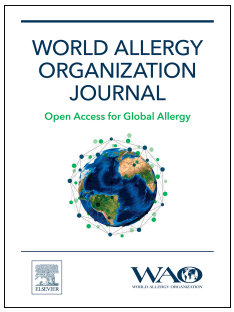


# Does hereditary angioedema make COVID-19 worse?

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**Title page**

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**Declaration**

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**Abstract**

The coronavirus disease 2019 (COVID-19) pandemic has spread rapidly worldwide. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent for COVID-19, enters host cells via angiotensin-converting enzyme 2 (ACE2) and depletes ACE2, which is necessary for bradykinin metabolism. The depletion of ACE2 results in the accumulation of des-Arg(9)-bradykinin and possible bradykinin, both of which bind to bradykinin receptors and induce vasodilation, lung injury and inflammation. It is well known that an overactivated contact system and excessive production of bradykinin comprise the key mechanisms that drive the pathogenesis of hereditary angioedema (HAE). It is reasonable to speculate that COVID-19 may increase disease activity in patients with HAE and vice versa. In this review, we explore the potential interactions between COVID-19 and HAE in terms of the contact system, the complement system, cytokine release, increased T helper 17 cells, and hematologic abnormalities. We conclude with the hypothesis that comorbidity with HAE might favor COVID-19 progression and may worsen its outcomes, while COVID-19 might in turn aggravate pre-existing HAE and prompt the onset of HAE in asymptomatic carriers of HAE-related mutations. Based on the pathophysiologic links, we suggest that long-term prophylaxis should be considered in patients with HAE at risk of SARS-CoV-2 infection, especially the prophylactic use of C1 inhibitor and lanadelumab and that HAE patients must have medications for acute attacks of

angioedema. Additionally, therapeutic strategies employed in HAE should be considered for the treatment of COVID-19, and clinical trials should be performed.

**Keywords:** COVID-19, hereditary angioedema, ACE2, contact system, complement system

**List of Abbreviations**

acute respiratory distress syndrome: ARDS; ADAM metallopeptidase domain 17: ADAM17; angiotensin-converting enzyme: ACE; bradykinin: BK; bradykinin receptor B1: B1R; bradykinin receptor B2: B2R; C1 inhibitor: C1-INH; Coronavirus disease 2019 : COVID-19; des-Arg(9)-bradykinin: DABK; granulocyte-colony stimulating factor: GCSF; granulocyte-macrophage colony stimulating factor: GM-CSF; hereditary angioedema: HAE; high-molecular-weight kininogen: HMWK; interleukin-1: IL-1; macrophage inflammatory protein: MIP; mannose-binding lectin: MBL; mannose-binding lectin associated serine protease: MASP; Middle East respiratory syndrome coronavirus: MERS-CoV; severe acute respiratory syndrome coronavirus 2: SARS-CoV-2; tumor necrosis factor γ: TNF-γ;

transforming growth factor-β: TGF-β; transforming growth factor-β: TGF-β.

## Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly across most of the world. According to the World Health Organization report of June 24, 2020, more than 9 million cases were confirmed, of which more than 480 000 died from this pandemic disease. The numbers of infection and death from COVID-19, globally, are still rising rapidly. Tremendous efforts have been made to unravel the pathophysiology and prognostic factors of COVID-19. It has been established that SARS-CoV-2 enters host cells in the respiratory tract via the transmembrane protein angiotensin-converting enzyme (ACE) 2 and uses the transmembrane serine protease TMPRSS2 for spike (S) protein priming [1]. After entering the host cell, SARS-CoV-2 elicits a series of innate and adaptive immune responses, which are responsible for virial clearance as well as inflammation [2]. In addition, interactions between SARS-CoV and the contact system, the coagulation systems, and the complement pathway are held to be of relevance for the course and outcome of COVID-19 [3-7].

Hereditary angioedema (HAE) is a rare genetic disease with an estimated prevalence of 1.1 to 1.6 per 100,000 worldwide [8], presenting with recurrent attacks of subcutaneous and submucosal edema. The pathophysiology of HAE involves the contact, complement and fibrinolytic systems, among which the contact system is the key pathway [9]. Certain cytokines such as interleukin-1(IL-1) and transforming growth factor-β (TGF-β), may also play a role in the pathophysiology of HAE [10]. Therefore, it is reasonable to hypothesize that there might be an interaction between

COVID-19 and HAE. As of now, there are no reports of HAE patients infected with SARS-CoV-2, and there is, therefore, no information on the course of COVID-19 in patients with HAE. Given the low prevalence and large spectrum of HAE, it is unlikely that guidance on the management of COVID-19 in patients with HAE will come from clinical observations or studies on HAE patients with COVID-19. It is, therefore, important to explore and analyze the potential association between the two clinical conditions in terms of their known underlying pathophysiologic mechanisms, which is what this review does.

***The role of contact system in HAE and COVID-19***

As depicted in Figure 1, mutations of the SERPING1 gene that result in a deficient or dysfunctional C1 inhibitor (C1-INH) are the cause of type 1 and 2 HAE. In patients with HAE type 1 or 2, the lack of functional C1-INH leads to overactivation of the contact system and its bradykinin (BK) forming cascade. The resulting overproduction of BK causes the attacks of angioedema. des-Arg(9)-bradykinin (DABK) is generated in the process, without claiming a role in the development of angioedema. As a multi-functional serine protease inhibitor, C1-INH has a wide range of substrates including prekallikrein, kallikrein, factor □, factor □a, factor □f, plasminogen, plasmin, C1r, C1s, and mannose-binding lectin (MBL)-associated serine protease (MASP)-1 and MASP-2 [11]. Thus, in addition to its central function in the contact system, C1-INH also regulates the complement system and the fibrinolytic and coagulation system (Figure 1). Without the inhibition of C1-INH, factor □

autoactivates to form factor □a by contact with the initiating surface, and then further generates a 28.5-kDa fragment called factor □f [12,13]. In peripheral blood, prekallikrein and high-molecular-weight kininogen (HMWK) form a biomolecular complex at a ratio of 1:1 [14]. Both factor □a and factor □f convert prekallikrein-HMWK complex to kallikrein-HMWK complex, while the generation of kallikrein results in feedback activation of factor □ [15]. Kallikrein then digests HMWK to BK, which is the essential mediator of swelling attacks. In type 1 and 2 HAE, excessive generation of BK is caused by overactivation of the plasma contact system [16]. Carboxypeptidase N/M removes the C-terminal peptide from bradykinin to generates DABK [9,17]. BK binds to bradykinin receptor B2 (B2R), while DABK binds mainly to the bradykinin receptor B1 (B1R) but also to B2R on the surface of endothelial cells, which leads to vasodilation and increased vascular permeability [18,19], and the production of vasodilators including nitric oxide and prostaglandin E2. In patients with HAE, especially during edema attacks, the level of BK can significantly increase, not only at the local site of involvement but also the circulation[16]. B1R can be induced by cytokines including IL-1 and tumor necrosis factor γ (TNF-γ). Lys-des-Arg(9)-BK, another BK metabolite, stimulates the production of IL-1β, both of which can upregulate the expression of B1R [20,21]. In addition, BK can be degraded into inactive fragments by ACE, as well as aminopeptidase P and neutral endopeptidase [17,22]. To summarize, in type 1 and 2 HAE, the deficiency of C1-INH leads to overactivation of the BK-formation cascade and the overproduction of BK and DABK, which cause the attacks of angioedema

(Figure 1). For HAE patients with normal levels of C1-INH, the underlying mechanism is thought to be related to mutations affecting the BK-formation cascade, which includes genes that encode factor XII, angiopoietin-1, plasminogen and kininogen [23-26].

In COVID-19, the S protein on the surface of SARS-CoV-2 has been shown to bind to ACE2 in the lung, which is similar to the mechanism of SARS-CoV-1 [27]. To prepare the host endothelial cells for viral entry, SARS-CoV-1 interacts with ACE2 on the cell surface, inducing membrane fusion and then endocytosis [28]. The translocation of ACE2 from the cell surface to the intracellular space is the part of the process called internalization. It has been reported that the interaction between SARS-CoV-2 and ACE2 increases the activity of ADAM metallopeptidase domain 17 (ADAM17), which can induce the cleavage of ACE2 and the shedding of the ACE2 extracellular domain. Therefore, SARS-CoV infection and S protein on the virion surface reduce the cell-surface expression of ACE2 by both internalization and shedding of ACE2 [29]. ACE2 is a homologue of ACE and participates in the degradation of DABK by cleaving it into inactive products[30]. Partly owing to DABK/B1R axis mediated chemokines release including C-X-C motif chemokine 5, macrophage inflammatory protein-2 (MIP2), C-X-C motif chemokine 1, and TNF-α, ACE2 plays an essential role in the development of pulmonary inflammation [30]. Thus, the depletion of ACE2 by SARS-CoV-2 infection results in impaired DABK inactivation. Binding of DABK to B1R can prompt neutrophil infiltration, increased

capillary leakage [10] which comprise the key features of acute respiratory distress syndrome (ARDS), and lead to more sever lung injury and inflammation [30,31]. The accumulation of DABK might result in negative feedback of BK degradation and leave BK binding to B2R on the surface of endothelial cells. Binding of BK to B2R also result in increased vascular permeability and angioedema in lung tissue [9]. Moreover, BK, histamine and serotonin are known as the essential mediators of acute lung inflammation [32].

It is possible that the pathophysiologic changes in HAE patients, including a overproduction of BK and subsequently of DABK, followed by upregulated expression of B1R, could facilitate SARS-CoV-2 induced tissue damage in patients with COVID-19 by enhancing vasopermeability and local pulmonary edema via the kinin-kallikrein system, possibly worsening its outcome. Therefore, some researchers have proposed that therapeutic approaches targeting the kinin-kallikrein system, such as the antagonist of B2R (icatibant), C1-INH and selective inhibitors of plasma kallikrein (ecallantide, lanadelumab), may be helpful for the prevention of ARDS in COVID-19 patients [3,5]. Similarly, in the Chinese recommendation for management of hypertension, experts suggest that icatibant should be considered as a treatment option for COVID-19 patients with respiratory distress or angioedema [33]. As a selective B2R antagonist, icatibant can dysregulate the downstream activity of BK and has been approved for use in the management of acute attacks in patients with HAE in the US and Europe [34]. Additionally, icatibant has been demonstrated to be

effective in the treatment of ACE inhibitor-induced angioedema of the upper aerodigestive tract, which is mediated by the inhibition of the breakdown of BK and subsequent accumulation of BK [35]. C1-INH is a replacement therapy for HAE and has been approved to be used as on-demand and prophylactic treatment. The multi-inhibitory function of C1-INH in not only contact system but also the complements system and the fibrinolytic and coagulation system which are discussed below, might play a beneficial role in the management of patients with COVID-19. The plasma kallikrein inhibitor, ecallantide, and the monoclonal antibody against kallikrein, lanadelumab, which function via inhibition of kallikrein activity and activation of the BK forming cascade, might be also promising treatment strategies in COVID-19 patients with respiratory distress or angioedema. All three of these drugs are already approved for the treatment of HAE, have well-established safety and side-effect profiles, and are available in clinics. Pharmacologic inhibition of FXIIa or FXI also shows promising protective effects against systemic inflammatory response syndrome in animal models, while exerting little impact on hemostasis and host immunity, indicating that the contact activation system may serve as a potential therapeutic target for the treatment of patients with COVID-19 [36].

***Coagulation and fibrinolytic systems in HAE and COVID-19***

The contact system has close interactions with the coagulation and fibrinolytic systems (Figure 1). In HAE patients, increased coagulation and fibrinolytic activity have been demonstrated during both attacks and remission periods [37,38]. As

illustrated in Figure 1, C1-INH inhibits the activation of factor □, HMWK-factor □ and plasminogen, the formation of thrombin, and the activity of plasmin [9]. When functional C1-INH is deficient, the levels of prothrombin fragment 1 + 2, thrombin, and fibrin D-dimer have been observed to be higher in HAE patients than in healthy controls; these parameters were elevated even further during attacks compared with remission [37-39]. For HAE patients with normal C1-INH levels, mutations in the factor XII gene that cause a reduced activation threshold of the contact system is a common mechanism [9]. However, the risk for bleeding or thrombosis does not increase.[39] The coagulable state in HAE patients has not been fully explained.

Concerns about hematologic abnormalities associated with COVID-19 are increasing. Based on well-known information, the initial hematologic abnormality is an elevation of D-dimer and other fibrin degradation products, but without overt bleeding, which is likely to be a result of the inflammatory response [40-42]. The immunologic and inflammatory responses can lead to further progression of hematologic changes, culminating in symptoms of ischemia and thrombotic events in critically ill patients [7]. A D-dimer level greater than 1 μg/mL on admission is a potential risk factor for poor outcomes in COVID-19 [43]. An elevated D-dimer level is the result of not only the activation of coagulation, but also the COVID-19 related inflammatory response [40]. Severe infection can lead to disseminated intravascular coagulopathy in critically ill patients via coagulation activation and inflammatory response [44].

It is reasonable to investigate whether the known increased coagulation and

fibrinolytic activity in HAE patients predisposes them to develop a more severe condition after infection with SARS-CoV-2, and also whether strategies targeting the hematologic response will benefit HAE patients with COVID-19.

***Complement system in HAE and COVID-19***

As a serpin, C1-INH regulates the complement system by inactivating C1r, C1s and MASP-2. In HAE patients, without the inhibition of C1-INH, C1r and C1s transform to their respective activated types $C1\bar{r}$ and $C1\bar{s}$ then form the complex $C1\overline{qrs}$, which digests C4 and C2, and may initiate or facilitate the activation of the complement cascade (Figure 1). Concerning the involvement of MASP-2 in the lectin pathway of complement activation, it is presumed that MASP activity and the lectin pathway would be enhanced during C1-INH deficiency. However, compared with healthy controls, the activity of the MBL pathway and MASP-2 were found to be similar or even lower in HAE patients [45,46]. It was explained that the lower MASP-2 levels were due to the consumption, and that the lectin pathway was still activated but depressed in HAE [46]. In one study, the concentrations of MASP-2 and ficolin-3/MASP-2 complex were increased during angioedema attacks compared with remission periods in the same HAE patient [47], indicating that the lectin pathway was activated during attacks. Apart from its protease inhibitor role, C1-INH has many other biofunctions. C1-INH has been demonstrated to interact with components of the extracellular matrix, including type IV collagen, laminin and entactin, leading to the hypothesis that these components concentrate C1-INH at the local site of

inflammation in order to regulate the local complement and contact system [11]. In vitro, C1-INH can interact with C3b in a reversible manner, operating as a down regulator for the alternative pathway of complement activation [48]. As shown in Figure 1, C3b is an essential component of the C5 convertase, C4b2b3b, initiating the common pathway of complement activation. In a study of C1-INH-HAE patients, the level of C3 was lower than in healthy controls and C3 was overactivated [46,49]. Thus, the activation of complement was increased in these patients [49].

The activation of the complement system has been observed in COVID-19. The nucleocapsid (N) proteins of SARS-CoV-2, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) all bind to MASP-2, which is the key to the lectin pathway of complement activation [50]. From the findings of lung and dermatologic lesions in five severe COVID-19 patients, extensive deposition of the C5b-9 membrane attack complex, C4d and MASP-2 proteins were observed in lung microvasculature, plus COVID-19 S protein in cutaneous microvasculature, suggesting activation of the lectin pathway of the complement system [51]. The activated complement system affected the coagulation pathway and mediated a diffuse thrombotic microangiopathy in both lung and skin [51]. During SARS-CoV infection, $C3^{-/-}$mice exhibited less respiratory dysfunction, neutrophil infiltration in lung tissue and IL-6 in circulation compared with wild-type mice, suggesting that complement activation contributes to SARS-CoV pathogenesis [52]. In mouse models, a blockade approach targeting complement proteins C3 and C5a was beneficial for

promoting improved outcomes of SARS-CoV and MERS-CoV infection [52,53]. These data collectively highlighted the role of complement activation in the pathophysiology of COVID-19 and lay a foundation for novel potential therapies for COVID-19, including anti-C3 agents and other blockade strategies aimed at this pathway [6].

In C1-INH-HAE patients infected with SARS-CoV-2, the loss of inhibition of C1r, C1s and interaction with C3 would be expected to lead to enhanced complement activation. In such a case, together with the loss of C1-INH regulation at local sites of extravascular inflammation, the impact of C1-INH deficiency on the complement system would further favor the development of inflammation, induce microvascular injury and ultimately worsen the prognosis.

***Cytokines and T helper 17 (Th17) in HAE and COVID-19***

Compared with healthy controls, the levels of IL-17, IL-21, transforming growth factor-β (TGF-β), and granulocyte-macrophage colony stimulating factor (GM-CSF) are significantly higher in HAE patients in remission [10]. These cytokines, plus IL-6, increase further in HAE patients during attacks compared with remission[10]. The above-mentioned cytokines are all produced by Th17 and other type 17 cells, including γδ T cells, natural killer cells, natural killer T cells and innate lymphoid cells [54-56]. Some of these cytokines (IL-6, IL-21 and TGF-β) can stimulate Th0 to differentiate to Th17 subsets, which play an important role in inducing local

inflammation [57,58]. In addition, IL-1 and TNF-α have been reported to stimulate endothelial cells and augment activation of the prekallikrein–HMWK complex, suggesting a possible role in the interaction network of HAE [59].

An elevated proinflammatory cytokine profile is very common in patients with severe COVID-19, indicating a potentially important role of hyperinflammation in the pathophysiology of COVID-19. Compared with healthy controls, higher levels of the following factors have been observed in COVID-19 patients: IL-1β, IL-1rα, IL-7, IL-8, IL-9, IL-10, basic fibroblast growth factor, granulocyte-colony stimulating factor (GCSF), GM-CSF, IFN-γ, IFN-γ-inducible protein 10, monocyte chemoattractant protein, macrophage inflammatory protein (MIP)-1α, MIP-1β, platelet derived growth factor, TNF-α, and vascular endothelial growth factor [60].

A pathologic study of COVID-19 found an increase in Th17 cells [61], which are differentiated from Th0 cells by the stimulation of IL-6, TGF-β, IL-21 and IL-23 [62]. IL-6, which is an important member of the cytokine storm in COVID-19 and has been found to be significantly elevated in patients with severe COVID-19 [63], works as a central participant in the acute phase of inflammation [64].

Taken together, it can be inferred that a pre-existing state of elevated cytokines and Th17 in HAE might favor the cytokine release storm in COVID-19, although further evidence is needed.

***Bi-directional interaction between COVID-19 and HAE***

HAE is a genetic disorder caused by mutations mainly found on SERPING1 and several other genes including FXII, ANGPT1, and PLG [9,23,25,26]. However, there is great heterogeneity in clinical manifestations among HAE patients, even when they carry the same mutation. These differences include the age of onset, severity of edema and the frequency of attacks. It has also been observed that not all carriers of SERPING1 mutations present with recurrent edema. Indeed, a minority of HAE patients never develop edema at any point in their lifetime.

It is possible that COVID-19 and HAE form a reciprocal interaction loop in which the pathophysiologic mechanisms of each disease reinforce those of the other. The pathophysiological overlap between COVID-19 and HAE was summarized in Table 1. The continued depletion of ACE2 by SARS-CoV-2 infection increases the extracellular levels of DABK and BK via the kinin-kallikrein pathway, as well as the injury and inflammation in lung tissue [19]. Cellular injury and inflammation upregulate the expression of B1R [65,66]. The excessive generation of BK and DABK, in addition to the upregulation of B1R, contribute to angioedema. Considering that C1-INH inhibits MASP-1 and MASP-2 by forming complexes with each [67], the activation of the lectin pathway in COVID-19 may further consume the innately low level of functional C1-INH in HAE patients. C1-INH is proposed to be an interactor for seven proteins in SARS-CoV-1, which is highly similar to their

orthologous in SARS-CoV-2 [68]. Thus, it is hypothesized that SARS-CoV-2 infection might cause a deficit of C1-INH by the interaction between the virus and C1-INH [68]. Additionally, SARS-CoV-2 infection of hepatocytes may affect the production of C1-INH. Both of the two hypothetical mechanisms result in a further decrease of functional C1-INH in HAE patients. Consequently, the changes in the BK pathway, the activation of complement, and the impact on C1-INH production in COVID-19 could worsen pre-existing HAE, or even predispose HAE onset in mutation carriers who have not presented with HAE symptoms. Conversely, the pre-existing activation of the contact activation system, complement system, and coagulation and fibrinolytic systems, as well as increased levels of certain cytokines and Th17 cells in HAE patients might also aggravate the inflammatory responses in COVID-19.

Fortunately, none of the 136 HAE patients registered at our HAE center have been diagnosed with COVID-19; this includes six patients from Hubei Province, three of whom reside in Wuhan. At present, because there is a shortage of other drugs for HAE in China, these patients were prescribed different dosages of danazol as long-term prophylactic treatment. The prevalent use of danazol, an attenuated androgen, during the COVID-19 pandemic is cause for concern. Currently, it is not known whether the poorer clinical outcomes and higher rate of death from COVID-19 in men compared with women represent a casual or causal relationship [69]. Two plausible mechanisms have been proposed [70]. The first is based on evidence that the co-receptor for

SARS-CoV-2 infection, TMPRSS2, can be regulated by androgen in a lung-derived cell line model, although the role of androgen in physiologic settings has not been specified [71]. In patients with prostate cancer, androgen-deprivation therapies can decrease the level of TMPRSS2 and partially protect these patients from SARS-CoV-2 infections [72]. The second possible mechanism involves the immune modulation effect of androgens, which might suppress the antiviral immune response to SARS-CoV-2 [70]. Considering the fact that danazol remains the mainstay medication for HAE in the many countries where first-line treatments are not available, the potential aggravating effect of androgen in COVID-19 deserves special attention during the pandemic. We suggest that danazol should only be used with great caution, or even discontinued, in HAE patients who contract COVID-19.

In summary, we hypothesize that HAE might play a detrimental role in COVID-19 progression based on emerging knowledge about the potential participation of the contact activation system, complement system, and coagulation and fibrinolytic systems, as well as certain cytokines and Th17 cells during SARS-CoV-2 infection. Furthermore, COVID-19 could worsen existing HAE or facilitate the onset of HAE in asymptomatic carriers. Thus, it is important for HAE patients to take precautions to reduce the likelihood of being infected by SARS-CoV-2. HAE patients who do become infected might be at high risk of developing severe COVID-19 and aggravated HAE attacks. Therefore, we suggest a two-pronged approach for the duration of the COVID-19 pandemic: 1) HAE patients should insist on more serious

long-term prophylaxis; and 2) medications for acute attacks of angioedema should be prepared. Considering the probable negative influence of danazol on COVID-19, it would be preferable to use C1-INH replacement agents or drugs that target the kinin-kallikrein system, i.e. icatibant, ecallantide or lanadelumab, whenever these first-line drugs are available. The therapeutic strategies employed in HAE may provide implications for COVID-19. The administration of drugs that act on the kinin-kallikrein pathway, for example, may offer benefits for both HAE and COVID-19, especially in patients with ARDS. We urgently await further observational and experimental data to verify these relationships.

**Reference**

1. Hoffmann M, Kleine-Weber H, Schroeder S, Nadine K, Tanja H, Sandra E, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181 :271-80.

2. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. J Med Virol. 2020;92:424-32.

3. van de Veerdonk FL, Netea MG, van Deuren M, van der Meer JW, de Mast Q, J Brüggemann R, et al. Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. Elife. 2020;9:e57555.

4. Brogi S, Calderone V. Off-target ACE2 ligands: possible therapeutic option for CoVid-19? Br J Clin Pharmacol 2020. doi: 10.1111/bcp.14343.

5. Roche JA, Roche R. A hypothesized role for dysregulated bradykinin signaling in

COVID-19 respiratory complications. FASEB J 2020.doi: 10.1096/fj.202000967.

6. Risitano AM, Mastellos DC, Huber-Lang M, Yancopoulou D, Garlanda C, Ciceri F, Lambris JD. Complement as a target in COVID-19? Nat Rev Immunol. 2020. doi: 10.1038/s41577-020-0320-7.

7. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. N Engl J Med. 2020;382:e38.

8. Aygören-Pürsün E, Magerl M, Maetzel A, Maurer M. Epidemiology of Bradykinin-mediated angioedema: a systematic investigation of epidemiological studies. Orphanet J Rare Dis. 2018;13:73.

9. Busse PJ, Christiansen SC. Hereditary Angioedema. N Engl J Med. 2020;382:1136-48.

10. Arcoleo F, Lo Pizzo M, Misiano G, Milano S, Romano GC, Muggeo V, et al. The complex alteration in the network of IL-17-type cytokines in patients with hereditary angioedema. Clin Exp Med. 2018;18:355-61.

11. Davis AE, Lu F, Mejia P. C1 inhibitor, a multi-functional serine protease inhibitor. Thromb Haemost. 2010;104:886-93.

12. Kaplan AP, Austen KF. A prealbumin activator of prekallikrein. II. Derivation of activators of prekallikrein from active Hageman factor by digestion with plasmin. J Exp Med. 1971;133:696-712.

13. Silverberg M, Dunn JT, Garen L, Kaplan AP. Autoactivation of human Hageman factor. Demonstration utilizing a synthetic substrate. J Biol Chem. 1980;255:7281-6.

14. Mandle RJ, Colman RW, Kaplan AP. Identification of prekallikrein and

high-molecular-weight kininogen as a complex in human plasma. Proc Natl Acad Sci USA. 1976;73:4179-83.

15. Kaplan AP, Joseph K. Complement, Kinins, and Hereditary Angioedema: Mechanisms of Plasma Instability when C1 Inhibitor is Absent. Clin Rev Allergy Immunol. 2016;51:207-15.

16. Nussberger J, Cugno M, Cicardi M, Agostoni A. Local bradykinin generation in hereditary angioedema. J Allergy Clin Immunol. 1999;104:1321-2.

17. Sheikh IA, Kaplan AP. Studies of the digestion of bradykinin, Lys-bradykinin, and des-Arg9-bradykinin by angiotensin converting enzyme. Biochem Pharmacol. 1986;35:1951-6.

18. Hofman ZLM, Relan A, Zeerleder S, Drouet C, Zuraw B, Hack CE. Angioedema attacks in patients with hereditary angioedema: Local manifestations of a systemic activation process. J Allergy Clin Immunol. 2016;138:359-66.

19. Leeb-Lundberg LMF, Marceau F, Müller-Esterl W, Pettibone DJ, Zuraw BL. International union of pharmacology. XLV. Classification of the kinin receptor family: from molecular mechanisms to pathophysiological consequences. Pharmacol Rev. 2005;57:27-77.

20. Phagoo SB, Poole S, Leeb-Lundberg LM. Autoregulation of bradykinin receptors: agonists in the presence of interleukin-1beta shift the repertoire of receptor subtypes from B2 to B1 in human lung fibroblasts. Mol Pharmacol. 1999;56:325-33.

21. Christiansen SC, Eddleston J, Woessner KM, Chambers SS, Ye R, Pan ZK, et al. Up-regulation of functional kinin B1 receptors in allergic airway inflammation. J

Immunol. 2002;169:2054-60.

22. Cugno M, Zanichelli A, Foieni F, Caccia S, Cicardi M. C1-inhibitor deficiency and angioedema: molecular mechanisms and clinical progress. Trends Mol Med. 2009;15:69-78.

23. Bork K, Wulff K, Witzke G, Hardt J. Hereditary angioedema with normal C1-INH with versus without specific F12 gene mutations. Allergy. 2015;70:1004-12.

24. Bork K, Wulff K, Witzke G, Hardt J. Treatment for hereditary angioedema with normal C1-INH and specific mutations in the F12 gene (HAE-FXII). Allergy. 2017;72:320-4.

25. Bafunno V, Firinu D, D'Apolito M, Cordisco G, Loffredo S, Leccese A, et al. Mutation of the angiopoietin-1 gene (ANGPT1) associates with a new type of hereditary angioedema. J Allergy Clin Immunol. 2018;141:1009-17.

26. Bork K, Wulff K, Rossmann H, Steinmüller-Magin L, Braenne I, Witzke G, et al. Hereditary angioedema cosegregating with a novel kininogen 1 gene mutation changing the N-terminal cleavage site of bradykinin. Allergy. 2019;74:2479-81.

27. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;367:1444-8.

28. Wang H, Yang P, Liu K, Guo F, Zhang Y, Zhang G, et al. SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway. Cell Res. 2008;18:290-301.

29. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury.

Nat Med. 2005;11:875-9.

30. Sodhi CP, Wohlford-Lenane C, Yamaguchi Y, Prindle T, Fulton WB, Wang S, et al. Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. Am J Physiol Lung Cell Mol Physiol. 2018;314:L17-L31.

31. Duchene J, Ahluwalia A. The kinin B(1) receptor and inflammation: new therapeutic target for cardiovascular disease. Curr Opin Pharmacol. 2009;9:125-31.

32. Breil I, Koch T, Belz M, Van Ackern K, Neuhof H. Effects of bradykinin, histamine and serotonin on pulmonary vascular resistance and permeability. Acta Physiol Scand. 1997;159:189-98.

33. Liu L, Zhang W, Zeng Z, Lu Y, Qing, Wang Q. Blood pressure management recommendation for patients with novel coronavirus pneumonia 2020 [Available from: http://www.bjlshf.org/UploadFile/Ueditor/file/20200314/6371979389839896437673076.pdf.

34. Cicardi M, Banerji A, Bracho F, Malbrán A, Rosenkranz B, Riedl M, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med. 2010;363:532-41.

35. Baş M, Greve J, Stelter K, Havel M, Strassen U, Rotter N, et al. A randomized trial of icatibant in ACE-inhibitor-induced angioedema. N Engl J Med. 2015;372:418-25.

36. Shatzel JJ, DeLoughery EP, Lorentz CU, Tucker EI, Aslan JE, Monica T Hinds

MT, et al. The contact activation system as a potential therapeutic target in patients with COVID□19. Research and Practice in Thrombosis and Haemostasis.2020.doi: 10.1002/rth2.12349.

37. Nielsen EW, Johansen HT, Høgåsen K, Wuillemin W, Hack CE, Mollnes TE. Activation of the complement, coagulation, fibrinolytic and kallikrein-kinin systems during attacks of hereditary angioedema. Scand J Immunol. 1996;44:185-92.

38. Cugno M, Cicardi M, Bottasso B, Coppola R, Paonessa R, Mannucci PM, et al. Activation of the coagulation cascade in C1-inhibitor deficiencies. Blood. 1997;89:3213-8.

39. Reshef A, Zanichelli A, Longhurst H, Relan A, Hack CE. Elevated D-dimers in attacks of hereditary angioedema are not associated with increased thrombotic risk. Allergy. 2015;70:506-13.

40. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020. doi: 10.1182/blood.2020006000.

41. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-13.

42. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844-7.

43. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort

study. Lancet. 2020;395:1054-62.

44. Iba T, Levy JH, Thachil J, Wada H, Levi M. The progression from coagulopathy to disseminated intravascular coagulation in representative underlying diseases. Thromb Res. 2019;179:11-4.

45. Cedzyński M, Madaliński K, Gregorek H, Swierzko AS, Nowicka E, Obtułowicz K, et al. Possible disease-modifying factors: the mannan-binding lectin pathway and infections in hereditary angioedema of children and adults. Arch Immunol Ther Exp (Warsz). 2008;56:69-75.

46. Varga L, Széplaki G, Laki J, Kocsis A, Kristóf K, Gál P, et al. Depressed activation of the lectin pathway of complement in hereditary angioedema. Clin Exp Immunol. 2008;153:68-74.

47. Csuka D, Munthe-Fog L, Hein E, Zotter Z, Prohászka Z, Farkas H, et al. Activation of the ficolin-lectin pathway during attacks of hereditary angioedema. J Allergy Clin Immunol. 2014;134.

48. Jiang H, Wagner E, Zhang H, Frank MM. Complement 1 inhibitor is a regulator of the alternative complement pathway. J Exp Med. 2001;194:1609-16.

49. Nielsen EW, Johansen HT, Gaudesen O, Osterud B, Olsen JO, Høgåsen K, et al. C3 is activated in hereditary angioedema, and C1/C1-inhibitor complexes rise during physical stress in untreated patients. Scand J Immunol. 1995;42:679-85.

50. Gao T, Hu M, Zhang X, Li H, Zhu L, Liu H, et al. Highly pathogenic coronavirus N protein aggravates lung injury by MASP-2-mediated complement over- activation. medRxiv 2020.doi: 10.1101/2020.03.29.20041962.

51. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res. 2020; 220:1-13.

52. Gralinski LE, Sheahan TP, Morrison TE, Menachery VD, Jensen K, Leist SR, et al. Complement Activation Contributes to Severe Acute Respiratory Syndrome Coronavirus Pathogenesis. mBio. 2018;9(5):e01753-18.

53. Jiang Y, Zhao G, Song N, Li P, Chen Y, Guo Y, et al. Blockade of the C5a-C5aR axis alleviates lung damage in hDPP4-transgenic mice infected with MERS-CoV. Emerg Microbes Infect. 2018;7:77.

54. Cua DJ, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. Nat Rev Immunol. 2010;10:479-89.

55. Zúñiga LA, Jain R, Haines C, Cua DJ. Th17 cell development: from the cradle to the grave. Immunol Rev. 2013;252:78-88.

56. Marks BR, Nowyhed HN, Choi J-Y, Poholek AC, Odegard JM, Flavell RA, et al. Thymic self-reactivity selects natural interleukin 17-producing T cells that can regulate peripheral inflammation. Nat Immunol. 2009;10:1125-32.

57. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J Exp Med. 2005;201:233-40.

58. Liang SC, Tan X-Y, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, et al. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. J Exp Med.

2006;203:2271-9.

59. Joseph K, Tholanikunnel BG, Kaplan AP. Cytokine and estrogen stimulation of endothelial cells augments activation of the prekallikrein-high molecular weight kininogen complex: Implications for hereditary angioedema. J Allergy Clin Immunol. 2017;140:170-6.

60. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.

61. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8:420-2.

62. Miossec P, Kolls JK. Targeting IL-17 and TH17 cells in chronic inflammation. Nat Rev Drug Discov. 2012;11:763-76.

63. Zhang C, Wu Z, Li J-W, Zhao H, Wang G-Q. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents. 2020; 55(5):105954.

64. Scheller J, Rose-John S. Interleukin-6 and its receptor: from bench to bedside. Med Microbiol Immunol. 2006;195:173-83.

65. Moreau ME, Garbacki N, Molinaro G, Brown NJ, Marceau F, Adam A. The kallikrein-kinin system: current and future pharmacological targets. J Pharmacol Sci. 2005;99.

66. Maas C. Plasminflammation-An Emerging Pathway to Bradykinin Production.

Front Immunol. 2019;10:2046.

67. Ambrus G, Gál P, Kojima M, Szilágyi K, Balczer J, Antalet J, al. Natural substrates and inhibitors of mannan-binding lectin-associated serine protease-1 and -2: a study on recombinant catalytic fragments. J Immunol. 2003;170:1374-82.

68. Thomson TM, Toscano E, Ernesto C, Paciucci R. C1-INH and the contact system in COVID-19-associated coagulopathy. Br J Haematol.2020. doi: 10.1111/bjh.16938.

69. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020; 323:1574-1581.

70. Sharifi N, Ryan CJ. Androgen hazards with COVID-19. Endocr Relat Cancer. 2020;27:E1-E3.

71. Mikkonen L, Pihlajamaa P, Sahu B, Zhang F-P, Jänne OA. Androgen receptor and androgen-dependent gene expression in lung. Mol Cell Endocrinol. 2010;317:14-24.

72. Montopoli M, Zumerle S, Vettor R, Rugge M, Zorzi M, Catapano CV, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (n=4532). Ann Oncol. 2020; S0923-7534(20)39797-0.

**Table 1. Overlaps in pathophysiology of COVID-19 and HAE.**

| Systems | COVID-19 | HAE |
|---|---|---|
| **Contact system** | • BK and DABK are expected to increase if ACE2 is depleted.<br>• Activation of the contact activation system could facilitate tissue damage by enhancing vasopermeability and local pulmonary edema. | • Activation of the contact activation system is the core pathophysiological change in HAE.<br>• Excessive generation of BK and DABK, and subsequent upregulation of B1R, lead to vasopermeability and angioedema. |
| **Complement system** | • The nucleocapsid (N) proteins of SARS-CoV-2 bind to MASP-2, which is key to the lectin pathway of complement activation.<br>• Extensive deposition of complement system components were observed in pulmonary and cutaneous lesions of severe COVID-19 patients | • Deficiency or dysfunction of C1-INH is the fundamental defect in the majority of HAE patients.<br>• Both the classical and the lectin complement pathway are activated during C1-INH deficiency. |
| **Coagulation and fibrinolytic system** | • Coagulopathy is common in critically ill COVID-19 patients, presenting as elevation D-dimer and other fibrin degradation productions, symptoms of ischemia and thrombotic events, and even DIC. | • Increased coagulation and fibrinolytic activity have been demonstrated during both attacks and remission periods in HAE. |
| **Cytokines** | • An elevated proinflammatory cytokine profile is very common in patients with severe COVID-19, indicating a potentially important role of hyperinflammation.<br>• An increase in Th17 cells has been found in COVID-19 patients. | • Some cytokines produced by Th17 and other type 17 cells are significantly higher during HAE attacks and remission than controls.<br>• IL-1 and TNF-α can augment activation of the prekallikrein-HMWK complex, representing a potential initiating event of angioedema attacks. |

ACE2, angiotensin-converting enzyme 2. BK, bradykinin. B1R, bradykinin receptor B1. C1-INH, complement 1 inhibitor. COVID-19, coronavirus disease 2019. DABK, des-Arg-bradykinin. DIC, disseminated intravascular coagulopathy. HAE, hereditary angioedema. HMWK, high-molecular-weight kininogen complex. IL, interleukin. MASP-2, mannose-binding lectin associated serine protease 2. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Th17, T helper 17. TNF-α, tumor necrosis factor alpha.

**Figure legends**

Figure 1. The putative interaction of known pathological network in HAE and COVIID-19

In hereditary angioedema (HAE) type 1 and 2, with the deficiency of functional C1 inhibitor (C1-INH), plasma contact system can be over activated, comprising of factor □ (F□), prekallikrein, kallikrein, high-molecular-weight kininogen (HMWK), and generate excessive bradykinin (BK). Factor □a (F□a), activated form of factor □, coverts prekallikrein-HMWK complex to kallikrein-HMWK complex, while factor □ fragment (F□f) can weakly stimulate this converting process. Kallikrein digests HMWK to BK and feedback activates factor □. By carboxypeptidase N/M, BK generates des-Arg (9)-bradykinin (DABK). BK binds to bradykinin receptor B2 (B2R) and DABK binds to both bradykinin receptor B1 (B1R) and B2R on the surface of endothelial cells, promoting vasodilation and increasing vascular permeability. The target site of available therapeutic approaches in HAE including C1-INH replacement, ecallantide, lanadelumab and icatibant, are shown in red line. In coronavirus disease 19 (COVID-19), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), enter host cell via angiotensin converting enzyme 2 (ACE2) on the cell surface and reduce the membrane expression of ACE2. Because ACE2 is an enzyme to cleave DABK, the depletion of ACE2 induces the accumulation of DABK and possible BK via negative feedback to BK degradation which mediate pulmonary edema and inflammation. The overactivated contact system in HAE might worsen BK and DABK mediated lung injury in COVID-19. The target site of available therapeutic

approaches in HAE including C1-INH replacement, ecallantide, lanadelumab and icatibant, are shown in red line, which might be benefit for COVID-19. C1-INH plays an inhibited role in complement system by inhibiting the activation of C1qrs, the digestion of C4 and C2, C3b and mannose-binding lectin (MBL)-associated serine protease (MASP). Without sufficient functional C1-INH, the complement system might be enhanced activated which was also observed in COVID-19, and facilitate the development of lung injury. An elevation of T helper cell 17 (Th17) cytokines such as interleukin-6 (IL-6), IL-17, IL-21, transforming growth factor-β (TGF-β) was found in HAE patients, while the proinflammatory cytokines release (IL-1β, IL-1rα, IL-7, etc.) and increased Th17 were observed in COVID-19. The pre-existing cytokines in HAE might favor the cytokines storm in COVID-19. IL-1β can upregulate the expression of B1R on the endothelial surface and worsen DABK-mediated inflammation. In HAE, the loss of inhibition on factor □, factor □ and plasminogen by C1-INH theoretically induce increased coagulation and fibrinolytic activity, but realistic coagulable state of HAE patients has not been clarified. A hypercoagulable state was observed in COVID-19, especially in critical ill patients. Whether the deficient of C1-INH could impact the hematologic responds in COVID-19 need to be further investigated.