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Endothelial cells and blood vessels are major targets for COVID-19-induced tissue injury and spreading to various organs

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Abstract

The coronavirus disease 2019 (COVID-19) infected so far over 250 million people and caused the death of over 5 million worldwide. Aging, diabetes, and cardiovascular diseases, conditions with preexisting impaired endothelial functions predispose to COVID-19. While respiratory epithelium is the main route of virus entry, the endothelial cells (ECs) lining pulmonary blood vessels are also an integral part of lung injury in COVID-19 patients. COVID-19 not only affects the lungs and respiratory system but also gastrointestinal (GI) tract, liver, pancreas, kidneys, heart, brain, and skin. Blood vessels are likely conduits for the virus dissemination to these distant organs. Importantly, ECs are also critical for vascular regeneration during injury/lesions healing and restoration of vascular network. The *World Journal of Gastroenterology* has published in last two years over 67 outstanding papers on COVID-19 infection with a focus on the GI tract, liver, pancreas, etc., however, the role of the endothelial and vascular components as major targets for COVID-19-induced tissue injury, spreading to various organs, and injury healing have not been sufficiently emphasized. In the present article, we focus on these subjects and on current treatments including the most recent oral drugs molnupiravir and paxlovid that show a dramatic, significant efficacy in controlling severe COVID-19 infection.

Key Words: Endothelial cells; Impaired endothelial function; Blood vessels; SARS-CoV-2; COVID-19; Cytokine storm

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Core Tip: The coronavirus disease 2019 (COVID-19) pandemic has enormous health care and economic impact on the entire world - infecting more than 250 million people in 213 countries and territories, causing death of more than 5 million (as of November 1, 2021). We comment here on some outstanding papers on COVID-19 published in *World Journal of Gastroenterology* and reviewed the important role of endothelium and blood vessels in COVID-19 infection. Endothelial cells and blood vessels are both the targets and a conduit for the spread of severe acute respiratory syndrome coronavirus 2 and play a critical role in COVID-19-induced tissue injury and dissemination to various organs. Pre-existing endothelial impaired function could make endothelial cells more sensitive to COVID-19 or at least COVID-19-induced impairment might be synergistic with pre-existing impairment. That could be one contributing factor explaining why older or diabetic patients have more severe responses to infection, since these conditions are already impacted impaired endothelial function.

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BIOGRAPHY

Andrzej S Tarnawski, MD, PhD, DSc (Med), AGAF, FACG: Received MD degree, PhD (pathology) and DSc (gastroenterology) from the University Medical School, Krakow, Poland, and became Associate Professor & V-Chair, Dept of Gastroenterology at that University. After completing GI fellowship at the University of Missouri, Columbia, MO, United States he joined the University of California, Irvine, USA as Associate Professor (1982-1986) and full Professor (1986-present). He served as: V-chair and Associate Chair, American Gastroenterological Association (AGA)/EGD 1997-1999 and 2008-2010; Scientific Director, Shimoda Symposia on Mucosal Defense in Japan (8 times); Chair, Research Fora DDW/AGA annual meetings (1996-2011); Chair, Pasteur Institute Euroconference and Chair/Co-chair of 68 other International Symposia. Publications, presentations & grants: 373 full, peer reviewed publications (*Lancet, Nature Med, JCI, Gastroenterology, Hepatology, Gut, PNAS, FASEB J, Am J Pathol, Cellular Mol Gastro Hepatol, Am J Physiol, Am J Gastroenterol, Endoscopy, Cell Signal, Cells*, and others); 20 book chapters; 533 presentations at international & U.S. meetings; 20 peer reviewed funded grants (NIH, VA Merit Review 1984-present), 4 US patents. Clinical and Research interest: Injury and protection of GI mucosa; cellular and molecular mechanisms of gastric, duodenal and esophageal healing-role of growth factors, signaling pathways, angiogenesis, NSAIDs, prostaglandins and *Helicobacter pylori* toxins; aging gastric mucosa; confocal endomicroscopy and molecular imaging; gene therapy. Awarded prestigious academic honors (e.g., Glaxo Intl. Res. Award, Athalie-Clarke Award, Merentibus Medal Award, Peregrinator of Science Awards, Andre Robert's Distinguished Award, Notable Biomedical Research Investigator Award). Memberships: AGA (Fellow), Am. College of Gastroenterology (Fellow), Brit. Soc. of Gastroenterology, Japanese Soc. of Gastroenterology (Honorary), Hungarian Soc. of Gastroenterology (Honorary), Am. Soc. for Investigative Pathology, Association of Am. Physicians (by election) and others. Editorial Boards - 6 scientific journals. Sixteen of his former trainees hold academic positions in US Medical Schools (4 being Chairs of Departments). Twenty of his former international trainees and/or associates hold academic positions abroad (France, Germany, Hungary, Japan, Poland, Sweden, Switzerland) (Figure 1A).

Amrita Ahluwalia, PhD: Research Scientist and coronavirus disease 2019 (COVID-19) Investigator, Veterans Affairs Long Beach Healthcare System, Long Beach, United States. Awarded PhD (Physiology) by the Medical Sciences Program, Indiana University Bloomington, IN, United States. Publications/presentations/grants: 60 peer-reviewed research publications (*PNAS, Am J Physiol, Gene Therapy, Endocrinology, Molecular Endocrinology etc.*); 95 presentations at International and US research

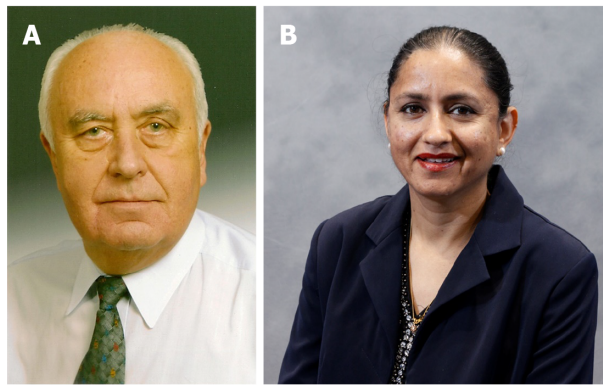


Figure 1 Authors. A: Andrzej S Tarnawski, Gastroenterology Research Department, University of California Irvine and the Veterans Administration Long Beach Healthcare System, Long Beach, CA 90822, United States; B: Amrita Ahluwalia, Research Service, Veterans Administration Long Beach Healthcare System, Long Beach, CA 90822, United States.

meetings; 6 peer-reviewed funded grants. Research Interests: Endothelial dysfunction, wound and tissue injury healing; gastroprotection; role of growth factors, angiogenesis, molecular imaging & gene therapy. Awards: Quest Diagnostics Young Investigator Award, AACR-AstraZeneca Scholar in Training Award, Robert W. Bullard Award - Outstanding Medical Science Student Award, Indiana University. Memberships: AGA, Am. Assoc. Physiology, Am. Heart Assoc.; Editorial Boards – 2 peer-reviewed scientific journals (Figure 1B).

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has had enormous health care and economic impact on the entire world - infecting more than 250 million people in 213 countries and territories, causing more than 5 million deaths (as of November 1, 2021). Its enormous magnitude is also reflected by an unprecedented number of publications related to COVID-19 so far approximate 210294 recorded in PubMed; 254358 recorded on PMC, and 3215 clinical trials just in 24 mo. These are staggering numbers compared to 47305 publications recorded on PubMed on *Helicobacter pylori* (*H. pylori*) - the world's most prevalent GI infection - published in about last 40 years.

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is highly infectious and transmitted by aerosol droplets. Therefore, it is not surprising that the respiratory tract including the lungs is the main affected organ by COVID-19 infection that leads to respiratory failure, hypoxia, multiorgan system failure and death. Numerous studies showed that COVID-19 not only affects the lungs and respiratory system but also the gastrointestinal tract (GI), liver, pancreas, kidneys, heart, brain, and skin[1-5]. SARS-CoV-2 RNA was detected in stool or rectal swabs in 34%-59% of infected patients[6]. The viral loads from stool samples peaked 2-3 wk after symptom onset and in some patients were detectable even after viral loads in the respiratory and/or sputum samples were not detectable[6]. The presence and persistence of viral RNA in the stool suggest the potential for enteric infection of SARS-CoV-2. This contention is supported by a study demonstrating that the GI tract is an alternative route for COVID-19 infection in the rhesus monkey model[7]. In that study, the authors showed that intranasal or gastric inoculation with SARS-CoV-2 induced infections and pathologic changes not only in respiratory tissues but also in digestive tissues[7]. In a recent letter to the *World Journal of Gastroenterology* (WJG) editor[8], Sica *et al*[8] contended that GI and hepatic involvement are the most common presenting symptoms of COVID-19 and multisystem inflammatory syndrome recently described in children and adolescents. This syndrome can lead to shock and multiple organ failure requiring intensive care[9].

Risk factors for COVID-19 severity include aging and comorbidities such as coronary artery disease, chronic kidney disease, hypertension, obesity, and diabetes [10-12], all of which exhibit preexisting endothelial dysfunction. However, the potential role of endothelial/vascular components as critical target sites for COVID-19-induced tissue injury and spreading to various organs, and the role of preexisting endothelial function impairment, *e.g.*, in aging or diabetes – conditions that facilitate

COVID-19 infection have not been sufficiently elaborated on. In the present article, we focus on these topics anticipating that providing a detailed information on endothelial cells (ECs) and vasculature in COVID-19 as critical targets may afford a better insight into the pathomechanism of this disease and add additional new therapies.

The SARS-CoV-2 virus spreads from its primary infection site (respiratory tract) to more distant organs indicating the involvement of ECs and blood vessels for disseminating infection. This contention is supported by some studies demonstrating the presence of SARS-CoV-2-like particles in ECs in several tissues *e.g.*, lung, kidneys, brain, and skin and observation that the clinical course of COVID-19 may include vascular complications such as thrombosis of blood vessels and thromboembolism[3,5,13-16].

The *WJG* has published in the last two years over 67 outstanding papers related to COVID-19 infection with a focus on GI tract and liver. These papers - original papers, retrospective studies and review articles on the pathophysiology, mechanisms, and clinical aspects and manifestations of COVID-19 related diseases of the digestive system including GI tubular system, liver, pancreas provided important information for the gastroenterologists, hepatologists, surgeons, researchers, pharmacologists, and clinicians. These papers provide information on the mechanisms of COVID-19 related tissue damage; the effects of immunosuppression in patients with inflammatory bowel disease and chronic liver disease; and the impact of COVID-19 on GI emergencies, endoscopy, diagnosis and treatments. These *WJG* articles were frequently viewed on the *WJG* website and cited in high-impact journals. We wish to point out one important paper by P. Samantha and AR Ghosh: "Environmental perspectives of COVID-19 outbreaks: A review" published in *World J Gastroenterol.* 2021 Sep 21;27(35):5822-585" [17]. In this paper the authors provided extensive information from an environmental perspective on the origin and current status of COVID-19[17] and summarized the geographical distribution of COVID-19 around the world including specific countries. They also elaborated on the details of coronavirus genus, species and receptors, virus susceptibility and incubation period, and summarized SARS-CoV-2 pathogenesis, the role of angiotensin-converting enzyme 2 (ACE2), the longevity of SARS-CoV-2 virus in the environment, meteorological influences, air quality and social impact. They emphasized that aging, cardiovascular diseases and diabetes predispose to COVID-19. The authors stressed that while drugs such as remdesivir, tocilizumab, lopinavir-ritonavir, azithromycin, *etc.*, are used in COVID-19 patients these drugs do not induce full recovery. The statement that there is no truly effective drug aimed at the causative agent, SARS-CoV-2 is no longer valid. On November 4 and 5, 2021 the released results of most recent clinical trials for COVID-19 treatments demonstrated that oral drugs inhibiting viral replication - Molnupiravir (Merck), and Paxlovid (Pfizer) showed very impressive efficacy in controlling severe COVID-19 infection. The interim analysis of the latter drug showed a dramatic approximate 90% reduction in risk of - hospitalization or death from COVID-19 compared to placebo in patients treated within three - five days of symptom onset. Most likely the vascular component of the disease was important part of this dramatic reduction.

Regarding COVID-19 pathomechanism, the potential role of endothelial and vascular components as critical target sites for COVID-19-induced tissue injury and spreading to various organs and the role of preexisting endothelial function impairment, *e.g.*, aging gastropathy has not been sufficiently emphasized. In this editorial article, we focus on the role vascular endothelium and blood vessels in COVID-19 infection (Table 1).

Increasing evidence suggests the essential role of endothelium and vasculature, in addition to the epithelial cells, in COVID-19 infection as a critical targets for SARS-CoV-2 and the resulting cytokine storm, and as the main effector for the pro-inflammatory and pro-coagulant state in COVID-19 patients[18,27-30]. Focus on ECs and vasculature in COVID-19 may also add additional insight into COVID-19 injury, its healing and tissue regeneration, and new therapies that impact endothelium and the blood vessels.

Although SARS-CoV-2 primarily targets the respiratory and alveolar epithelium, the high incidence of vascular complications in COVID-19 patients suggests that impaired function of ECs, which line the blood vessels and microvessels, may be critical factor in COVID-19 progression. SARS-CoV-2 causes endothelial dysfunction and thrombosis by two potential mechanisms: by directly infecting the endothelium, and disrupting its anti-thrombogenic and barrier properties, or indirectly by unleashing a local cytokine storm and systemic inflammatory response that results in endothelial injury (Table 2). Most likely, both these scenarios are in play in COVID-19.

Table 1 COVID-19 and endothelium/blood vessels**COVID-19 and endothelium/blood vessels**

Endothelium and blood vessels are integral parts of COVID-19-induced tissue injury. Their injury is likely due to either direct viral infection and/or cytokine storm triggered by infection of adjacent epithelial cells and inflammatory response[18].

Blood vessels are critical for virus dissemination to distant organs.

Preexisting-impaired endothelial function, *e.g.*, in aging or diabetes are likely predisposing factors COVID-19. Our studies demonstrated that aging gastric mucosa has increased susceptibility to injury and prominent EC abnormalities (decreased VEGF, NGF and impaired mitochondrial function)[19-21].

ECs are critical for vascular regeneration (through angiogenesis and vasculogenesis) during injury/lesions healing and therefore are essential for the delivery of oxygen and nutrients to the healing site[22,23].

Several growth factors *e.g.*, NGF, IGF-1, HGF and BMD-stem cells may facilitate tissue regeneration in the healing phase[20,24,25].

Long-term effects of COVID-19, its vaccines and treatment on endothelium and vasculature remain to be determined.

Recently, new oral drugs inhibiting viral replication–Molnupiravir (Merck) and Paxlovid (Pfizer) showed significant efficacy in controlling severe COVID-19 infection by inhibiting viral replication. The interim analysis of the latter drug showed an 89% reduction in risk of COVID-19-related hospitalization or death from any cause compared to placebo in patients treated within three-five days of symptom onset[26].

COVID-19: Coronavirus disease 2019; EC: Endothelial cell; VEGF: Vascular endothelial growth factor; NGF: Nerve growth factor.

Table 2 Scenarios by which SARS-CoV-2 elicits endothelial damage

Scenario A: SARS-CoV-2 infection	Scenario B: Cytokine storm
SARS-CoV-2 infects and replicates within vascular ECs and new virus particles are released into the blood vessel. These virions can infect neighboring cells or are carried to distant organs <i>via</i> circulation	<p>↑ IL-6, IL-1β, and TNFα release (cytokine storm) → endothelial damage</p> <p>↑ vascular permeability → plasma extravasation</p> <p>↑ vWF & FVIII (promote clot formation) and ↑ PAI-1 (inhibits clots lysis) → hypercoagulation</p>

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; IL: Interleukin; TNF: Tumor necrosis factor; vWF: von Willebrand factor.

Endothelium in normal and pathological conditions. Role in homeostasis, tissue repair and healing

The endothelium is a key player in vascular homeostasis[29,31-33]. ECs are critical for supplying oxygen and other nutrients to all cells and tissues, and are involved in coagulation and the generation of vasoactive substances, prostanoids, hormones and growth factors[33-38]. The unstimulated vascular endothelium is normally impermeable and acts as a selective barrier regulating exchange of fluids, nutrient delivery and waste removal while preventing entry of pathogens and harmful substances into the tissues. Microvessels consist of a single layer of thin (approximate 0.5-1 μm) ECs and occasional adherent cells such as pericytes[34-38]. The endothelial "barrier between neighboring ECs formed by prominent tight junctions prevents diffusion between cells. ECs act as a barrier between blood and the interstitial tissue, and regulate various physiological processes such as angiogenesis, inflammation, and immune response[31,35,36]. The endothelium contains special vesicles - Weibel-Palade bodies, which store various factors that regulate blood coagulation and leukocyte recruitment and extravasation such as von Willebrand factor (vWF), P-selectin, chemokines, interleukin-8, and eotaxin-3; endothelin-1, angiopoietin-2 and osteopontin[39-42].

In response to local stimuli, ECs secrete endothelin and leukotriene C4 (potent vasoconstrictors), nitric oxide (NO) and prostacyclin (PGI2) (vasodilators) and empty the contents of the Weibel-Palade vesicles that affect the tone of vascular smooth muscle and result in neutrophil adhesion and/or other autocrine and/or paracrine actions. NO, prostacyclin, prostaglandin E2 (PGE2), carbon monoxide (CO), tissue plasminogen activator, vascular endothelial growth factor (VEGF) and bFGF are endothelial mediators that reduce platelet and leukocyte activation, prevent thrombi formation, promote thrombolysis, maintain tissue perfusion, and protect the microvascular wall against acute damage[33,36-38,43-46]. For example, our previous study demonstrated that 16,16 dimethyl PGE2 protects human gastric mucosa against injury by 40% ethanol by protecting and preserving integrity of endothelial cells of

gastric microvessels[47]. In response to wounding, infections or injurious stimuli, attachment between ECs is lost, resulting in increased endothelial permeability and edema[48].

The endothelium and blood vessels are integral parts of any tissue injury including COVID-19. Our previous studies demonstrated that ECs are critical targets of gastric mucosal injury by NSAIDs and ethanol, they initiate angiogenesis, and that age-related endothelial dysfunction of human and rat gastric endothelial cells results in impaired angiogenesis and delayed healing[19,20,24]. Our studies on aging gastropathy showed aging-related defects in ECs functions - angiogenesis, cell migration, proliferation, and healing of injury[19-21,49]. In a recent study, we also showed the critical role of mitochondria in aging gastric ECs; aging ECs have fewer mitochondria, and reduced mitochondrial membrane potential[50] that result in reduced ATP generation (Figure 2). We also demonstrated that treatment with VEGF and nerve growth factor (NGF) restores angiogenesis in cultured aging gastric ECs [20], accelerates healing of gastric ulcers and improves the quality of mucosal regeneration *in vivo* in aging rats[20,24].

Endothelial cells and COVID-19

SARS-CoV-2 is a single, positive-stranded RNA virus that uses a spike-protein (S-protein) expressed on its envelope to bind to the host cell's human protein receptor ACE2[51-53]. The human ACE2 protein was initially identified as ACE-related carboxypeptidase membrane-associated and secreted enzyme expressed predominantly on the endothelium of the human heart, kidney, and testis [54]. However, it is widely expressed in various cells and tissues[55]. SARS-CoV-2 employs the ACE2 receptor, transmembrane serine protease 2 (TMPRSS-2), and cathepsin B and L (CTSB, and CTSL) for infection[51-53,56,57]. SARS-CoV-2 was detected in the respiratory tract, kidneys, liver, heart, and brain (all of which are highly vascularized tissues) of infected individuals[55]. ECs, which line the blood vessels of all organs and maintain microvascular integrity, express the ACE2 receptor and the cellular proteases TMPRSS-2, CTSB, and CTSL[57]. ECs are, therefore, a target for SARS-CoV-2 and blood vessels likely route of this virus dissemination to various organs. Electron microscopy (EM) and histologic studies detected SARS-CoV-2 virus-like particles and proteins in ECs of the kidney, small bowel, lung, myocardium, skin, and brain[3,5,13-16]. Ackerman *et al*[15] showed abnormalities within the pulmonary microvasculature with congestion and micro-thrombi in lungs of COVID-19 patients, and visualized endothelial injury and lumen filled with cell fragments and degenerated organelles by electron microscopy. That study also showed increased ACE2-positive ECs and significant changes in endothelial morphology in lung autopsies of COVID-19 patients [15]. Varga *et al*[5] using EM evaluation reported evidence of viral particles in renal ECs of COVID-19 patients presenting with endotheliitis, which is an immune and inflammatory response within the endothelium of blood vessels.

Other studies visualized SARS-CoV-2 proteins in dermal and renal endothelium[13, 58]. While some studies were not able to corroborate presence of SARS-CoV-2 in ECs of some tissues, there is strong evidence to support that SARS-CoV-2 infects ECs. Monteil *et al*[59] demonstrated that SARS-CoV-2 infects blood vessel organoids. SARS-CoV-2 virus particles range from approximate 70 to 120 nm[60-63]; therefore, in the absence of preexisting tissue injury, the virus would need to pass through the ECs to infect other tissues.

Endothelial dysfunction

The term endothelial dysfunction was originally used to identify the shift from a normal quiescent endothelium to an impaired endothelium with the inability to generate nitric oxide and other vasodilators. In a broader definition, endothelial dysfunction includes impairment of endothelial function (that we used for aging endothelium in our previous papers) - reduced angiogenesis, pro-inflammatory, pro-vasoconstriction, proliferative, and pro-coagulant phenotype[18,64-66]. In certain pathological conditions characterized by preexisting endothelial dysfunction, the ACE/Ang II axis is upregulated resulting in vasoconstriction, thrombosis, fibrosis, coagulopathy, and thrombophilia.

Endothelial dysfunction and endotheliitis in COVID-19

Emerging evidence indicates that preexisting endothelial dysfunction predisposes to COVID-19 infection and that COVID-19 induced endotheliitis further impairs endothelial integrity and function[27-30,32,34,67-76]. This is evidenced by the critical role of vascular endothelium in inflammation that results in dysregulation of cytokines

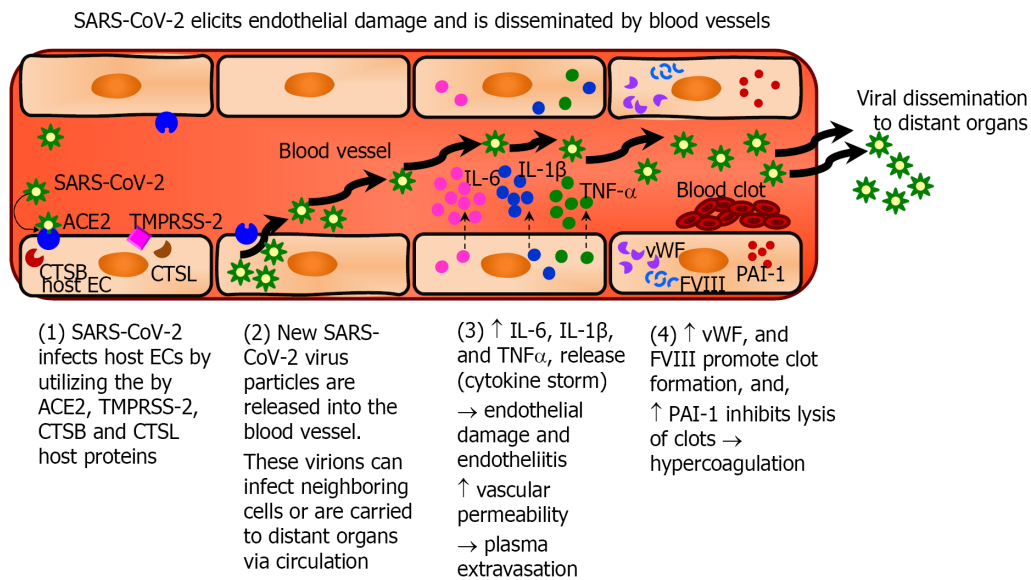


Figure 3 Sequential steps of SARS-CoV-2 infection of endothelial cells and endothelial damage. SARS-CoV-2 infects endothelial cells (ECs) using the host angiotensin-converting enzyme 2 receptors and cellular proteases (transmembrane serine protease 2, and cathepsin B and L). The virus then replicates within the cells and is released into the blood vessels, which then disseminate the virus to distant organs. Severe COVID-19 results in a cytokine storm wherein there is increased production of pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-1, interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α), and results in endothelial damage and endotheliitis, and demonstrated increased vascular permeability that cause plasma extravasation. Activated ECs produce increased amounts of vWF and factor VIII, and PAI-1, which induce a pro-coagulant, hypofibrinolytic state. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ECs: Endothelial cells; ACE2: Angiotensin-converting enzyme 2; TMPRSS-2: Transmembrane serine protease 2; CTSB: Cathepsin B; CTSL: Cathepsin L; IL: Interleukin; TNF- α : Tumor necrosis factor- α .

angiogenesis, promoted revascularization, and accelerated gastric ulcer healing in aging rats[20].

The long-term effects of COVID-19 and its vaccines on endothelium and vasculature remains unknown

SARS-CoV-2 infection was first reported in 2019 and rapid, breakthrough research resulted in the development of several effective COVID-19 vaccines. Although these vaccines have proven effective in reducing the infection and severity of COVID-19, the long-term effects of the disease and the vaccines on ECs and blood vasculature are still to be determined.

POTENTIAL TREATMENTS

Two recent outstanding studies published by the Baishideng Publishing Group in the *World Journal of Virology* outlined the current therapies that have been utilized in COVID-19 treatment[86,87]. We wish to add to this list additional investigational treatments in ongoing clinical trials (Table 3) and describe two additional oral drugs that were announced in early November 2021 as potential COVID-19 treatments Molnupiravir (Merck) and Paxlovid (PF-07321332).

During recent press releases two newest oral drugs inhibiting SARS-CoV-2 replication were recently presented. Are they game changers? On November 4 and 5, 2021 two oral drugs were announced as novel COVID-19 treatments - Molnupiravir (Merck) and Paxlovid (PF-07321332). Both these drugs showed dramatic efficacy in controlling severe COVID-19 infection. The oral drug Molnupiravir (EIDD-2801) was developed by US-based Merck & Co Inc and Ridgeback Biotherapeutics[88] and investigated in a clinical trial (NCT04405570) to eliminate SARS-CoV-2 virus load in infected patients, has since been approved in the UK to treat patients with mild to moderate COVID-19 and at least one risk factor such as older age, diabetes, obesity, and heart disease that predisposes them for developing severe illness. Molnupiravir is the prodrug of the ribonucleoside analog β -D-N4-hydroxycytidine and is rapidly converted by host kinases in plasma to the active 5'-triphosphate form. The latter is a competitive substrate for SARS-CoV-2 RNA-dependent RNA polymerase and causes mutations in the viral genome during replication that makes the virus non-viable. The

Table 3 Summary of the investigational interventions/treatments for COVID-19 in clinical trials

Intervention/ Treatment	Mode of action	Dose	Route	ClinicalTrials.gov Identifier
Ronapreve/REGN-COV2 (REGN10933 and REGN10987)	Monoclonal antibodies against spike proteins	8 g once, or 4 g twice	IV	NCT04425629
Lopinavir/Ritonavir	Inhibitor of the HIV protease and cytochrome P-450 CYP3A	200/ 50 mg; (4 tablets twice a day on day 1 followed by 2 tablets twice a day for 9 d)	Oral	NCT04403100
Remdesivir (RDV, GS-5734, Veklury)	Inhibitor of RNA-dependent RNA polymerase	200 mg on day 1 followed by 100 mg for 4-9 d	IV	NCT04292899
Hyperimmune Plasma (COV19-PLASMA)	Immunotherapy	250-300 mL up to 3 times over 5 d	IV	NCT04321421
Tocilizumab (TCZ, ROACTEMRA)	Humanized anti-IL6 receptor monoclonal antibody	8 mg/kg single infusion, up to 800 mg	IV	NCT04320615
Sarilumab (Kevzara, REGN88, SAR153191)	Monoclonal antibody against IL-6 receptor alpha	200 mg or 400 mg; single dose and multiple doses	IV	NCT04315298
Anakinra (KINERET)	Monoclonal antibody against the IL-1 receptor	100 mg daily up to 28 d	SC	NCT04330638
Siltuximab (SYLVANT)	Chimeric anti-IL-6 antibody	11 mg/kg single infusion	IV	NCT04330638
Eculizumab	Monoclonal antibody against complement protein C5	900 mg every 7 d	IV	NCT04288713
Methyl-prednisolone (MP)	Immunosuppression against cytokine storm	80 mg/kg IV bolus, followed by infusion of 80 mg/d for at least 8 d and then oral MP 16 mg or 20 mg IV twice daily	Oral-IV	NCT04323592
Heparin	Antithrombotic agents	10 units/kg/h	IV	NCT04367831
Enoxaparin (Lovenox)	Antithrombotic agents	1 mg/kg	SC	NCT04367831
Dexamethasone	Immunosuppression against cytokine storm	20 mg/d (5 d) then 10 mg/d (5 d)	IV	NCT04325061
Vitamin C	Antioxidant	12 g infusion twice a day for 7 d	IV	NCT04264533
Melatonin	Antioxidant	3 or 30 mg three times a day for 14 d	Oral	NCT04784754
CoQ10	Antioxidant	500 mg/day for 6 wk	Oral	NCT04960215

IL: Interleukin.

specific action of this drug on SARS-CoV-2 infection of ECs is not known.

The second drug, Paxlovid (PF-07321332; ritonavir) is a SARS-CoV-2 protease inhibitor antiviral therapy[26]. PF-07321332 is an inhibitor of the SARS-CoV-2 3-chymotrypsin-like cysteine protease that is essential for SARS-CoV-2 replication[26, 89]. Ritonavir is a protease inhibitor that slows down the metabolism/breakdown and therefore, increasing the bioavailability of other protease inhibitors including PF-07321332 in the body[90]. Studies published on November 2, 2021, in Science reported the discovery and characterization of PF-07321332 (Paxlovid)[26]. These studies demonstrated that Paxlovid inhibits SARS-CoV-2 replication *in vitro* in human adenocarcinoma-derived alveolar basal epithelial and differentiated normal human bronchial epithelial cells[26]. This drug showed *in vitro* coronavirus antiviral activity against all coronaviruses infecting humans and excellent off-target selectivity and *in vivo* safety profiles.

That study also showed the efficacy of orally administered 300 or 1000 mg/kg PF-07321332 against SARS-CoV-2 infection *in vivo* in a mouse model challenged intranasally with SARS-CoV-2 MA10 (CCID50). PF-07321332 Limited cellular infiltration by SARS-CoV-2 and protected lung tissue from damage compared to placebo treatment in that study[26]. Most importantly, the interim analysis of the Paxlovid human clinical trial demonstrated a dramatic approximate 90% reduction in COVID-19-related hospitalization or death in high-risk patients treated within 3 to 5 d of symptom onset compared to placebo. Since this drug inhibits virus replication the chance of endothelial infection and dissemination of virus *via* blood vessel is reduced. We postulate that ECs and blood vessels are likely an important part of this drug's clinical efficacy. Naturally, this contention requires further careful analysis and confirmation, and in-depth insight, since the biological effects of these drugs are

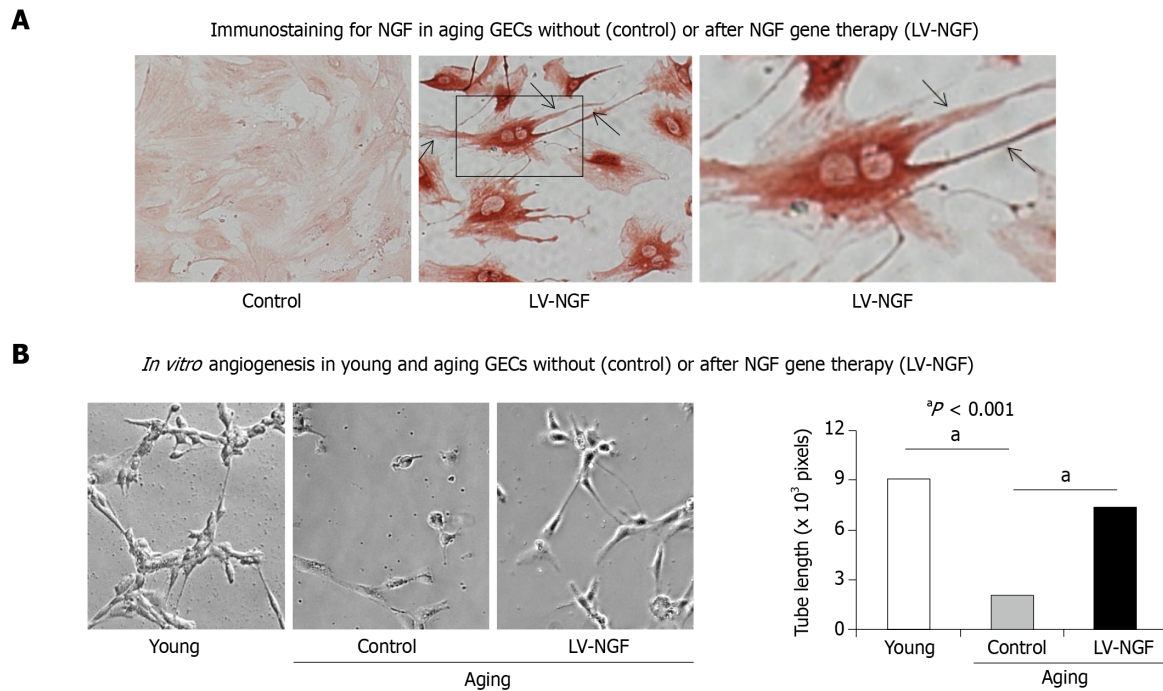


Figure 4 Nerve growth factor gene therapy increases nerve growth factor expression and reverses impaired *in vitro* angiogenesis in aging gastric endothelial cells. A: Nerve growth factor (NGF) gene therapy of aging Gastric endothelial cells (GECs) using lentiviral-NGF (LV-NGF) induced NGF expression (brown staining) and extensive, long filopodia (arrows) reflecting a change in these cells to an angiogenic phenotype; aging GECs without gene therapy (negative controls) have minimal NGF expression and lack filopodia; B: NGF gene therapy with LV-NGF resulted in 3.7-fold increased *in vitro* angiogenesis at 6 h in aging GECs vs negative controls (control). Panels are representative images of capillary-like tube formation. Original magnification: $\times 200$. Data are means \pm SD ($n = 6$). ($^aP < 0.001$). NGF: Nerve growth factor; GEC: Gastric endothelial cells; LV: Lentiviral. Reproduced with permission from reference[20], which is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

largely unknown[91,92]. This sentiment and discussion regarding these oral drugs are summarized in the November 10, 2021 Nature article titled COVID antiviral pills: what scientists still want to know[91]. On December 22, 2021, the US Food and Drug Administration issued an emergency use authorization of Paxlovid to treat mild and moderate COVID-19 (<https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19>).

Other drugs that may be repurposed for COVID-19 treatment include melatonin, coenzyme Q 10 (CoQ10). Melatonin with its anti-inflammatory and anti-oxidative effects can protect against bacterial and viral infections[93-95] and an ongoing clinical study is investigating the efficacy of melatonin in COVID-19 (NCT: 04784754). A clinical trial is investigating the effect of high-dose CoQ10 in long-term COVID-19 patients (NCT: 04960215). The use of growth factors - VEGF, NGF, EGF and KGF, and treatment with adipose-derived stem cells (ADSCs) may be useful for COVID-19 therapy in both the initial and especially the regenerative, healing phase of the disease. A recent study demonstrated that ADSCs release exosomes that secrete various growth factors such as NGF, IGF1, HGF, *etc.*) that may alleviate the cytokine storm in COVID-19 patients[96].

CONCLUSION

While respiratory epithelium is the main route of virus entry, the ECs lining blood vessels are an integral part of COVID-19 disease progression and multi-organ spread. COVID-19 not only affects the lungs and respiratory system but also gastrointestinal tract, liver, pancreas, kidneys, heart, brain, and skin. Blood vessels serve as conduits for the virus dissemination to these distant organs. Importantly, ECs are also critical for vascular regeneration during injury/lesions healing and restoration of vascular network. In the present article, we reviewed the role of the endothelial and vascular components as major targets for COVID-19-induced tissue injury, spreading to various organs, and injury healing, and the current treatments for COVID-19 including the most recent oral drugs Molnupiravir and Paxlovid.

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