



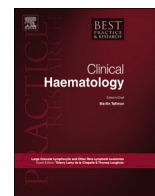
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Coagulopathy in COVID-19 and anticoagulation clinical trials

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ABSTRACT

Severe acute respiratory disease coronavirus 2 (SARS-CoV-2) first emerged in Wuhan, China, in December 2019 and has caused a global pandemic of a scale unprecedented in the modern era. People infected with SARS-CoV-2 can be asymptomatic, moderate symptomatic or develop severe COVID-19. Other than the typical acute respiratory distress syndrome (ARDS), patients with moderate or severe COVID-19 also develop a distinctive systemic coagulopathy, known as COVID-19-associated coagulopathy (CAC), which is different from sepsis-related forms of disseminated intravascular coagulation (DIC). Endotheliopathy or endotheliitis are other unique features of CAC. The endothelial cell perturbation can further increase the risk of thrombotic events in COVID-19 patients. In this review, we will summarize the current knowledge on COVID-19 coagulopathy and the possible mechanisms for the condition. We also discuss the results of clinical trials testing methods for mitigating thrombosis events in COVID-19 patients.

1. Clinical and lab findings related to COVID-19 coagulopathy

One of the early evaluations of thrombotic events in COVID-19 patients admitted to the intensive care unit (ICU) showed that the incidence of thrombotic events was 31%, of which venous thromboembolic events (VTEs) were the most common, accounting for some 27% of events [1]. This evaluation is consistent with a more recent meta-analysis of VTEs in hospitalized COVID-19 patients [2]. It is also noteworthy to mention that the thrombotic events developed in most COVID-19 patients showed distinct features compared to the well-known DIC, and hence it was named CAC (Table 1) [3].

Studies from different groups suggested that the level of D-dimer, a fibrin (ogen) degradation product, is dramatically elevated in COVID-19 patients with thrombotic events [4–6]. D-dimer is widely used as a biomarker for diagnosis of thrombotic disorders. Although multiple studies have shown that D-dimer level on hospital admission predicts disease severity, some reports, such as Vincent et al., suggest that, unless DIC is suspected, repeated measurement of D-dimer level has little value [3].

Other important characteristics of CAC include significantly increased circulating levels of Von Willebrand factor (VWF) and factor VIII, as well as increased activity of VWF [7]. The elevated levels of coagulation factors in CAC do not cause prolongation of activated partial thromboplastin time (aPTT) or prothrombin time (PT). This is in contrast to DIC, in which the PT is prolonged [8].

Another important finding related to CAC is endotheliopathy or endotheliitis, indicating the direct infection of endothelial cells by the virus. Indeed, biopsies from patients showed the presence of viral particles in endothelial cells within different organs [9].

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Table 1
Similarities and differences between CAC and DIC.

	DIC	CAC
Platelet count	↓	↑↓
D-dimer	↑	↑
PT/aPTT	↑	↔↑
Fibrinogen	↓	↑
Antithrombin	↓	↔
VWF	↑	↑
FVIII	↑↓	↑
Thrombosis	↑	↑
bleeding	↑	↔↑

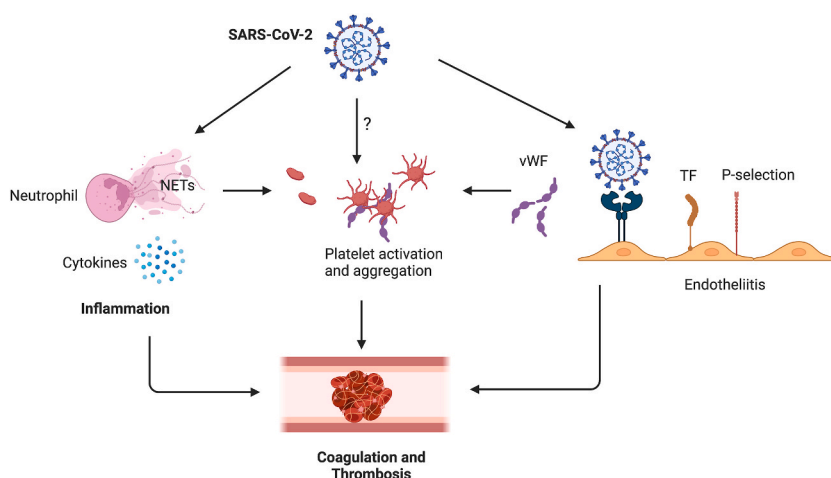


Fig. 1. Formation of CAC in COVID-19 patients. SARS-CoV-2 infection will cause neutrophil activation and NET release, resulting in pathological prothrombotic environment. Pro-inflammatory cytokines can activate neutrophils and endothelial cells, which will further stimulate thrombosis. SARS-CoV-2 might be able to interact with platelets directly, leading to platelet activation and thrombosis. SARS-CoV-2 binding to ACE2 on endothelial cells causes endotheliitis, shifting the vascular equilibrium towards a procoagulant state.

Endotheliitis increases the risk of thrombotic events in patients with COVID-19 pneumonia, and autopsy studies have confirmed the presence of macrovascular and microvascular thrombi in the lungs and other organs of non-survivors of COVID-19 [9–11].

Although platelets play an important role in thrombosis, many patients with COVID-19 have only slightly lowered platelet count (between 100×10^9 and $150 \times 10^9/L$). Severe thrombocytopenia is rarely seen, only occurring in less than 5% of patients [12]. Importantly, thrombocytopenia associated with a higher risk of severe COVID disease [13].

2. Possible mechanisms of COVID-19 coagulopathy

2.1. Platelets

Since platelets are pivotal for thrombus formation, their role in SARS-CoV-2 mediated coagulopathy has been widely-studied. Evidence has shown that traces of SARS-CoV-2 mRNA are detectable in isolated platelets by RT-qPCR, and virions have been visualized within platelet sections by electron microscopy [14–16]. In contrast, Bury et al. couldn't detect SARS-CoV-2 mRNA in either platelets or serum samples, despite the fact that some patients had high viral loads [17]. They concluded that SARS-CoV-2 could only occasionally enter into platelets and this was not considered clinically significant.

Although whether or not platelets can interact with and internalize SARS-CoV-2 is still controversial, several receptors on platelets have been suggested to mediate the binding and internalization of SARS-CoV-2; however, published data on this is controversial. Angiotensin converting enzyme-2 (ACE2) is the major receptor for RBD (receptor binding domain) of SARS-CoV-2 spike protein [18], and its expression on platelets was only recently explored. Manne et al. [19] couldn't detect platelet ACE2 mRNA or ACE2 protein

Table 2
Anti-COVID-19 drugs in clinical trials targeting coagulopathy.

Intervention	Trial No.	Patient status	Cohort size	Significant or not of primary outcome	Reference No.
Prophylactic heparin	N/A	Hospitalized	4297	Yes	[55]
	NCT04662684	Discharged at high risk of VT	320	Yes	[64]
Therapeutic-dose heparin	NCT04372589, NCT04505774, NCT02735707, NCT04359277	Noncritically ill	2219	Yes	[56]
	NCT02735707, NCT04505774, NCT04359277, NCT04372589	Critically ill	1098	No	[57]
	NCT04362085	Moderately ill with increased D-dimer level	465	No	[59]
	NCT04394377	Hospitalized with increased D-dimer level	615	No	[60]
	REBEC RBR-949z6v	Requiring mechanical ventilation	20	Yes	[61]
Therapeutic or intermediate-dose heparin	NCT04401293	Hospitalized with increased D-dimer level	257	No	[58]
Intermediate or standard-dose heparin	N/A	Critically ill	562	No	[62]
	NCT04360824	ICU and/or had coagulopathy	176	No	[63]
Aspirin	NCT04381936	Hospitalized	14,892	No	[65]
Aspirin or therapeutic dose heparin	NCT04498273	outpatients	700	No	[66]
Aspirin or P2Y12 inhibitor	NCT02735707	Critically ill	1557	No	[67]
Therapeutic dose heparin with or without P2Y12 inhibitor	NCT04505774	Non-critically ill	562	No	[68]
TCZ	N/A	Patients with COVID-19	11	No	[71]
	CTRI/2020/05/025,369	Hospitalized	180	No	[73]
	NCT04356937	Moderately ill	243	No	[74]
	NCT04372186	Hospitalized without mechanical ventilation	389	No	[75]
	NCT04403685	Severely or critically ill	129	No	[76]
	N/A		42	Yes	[80]
	ChiCTR2000029765	Patients confirmed by PCR	65	Yes	[77]
	NCT04317092		1221	Yes	[79]
Methylprednisolone with or without TCZ	N/A	Hospitalized	76	No	[72]
TCZ or sarilumab	NCT02735707	Critically ill	895	Yes	[78]
Subcutaneous TCZ	IRCT20150303021315N17	Severely and critically ill	126	Yes	[81]
Low-dose TCZ	NCT04331795	Hospitalized	32	Yes	[82]
Colchicine	NCT04322682	PCR confirmed	4488	No	[84]
	N/A	Suspects in the community	2755	No	[85]
	NCT04381936	Hospitalized	11,340	No	[86]
	NCT04326790		105	Yes	[87]
	NCT04350320		103	No	[88]
	NCT04328480		1279	No	[91]
	IRCT20190810044500N5	Moderately to severely ill	153	Yes	[89]
	RBR- 8jyhkh		72	Yes	[92]
	NCT04367168	Severely ill	116	No	[90]
Dexamethasone	NCT04381936	Hospitalized	6425	Yes	[93]
	NCT04327401	Moderately to severely ill	299	Yes	[94]
High vs standard dose dexamethasone	NCT04509973	Severe hypoxemia	1000	No	[95]
	NCT04509973		1000	Yes	[96]
Low vs medium vs high dose dexamethasone	IRCT20100228003449N31	Moderately to severely ill	133	No	[97]
High vs low dose dexamethasone	NCT04395105	ARDS	98	Yes	[98]
Systemic corticosteroids with or without TCZ	NCT04381936	Hypoxia and systemic inflammation	4116	Yes	[99]
Systemic corticosteroids with or without baricitinib	NCT04421027	Hospitalized	1525	No	[100]
Inhaled budesonide	NCT04416399	Mild	146	Yes	[101]
	ISRCTN86534580	At higher risk of complications	2530	Yes	[102]
Inhaled ciclesonide	NCT04377711	Nonhospitalized	413	No	[103]
Inhaled and intranasal ciclesonide	NCT04435795	Outpatients	203	No	[104]

N/A, not applicable; VT, venous thromboembolism.

using RNA-seq, RT-PCR, and western blotting. These findings were confirmed by Zaid et al. [14] using qRT-PCR analysis. However, Zhang et al. [15] could detect robust expression of ACE2 in both human and mouse platelets using RT-PCR and western blotting. The possibility of those different results could be due to the way platelets were prepared, as suggested by Campbell et al. [16].

Another plausible receptor group is the RGD (Arg-Gly-Asp) binding integrins, particularly platelet expressing integrin α IIb β 3. Early studies noted the presence of an RGD motif in the RBD of SARS-CoV-2 spike glycoprotein, leading to the hypothesis that RGD binding integrins may be involved in SARS-CoV-2 infection [20,21]. However, a recent molecular dynamics microscale simulation did not support this hypothesis [22]. Unlike the RGD motifs of known integrin ligands, usually located in a flexible loop (so-called RGD finger), the SARS2-S RGD motif resides in a rigid α -helical structure, leaving the sidechain orientation unfavorable for integrin binding.

Another potential receptor for SARS-CoV-2 on platelets is CD147 (basigin). Direct interaction between CD147 and SARS-CoV-2 spike protein has been reported using a range of different techniques [23]. Another paper from the same group suggests that CD147 is a universal receptor for different strains of SARS-CoV-2 [24]. However, Shilts et al. [25] couldn't detect the interaction between overexpressed CD147 and recombinant spike protein using flow cytometry. Similarly, ELISA and avidity-based binding assays failed to detect their interaction. Moreover, Ragotte et al. [26] also failed to detect the interaction using both size exclusion chromatography and SPR.

2.2. Endotheliitis

Endothelial cells play a pivotal role in inflammation-induced coagulation in COVID-19 (Fig. 1). The pro-inflammatory response to COVID-19 results in the release of pro-inflammatory cytokines, such as cytokines interleukin-1 beta (IL1 β), interleukin-6 (IL6), and TNF, all of which contribute to endotheliitis in COVID-19 patients [27,28]. IL6 can further promote the release of pro-inflammatory cytokines by endothelial cells, which enhances cytokine secretion [29]. IL-1 β and TNF can activate glucuronidases, which can degrade the glycocalyx, increase the deposition of hyaluronic acid in the extracellular matrix, and promote fluid retention via upregulation of expression of hyaluronic acid synthase 2 [29]. Since ACE2 receptors are also expressed by endothelial cells, binding of SARS-CoV-2 to ACE2 on endothelial cells impairs the activity of ACE2 [30] and results in endothelial cell activation [31,32]. All of these events can lead to the disruption of vascular integrity and endothelial cell death, thereby causing exposure of the thrombogenic basement membrane and the activation of the clotting cascade [33]. Further, endothelial cell activation can lead to elevated plasma VWF antigen and down-regulation of the protein disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13), which results in an abnormal ratio of VWF to ADAMTS-13 [34]. Endothelial cell activation can also increase the level of plasminogen activator inhibitor 1 (PAI-1), inhibiting tissue plasminogen activator (tPA), thereby reducing fibrinolysis [35,36]. The resulting hypofibrinolytic state can increase fibrin deposition in alveolar tissues and the microvasculature, leading to ARDS [37].

2.3. Neutrophil extracellular traps (NETs)

Another important factor contributing to coagulation in COVID-19 is the elevated NETs released by circulatory or infiltrating neutrophils in COVID-19 patients. Although NETs are important for preventing pathogen invasion, activated neutrophils and NETs can also contribute to a pathological prothrombotic environment (Fig. 1) [38,39]. NETs can stimulate DVT via a third thrombus scaffold acting with elevated fibrin and VWF [40]. Additionally, cell-free DNA from NETs have been implicated in activation of the coagulation pathway [41,42]. Moreover, the expression of tissue factor in NETs and neutrophil-derived microparticles can directly activate the coagulation pathway [43–45].

Several mechanisms potentially contribute to COVID-19 induced NET formation. Both *in vivo* and *in vitro* studies have shown that SARS-CoV-2 can directly interact with healthy neutrophils and induce NET release through ACE2, virus replication, and PAD-4 signaling [46,47]. Pro-inflammatory cytokines such as IL-8 and IL-1 β can also induce NET release in tissues and intravascular neutrophils [48,49]. Platelet activation is another factor triggering NET release through toll-like receptor 4 (TLR4), platelet factor 4 (PF4), and extracellular vesicle-dependent processes [50,51]. The direct interaction between activated platelets and neutrophils could also enhance NET formation and thromboinflammation in COVID-19 patients. Indeed, previous studies have shown that platelet surface proteins, such as P-selectin, TLR4, ICAM-2, platelet glycoprotein GPIb, CD40L, could bind to their receptors on the neutrophil, promoting NET release [51–54].

3. Clinical trials related to COVID-19 coagulopathy so far

In order to prevent or treat coagulopathy in COVID-19 patients, several drugs have been tested in clinical trials (Table 2). Here, we summarized the clinical trial results and the efficacy of tested drugs in anticoagulation.

3.1. Heparin-related clinical trials

An observational clinical trial evaluated whether early initiation of prophylactic anticoagulation compared with no anticoagulation was associated with decreased risk of death in hospitalized patients with COVID-19 [55]. This large trial found that prophylactic heparin treatment reduced 30-day mortality and didn't increase serious bleeding events.

Several clinical trials have evaluated the efficacy of therapeutic-dose anticoagulation in hospitalized patients. The large ATTACC, ACTIV-4a, and REMAP-CAP multiplatform trial is designed to evaluate the effects of therapeutic-dose anticoagulation with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) in non-critically ill and critically ill patients with COVID-19,

respectively [56,57]. For non-critically ill patients, therapeutic-dose heparin improved organ support-free days but didn't improve mortality or length of hospitalization. For critically ill patients, therapeutic-dose heparin did not improve the primary outcome. The HEP-COVID clinical trial tested the efficacy of therapeutic-dose LMWH vs standard prophylactic, or intermediate-dose LMWH in high-risk patients hospitalized with COVID-19 [58]. Their results showed that therapeutic-dose LMWH reduced VTE, arterial thromboembolism (ATE), and death in non-ICU patients with highly elevated levels of D-dimer. The RAPID randomized clinical trial also investigated the efficacy of therapeutic dose heparin (LMWH or UFH) in adult COVID-19 patients with elevated D-dimer levels [59]. Although there was no significant improvement of the primary outcome, therapeutic dose heparin was found to significantly reduce mortality. The ACTION clinical trial evaluated whether therapeutic anticoagulation can improve clinical outcomes in hospitalized patients displaying an elevated level of D-dimer [60]. Compared with prophylactic anticoagulation, therapeutic dose of rivaroxaban did not improve clinical outcomes. The HESACOVID studied whether therapeutic enoxaparin can improve gas exchange and increase the mechanical ventilation-free days in severely ill COVID-19 patients [61]. Although therapeutic enoxaparin intervention resulted in improved primary outcome and increased mechanical ventilation-free days, due to the small sample size, this investigation cannot accurately assess the difference in mortality between these two groups.

Two clinical trials also examined the effects of intermediate-dose heparin treatment in COVID-19 patients. The INSPIRATION clinical trial evaluated the efficacy of intermediate-dose enoxaparin in COVID-19 patients admitted to ICU [62]. Trial results suggest that intermediate-dose, compared with standard-dose, prophylactic enoxaparin had no benefit in ICU patients. Another smaller trial also found that intermediate-dose enoxaparin did not prevent mortality and thrombosis in adult patients admitted to ICU and/or with laboratory test evidence of coagulopathy [63].

3.2. Clinical trials after patient discharge

The MICHELLE trial examined the efficacy of rivaroxaban for post-discharge thromboprophylaxis in 320 patients hospitalized with COVID-19 and at increased risk for venous thromboembolism [64]. Extended post-discharge thromboprophylaxis with rivaroxaban 10 mg/day for 35 days significantly improved primary clinical outcomes without increasing bleeding events.

4. Clinical trials targeting platelets

The large RECOVERY trial examined whether standard care plus 150 mg aspirin could reduce 28-day mortality in patients hospitalized with COVID-19 [65]. Their results suggested that aspirin intervention didn't improve the primary outcome. The ACTIV-4B outpatient thrombosis prevention trial examined the benefits of aspirin and therapeutic-dose apixaban in symptomatic but clinically stable outpatients with COVID-19 [66]. The study was terminated after enrolment of 9% of participants since treatment with aspirin or apixaban did not improve the composite clinical outcome. The large REMAP-CAP trial tested whether aspirin or P2Y12 inhibitor could improve outcomes in critically ill patients with COVID-19 [67]. Their results showed that treatment with aspirin or P2Y12 inhibitor didn't improve the organ support-free days within 21 days. Another randomized clinical trial investigated the addition of P2Y12 inhibitor to anticoagulant therapy in non-critically ill patients hospitalized for COVID-19 [68]. Compared to therapeutic dose of heparin alone, addition of P2Y12 inhibitor didn't improve organ support-free days within 21 days of hospitalization.

4.1. Clinical trials related to anti-inflammation

4.1.1. Tocilizumab

Tocilizumab (TCZ) is a humanized monoclonal antibody which blocks the IL-6 signaling pathway through competitive inhibition of IL-6 receptor (IL-6R). Several clinical trials have evaluated its therapeutic effect and its effect on the cytokine storm in COVID-19 patients. Most of the clinical trials did not show improvement in COVID-19 patients with TCZ intervention [69–76]. It is noticeable that in one clinical trial significantly increased IL-6, α -defensin, a pro-thrombotic peptide, and D-dimers were observed after TCZ intervention [69]. Another clinical trial examined the serum profile of 12 cytokines from COVID-19 patients before and after TCZ administration [70]. Their result indicated that except IL-6, the concentration of IL-1 β , -2, -4, -10, -12p70, -18 and sIL-6R were all unexpectedly increased after TCZ treatment, suggesting that some inflammatory pathways escape IL-6R blockade and were even amplified by treatment. However, several clinical trials indicated that TCZ could be beneficial for COVID-19 patients [77–82]. The major improvement after TCZ administration was for hypoxia in moderate, severe or critically ill patients with COVID-19 [77–81]. Two clinical trials also showed that TCZ, if used at the early stages of respiratory failure, could improve clinical parameters and reduce the risk of death for severe or critically ill patients [80,81].

4.1.2. Colchicine

Colchicine is an alkaloidal anti-inflammatory compound and can bind to free tubulin dimers and prevent microtubule polymerization, which is considered to be important in inhibiting coronavirus infection [83]. The COLCORONA and PRINCIPLE trials were two large scale clinical trials to examine the efficacy of colchicine in non-hospitalized patients [84,85]. The COLCORONA trial found only subtle improvement in patients whose diagnosis was confirmed by a positive PCR result. Similarly, the PRINCIPAL trial didn't find any benefits for patients treated with colchicine. The RECOVERY, COLCOVID, and GRECCO-19 trials investigated the effect of colchicine in hospitalized patients [86–88]. There were no statistically significant differences between the colchicine and usual care patients in both RECOVERY and COLCOVID trials. Although the GRECCO-19 trial suggested that colchicine intervention could reduce clinical deterioration, the interpretation of this result should be viewed with caution as the study was open-label and both the sample size and

Practice points.

- In hospitalized COVID patients, LMWH or UFH is preferred for treatment.
- Therapeutic doses of heparin is beneficial to non-ICU patients but not ICU patients.
- Dexamethasone, TCZ or sarilumab can be applied to patients under certain conditions.

Research agenda.

- Investigate the causes of CAC in COVID-19 patients.
- Investigate the clinical trials targeting coagulopathy in COVID-19 patients.

number of clinical events were relatively small. Several small, randomized trials have also evaluated colchicine in hospitalized patients [89–92]. Some of those trials suggested benefits of intervention with colchicine, which could reduce oxygen supplement and levels of certain inflammatory markers. However, the results were again difficult to interpret due to small sample size and open-label design.

4.1.3. Corticosteroids

Several clinical trials have investigated the efficacy and dosage of corticosteroids for treatment of COVID-19. The RECOVERY trial reported that dexamethasone was beneficial in hospitalized patients who were mechanically ventilated or who required supplemental oxygen at enrolment [93]. However, there was no benefit in patients who did not require supplemental oxygen at enrolment of dexamethasone. Although the CoDEX clinical trial terminated early, the results suggested that dexamethasone was beneficial in hospitalized patients [94]. The COVID STEROID 2 trial investigated the use of dexamethasone with 6 mg or 12 mg once a day for up to 10 days in hospitalized patients with severe hypoxemia [95]. A higher dose of dexamethasone did not result in better primary outcomes compared with low dose. However, a pre-planned secondary Bayesian analysis of the COVID STEROID 2 trial found a higher probability of benefit and a lower probability of harm for the high dose compared with low dose [96]. Another two small randomized trials also examined the dosage of dexamethasone in COVID-19 patients. Data from one trial suggested that a lower dose of dexamethasone (8 mg once daily) resulted in a shorter time to clinical improvement, a lower frequency of adverse events, and lower mortality rate compared to intermediate or high dose of dexamethasone treatment [97]. However, the second small randomized trial did not find any difference in primary outcome [98]. Moreover, several clinical trials also investigated the efficacy of systemic corticosteroid in combination with other immunomodulators, such as TCZ [99,78] and baricitinib [100]. Their results showed benefits in certain subsets of hospitalized patients, especially those with early critical illness or with signs of systemic inflammation. Inhaled corticosteroids, because of their direct anti-inflammatory effects on the lungs, have also been tested for treatment of COVID-19. Although inhaled budesonide [101,102] and ciclesonide [103,104] have shown some benefits to patients with COVID-19, these findings should be interpreted with caution due to the small sample size and open-label design.

5. Conclusion

Patients with moderate or severe COVID-19 developed a distinctive systemic coagulopathy, known as CAC. In addition to classical coagulation pathways, the acute inflammatory response caused endotheliitis and NETs also contributed to CAC. Based on the current literature and clinical trial data, there is evidence that several procedures are beneficial in management of coagulopathy in COVID-19 patients. For non-hospitalized patients without evidence of VTE, anticoagulants or anti-platelet therapy should be avoided. VTE prophylaxis should not be used in patients after hospital discharge. In hospitalized COVID patients, LMWH or UFH, rather than oral anticoagulants, is recommended for treatment. For adult patients who require low-flow oxygen, but not ICU care, therapeutic doses of heparin seem to be clinically beneficial. For adult patients who require ICU care, prophylactic doses of heparin can be used for treatment but intermediate or therapeutic doses of heparin should be avoided. Of the drugs designed to mitigate inflammation responses, colchicine should be avoided for treatment of both non-hospitalized and hospitalized patients. Dexamethasone can be applied to non-hospitalized patients for an underlining condition and to hospitalized patients who require supplemental oxygen. Finally, data supports the cautious use of TCZ or sarilumab in hospitalized patients who need oxygen supplementation.

Declaration of competing interest

Authors declare that they have no competing interests.

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