its agonist melatonin), have all been associated with reduced mortality in various studies. Even immunosuppression directed at the rapidly expanding monocyte population in critically ill patients has been advocated using topoisomerase I–II inhibitors, from both initial beneficial findings in clinical research and artificial intelligence–guided recommendations [336-341]. However, no single therapeutic agent appears sufficient to fully suppress the complex and multifactorial inflammatory pathways activated in response to ssRNA viruses. This suggests that coordinated, multi-agent treatment regimens, with minimal adverse effects, are required to effectively manage severe disease. For hospitalized or critically ill patients, interventions to prevent the polarization of recruited monocytes into pro-inflammatory macrophages seem to be essential. ARBs and PPAR-γ agonists (e.g. melatonin, statins) are low-cost, well-tolerated treatments that may serve this purpose effectively as first line therapies. The use of corticosteroids, aimed at suppressing the release of inflammatory mediators, has shown some clinical benefit when combined with other therapeutic strategies.

IFN-γ, a potent inducer of inducible nitric oxide synthase (iNOS), has been implicated in life-threatening complications and septic shock [172]. Its inhibition may represent a valuable next step in managing severely ill patients. Short-term therapy with topoisomerase II inhibitors (e.g., two-dose regimens) may also be considered as part of an escalated treatment strategy. To support infected cells production of the endogenously antiviral peptide - cathelicidin, by maintaining the vitamin D concentration, may also play a role in early prophylaxis. Vitamin D is activated and depleted during long lasting infections and maintaining adequate vitamin D levels has been associated with improved outcomes [205, 209, 342].

Due to the high frequency of arterial and venous thromboembolism despite thromboprophylaxis, antithrombin treatment should always be considered early in the course. Since the viral antigen can be long-lasting antithrombin treatment should not be stopped to early after the acute phase of illness [343, 344].

**(b) The subacute phase and children with MIS-C**

Children generally exhibit greater resilience to acute ssRNA virus infections compared to adults, with significantly lower morbidity and mortality. However, a subset of children develops difficulty in clearing the virus or its antigens, leading to the onset of multisystem inflammatory syndrome in children (MIS-C) [345]. This condition typically manifests 4–6 weeks after exposure to SARS-CoV-2, coinciding with the development and peak of the IgG immune response, which rises to active levels around 10–20 days and peaks between 20–30 days after infection onset [346]. MIS-C is characterized by a persistent fever lasting more than three days, accompanied by two or more clinical symptoms affecting various organ systems. Common manifestations include:

- Gastrointestinal symptoms: right-sided abdominal pain (62–92%), vomiting, or diarrhea.
- Cardiovascular involvement: varying degrees of hypotension (60–80%), and reduced cardiac contractility.
- Dermatologic and mucosal symptoms: rashes, conjunctivitis (74%), and mucosal changes.
- Hematologic abnormalities: signs of coagulopathy such as prolonged INR and aPTT, and elevated D-dimer levels.
- Respiratory symptoms: cough or dyspnea are present in 40–70% of cases.

Laboratory findings typically show elevated markers of inflammation and a positive history of SARS-CoV-2 exposure, confirmed by PCR or serology and [347].

Multiple inflammatory mediators are elevated during MIS-C, particularly IFN-γ and tumor necrosis factor-alpha (TNF-α) [173, 175, 252]. Notably, the gastrointestinal, dermatologic, and cardiovascular symptoms of MIS-C correspond with known effects of IFN-γ [169, 180, 182], which may serve as a clinical clue for its involvement. Given that MIS-C onset typically coincides with peak SARS-CoV-2-specific IgG levels and viral antigen persistency, one treatment option has focused on trying to block the interaction between the IgG-antigen complex and the Fc-γ receptors on the macrophages, thereby minimize the release of inflammatory mediators, such as TNF-α and INF-γ. This is achieved by administering high-dose intravenous immunoglobulin (IVIG), which binds to and block the Fc-γ receptors on the macrophages. IgG without antigenic content will not triggering cytokine release [348]. IVIG is usually combined with high-dose corticosteroids to further suppress inflammatory mediator release.

Since IFN-γ signals via Janus kinase (JAK) receptors, JAK inhibitors may represent a promising therapeutic option. Similarly, IL-18 inhibition, which is an IFN-γ inducing factor and reduce IFN-γ mediated symptoms, may be an attractive alternative [261, 262].

An interesting clinical observation is the consistently low or undetectable serum levels of vitamin D in patients with MIS-C (based on the author's experience from eight consecutive cases). Vitamin D deficiency may have impaired viral antigen elimination, thereby, contributing to sustained IgG-antigen exposure for the macrophages and an escalating inflammatory response and macrophage activation.

In contrast, IL-1β levels are typically low or within normal range in MIS-C, arguing against the use of IL-1 inhibition therapies such as anakinra in MIS-C [251, 252, 349].

For cases of IVIG- and steroid-resistant hyperinflammation—

particularly in the context of MIS-C, Kawasaki disease, hemophagocytic lymphohistiocytosis (HLH), or macrophage activation syndrome (MAS)—etoposide, a topoisomerase inhibitor, has demonstrated clinical efficacy by targeting and suppressing monocytic/macrophagic cell activation [339, 340, 350-352]. Short-term therapy (two doses) with a topoisomerase II inhibitor may offer a potential alternative therapeutic pathway in severe, refractory MIS-C cases not responding to IFN-γ inhibition.

**(c) The chronic phase and the long COVID syndrome.**

Approximately 2–3 months after infection with ssRNA viruses, a subset of patients develops a persistent post-viral fatigue syndrome. In the context of SARS-CoV-2, this condition—referred to as "long COVID"—occurs in over 10% of cases and persists for more than two months. Long COVID arises after the resolution of acute inflammation and peak immunoglobulin response, suggesting a link to ongoing activity in T cells and long lasting inflammatory response.

Symptoms are heterogeneous but primarily neurological, characterized by varying degrees of cognitive dysfunction. Common complaints include general malaise, intractable fatigue, memory impairment, and difficulty concentrating—collectively referred to as "brain fog." In severe cases, symptoms significantly impair activities of daily living [353]. Unlike vascular complications, long COVID does not typically present with paresis; rather, it is suggestive of inflammatory edema affecting cerebral signaling pathways. The syndrome shares features with other post-infectious syndromes such as chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) [354]. Although SARS-CoV-2 has been shown to disseminate throughout the body during acute infection, limited viral presence is found in the central nervous system (CNS), and no direct antiviral immune response has been observed in the CNS, arguing against direct viral cytotoxicity [53, 355]. Furthermore, there is no evidence of virus-induced structural brain damages. Nonetheless, autopsy findings from patients with acute COVID-19 have revealed neuro-inflammatory activation, including perivascular T-cell infiltration and widespread microglial activation, independent of viral antigen presence [354, 356].

Under normal conditions, microglial expression of the co-stimulatory molecule CD40 is low. During ssRNA virus infections the cytokines INF-γ and TNF-α significantly upregulate CD40 expression on microglia. These CD40+ microglia become highly responsive to CD40 ligand (CD40L) expressed on activated CD4+ T cells or present in its soluble form, leading to microglial release of pro-inflammatory mediators and chemokines [165, 194].

Neuro-inflammation mediated by activated microglia is a plausible mechanism underlying symptoms such as brain fog [357]. Elevated levels of the chemokine CCL11—linked to cognitive impairment—have also been observed in long COVID patients [357]. CCL11 appears to be released by the choroid plexus in association with T-cell infiltration and elevated IL-4 levels, the latter uniquely increased in long COVID [358].

CCL11 induces activated microglia to release reactive oxygen species (ROS), contributing to neuronal toxicity [359].

Patients with severe COVID-19 exhibit elevated levels of soluble CD40L and enhanced CD4+ T-cell activity, both of which can contribute to CD40-mediated microglial activation [84]. Activation of the CD40–CD40L axis in the brain disrupts the blood–brain barrier, induces cerebral edema, injures glial cells, and promotes microthrombosis [195]. It also initiates intracellular signaling cascades that increase the production of cytokines, chemokines, and neurotoxins, amplifying neuro-inflammation in the CNS [194]. These mechanisms are closely linked to the cognitive dysfunction, fatigue, and other nonspecific neurological symptoms seen in both ICU patients and those with long COVID [196, 197].

A persistent T-cell–mediated inflammatory response has also been documented in long COVID, possibly driven by limited viral replication in tissue reservoirs [360, 361].

This inability to fully eliminate the virus may also relate to vitamin D deficiency, which compromises cathelicidin production and the elimination of the virus. In fact, low serum 25(OH)D levels, particularly in patients with neurocognitive symptoms, were the only variable significantly associated with long COVID in a multivariate analysis [206].

Long COVID-19 is characterized by prolonged expression of CD40L on activated T cells, and this can activate microglial cells in the brain, similar to the mechanism that may underlie the therapeutic efficacy of monoclonal antibodies targeting CD40L in MS [362].

The CD40–CD40L pathway represents a critical immunological bridge between the immune system and the CNS and is recognized as a key factor in several neurological diseases [195]. Targeting this pathway has gained therapeutic interest following positive results from a phase 2 trial of frexalimab, a monoclonal antibody that blocks CD40–CD40L interaction, in MS [362].

Despite the compelling indication implicating the CD40–CD40L pathway in long COVID and its therapeutic potential, there are currently no known ongoing clinical studies investigating this target in the context of long COVID [360].

## Conclusion

This narrative review, in two parts, analyzes and describes the immunopathological pathways involved in human infections caused by single-stranded RNA (ssRNA) viruses. These infections influence host immune responses in diverse ways and to varying degrees. A plausible pathophysiological course is proposed, outlining distinct temporal phases of the

disease. From a pathophysiological perspective, current and potential treatment strategies are discussed in relation to these mechanisms. Overall, it can be concluded that adopting a broad immunopathological perspective is essential when managing and developing therapeutic strategies for diseases caused by ssRNA viruses.

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