

COVID-19 and the Cardiologist : Drug Therapeutic Options

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ABSTRACT

The emerging novel coronavirus outbreak (COVID-19) represents a global challenge and a crucial query concerns its prevention and treatment. Signs of severe myocardial damage can present closely related to the severity of the disease and even the prognosis and several mechanisms related to cardiovascular involvement has been postulated. At present, there is no definite and effective treatment but research has demonstrated that cytokine storm is an important factor leading to the light-to-severe transition of COVID-19 patients and that preventing and combatting cytokine storms is mandatory for clinicians focusing attention to several proven drug target of crucial importance in viral life-cycle and in its deleterious consequences. Research has called attention to several proven drug target and new findings are ongoing. The use of verified repurposed drugs remains as an important opportunity of treatment although it will require cer-

tainly further evaluation as well as further studies are needed about new therapies. Cardiologists should be aware of the risk of COVID-19 drug effects, interactions and toxicities as well of the current precautions and opportunities. Worldwide there is a great expectancy of a vaccine. Several clinical trials have already been conducted or are currently ongoing evaluating drugs and it will be important to helping treat COVID-19 patients. The world is desperately waiting for an effective and safe therapy for Covid-19 in the hope that an equally effective and safe vaccine will soon arrive.

Key words: COVID-19; SARS-CoV-2, Therapy

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TEXT

The emerging novel coronavirus outbreak (COVID-19)^[1] represents a global challenge and a crucial query^[2] concerns its prevention and treatment^[2]. Patients with clinical COVID-19 have often mild symptoms but severe patients quickly develop complications especially in presence of comorbid conditions such as diabetes or hypertension, underlying cardiovascular disease including CHD, and in the elderly patients^[1]. Signs of severe myocardial damage can present closely related to the severity of the disease and even the prognosis. Research has called attention to several mechanisms related to cardiovascular involvement such as direct virus induced cardiomyocyte damage, insufficient myocardial oxygen supply and demand imbalances, cytokine storms induced myocardial damage and severe organ failure^[1]. At present, there is no definite and effective treatment^[1,11,12] but research has demonstrated that cytokine storm is an important factor leading to the light-to-severe transition of COVID-19 patients^[13]. After invasion, the SARS-CoV-2 (the COVID-19 agent) rapidly activates CD4 + T cells, leading them to proliferation and differentiation into Th1 cells and to secretion of pro-inflammatory properties such as IL-6, interferon gamma, and granulocyte-macrophage colony-stimulating factor (GM-CSF) Cytokine^[13]. GM-CSF can activate monocytes to further release IL-6 and other factors, leading to the formation of a cytokine storm, which makes patients develop Acute respiratory distress syndrome

(ARDS), Multiple Organ Failure Syndrome (MOFS) and even die^[13]. Preventing and combatting cytokine storms is mandatory for clinicians and it can be made inhibiting any SARS-CoV-2 proteins essential for viral life-cycle and blocking any pathway leading to cytokine storms. Research has called attention to several proven drug target^[2,14]: the viral protein papain-like protease (PLpro)^[15,16], the lipid dependent attachment site to human host cells^[13], the cleavage site for cathepsin L spike protein^[18], the spike glycoprotein ACE2 binding^[1,6,9-16], the spike glycoprotein sialic acid cells receptors binding^[17-19], the cellular protease transmembrane protease serine 2 (TMPRSS2)^[21-34], the viral NSP1^[6], the viral NSP3^[6], the viral 3-chymotrypsin-like cysteine protease (3CLpro) enzyme also known as Nsp5 also known 6LU7^[4,6-35], the *Nsp7*^[6], the *Nsp8*^[6], the Nsp12 protein RNA-dependent RNA polymerase (RdRp)^[6,36], the Helicase (Nsp13)^[6,37], the *viral NSP15*^[38], and to related treatments to prevents and to combat cytokine storms^[2,3,9,39-47], and coagulation diseases^[7,48-51]. Of interest, the ORF1a and ORF1ab polyproteins are proteolytically cleaved into 16 nonstructural proteins designated nsp1-16^[29]. Research has also postulated as anti- Covid-19 the use of convalescent plasma^[52-53], the possible use of propose nicotine and nicotinic orthosteric and/or allosteric agents according to nicotinic hypothesis^[54], the Stem Cell Therapy^[55], the challenge for vaccine development^[56], a siRNA based therapy^[57], a TGF- β blockade therapy^[58], a possible application of H2S-producing compounds^[59], adjunctive immunomodulatory statins action^[60-61] and future studies to examine the efficacy of interferon beta-1b therapy alone or in combination with other drugs^[62-63].

The viral protein papain-like protease (PLpro)

The viral protein papain-like protease (PLpro) cleavages N-terminus of the replicase poly-protein releasing Nsp1, Nsp2 and Nsp3, having an essential role for correcting virus replication. PLpro also antagonizes the host's innate immunity. A series of anti-virus drugs (ribavirin, valganciclovir and thymidine), of anti-bacterial drugs (chloramphenicol, cefamandole and tigecycline), a muscle relaxant drug (chlorphenesin carbamate), an anti-tussive drug (levodropropizine) may have high PLpro binding affinity^[5,6]. Several FDA approved drugs are PLpro antagonists, including chloroquine and formoterol^[2], darunavir^[6], chlorothiazide, formoterol, naphazoline, terbinafine, tetrahydrozoline, biltricide, cinacalcet, procainamide, pethidine, labetalol, ticlopidine, ethoheptazine, levamisole, amitriptyline, benzylpenicillin^[2,5].

The lipid dependent attachment site to human host cells

Cyclodextrin and sterols, could reduce the infectivity of many types of viruses, including the coronavirus family, through interference with lipid dependent attachment to human host cells^[7].

The cleavage of the viral spike protein by cathepsin L

Teicoplanin acts on the early step of the viral life cycle by inhibiting the low pH cleavage of the viral spike protein by cathepsin L in the late endosomes thereby preventing the release of genomic viral RNA and the continuation of virus replication cycle^[8].

ACE2-spike S protein binding

Research has confirmed Angiotensin-converting enzyme 2 (ACE2) as the key SARS-CoV-2 (the COVID-19 causative agent) cell entry receptor due to ACE2-spike S protein binding^[1]. The S protein has showing having 2 subunits: S1 and S2, facilitating target cell internalization. SARS-Cov-2 contains a polybasic (furin) cleavage site^[12] inserted at the boundary of the S1/S2 subunits of the spike

S-protein and a furin-mediated proteolytic cut of the Spike protein is necessary for viral entry into the cell^[13]. Hesperidin target the binding interface between Spike and ACE2 and may disrupt the interaction of ACE2 with Spike-receptor binding domain (RBD)^[6]. Inhibiting the expression of furin could then be a possible approach to prevent SARS-CoV-2 infection^[13] Research has found several furin antagonists: Aminopterin, Andrographolide, Andrographolide derivatives, biorobine, cefoperazone, chenodeoxycholic acid, diminazene, (-)- epigallocatechin gallate, fludarabine phosphate, folic acid, folinic acid, fosaprepitant, glycerol 3 phosphate, hydroxystilbamidine, irinotecan, glutathione, famotidine, Kouitchenside J, Kouitchenside F, L-dopa, lomefloxacin, methotrexate, Phyllaemblicin G7, sulfoxone, L-arginine, Stigmast-5-en-3-ol, sylibin, theaflavin 3,3'- di-O-gallate, valgancyclovir, 14-deoxy-11,12-didehydroandrographiside, 14-deoxy-11,12-didehydroandrographolyde, 2 β ,30 β -dihydroxy-3,4-seco-friedelolactone-27-lactone-2-[2-O-(6-deoxy- α -L-, mannopyranosyl)- β -D-xylopyrano syl]oxy]-1,8-dihydro xy-6-methoxy-9H-xanthen-9-one^[15]. There has been much controversy regarding the role of RAS-interfering agents, such as ACE inhibitors or angiotensin receptor blockers (ARB's), on the levels of ACE2 expression^[30], and research suggests to continue prescribed drugs because the benefit may outweigh the risk^[30] and further investigations are needed to provide definitive answers to this question^[30]. Another approach to prevent viral infection could be the downregulation of ACE2 on cell membrane increasing A Disintegrin And Metalloproteases 17 (ADAM17) levels^[13]. Of relevance, estradiol increases the expression levels and activity of ADAM17. This last finding would suggest higher shedding of ACE2 in women and could, at least partially, explain the reduced incidence of COVID-19 in women compared to men. Another mechanism of reduced incidence of COVID-19 in women compared to men involves replication cycle of Coronavirus Nitric oxide^[31] (NO) inhibition by two distinct mechanisms. 1) reduction in the nascently expressed spike (S) protein palmitoylation affecting the fusion between the S protein and 2) due to an effect on one or both of the cysteine proteases encoded in Orf1a of Coronavirus^[64]. Research has reported enhanced S-nitrosylation (SNO) protein levels in female hearts implicated as an essential mediator of nitric oxide-dependent cardioprotection and that compared to males, female hearts exhibit higher baseline levels of protein SNO^[65,66]. Furthermore The Notch signalling is a positive regulator of furin and a negative regulator of ADAM17 (through the transcription of miRNA-145) and thus preventing Notch activation with^[13] γ -secretase inhibitor (GSI) may represent a strategy to interfere with the virus entry into the cells by reducing furin and increase ADAM17 shedding. An antagomir to miRNA-145 could represent an alternative approach for upregulation of ADAM17^[13]. Unfortunately, GSI have shown limited clinical efficacy and dose-limiting toxicities but, interestingly, the addition of Chloroquine (as NOTCH activity blocker agent) synergizes with GSI enabling equal efficacy at a lower concentration increasing its therapeutic ratio^[14]. Chloroquine is a known 4-aminoquinoline and has a wide range of antiviral effects interfering with intracellular DNA replication and gene expression. Chloroquine can change the pH of endosomes, chloroquine inhibits virus replication by reducing the terminal glycosylation of angiotensin-converting enzyme 2 (ACE2) receptors and interfering with the binding of SARS-CoV2 and ACE2 receptors^[6,9,15] inhibits p38 mitogen-activated protein kinase (MAPK) activation^[11] Molecular docking showed that UDP-GlcNAc has more binding affinity with Ser-787 than the phosphoryl group. Moreover, chloroquine and 2-hydroxybenzohydrazine also

showed great potential to bind at Ser-787 thus resulting in inhibition of Ser-787 phosphorylation and downstream signaling. Furthermore, O- β -GlcNAcylation, chloroquine and 2-hydroxybenzohydrazine showed their high affinity at ACE2-SARS-CoV-2 receptor binding domain preventing SARS-CoV-2 entry of into human body inducing disruption of virus-ACE2 binding^[16].

The spike glycoprotein sialic acid cells receptors binding

Moreover, research has shown that SARS-CoV-2 uses a dual strategy: its spike protein could also interact with sialic acid receptors of the cells in the upper airways, in addition to the known ACE2 binding^[17]. Research has also shown that Chloroquine binds sialic acids and gangliosides with high affinity and that in presence of CLQ (or of the more active derivative hydroxychloroquine, CLQ-OH), the viral SARS-CoV-2 spike (S) protein is no longer able to bind gangliosides^[18]. Moreover chloroquine reduces inflammation through inducing T-bet expression in T cells and reducing Th17 differentiation. Interestingly, the shift in the balance between Th17/Th1 cells towards IFN- γ production may reflect another pathway by which CQ augments antiviral responses^[19]. Cardiologists have called attention to the cardiovascular arrhythmic side effects of chloroquine and of hydroxychloroquine, increased by co-prescription of other drugs such as azithromycin used for COVID-19 treatment^[20].

TMPRSS2

A nuclear factor erythroid 2-related factor 2 (Nrf2)- secretory leukocyte protease inhibitor (SLPI)-Dependent Inhibition of TMPRSS2 Activity has shown as protective against virus infection^[1] and multiple lines of evidence support the potential of dialing up the Nrf2 pathway for cardiac protection^[21] the clinically proven serine protease inhibitor camostat mesylate, which is active against TMPRSS2 (Kawase et al., 2012), partially blocked SARS-2-S-driven entry^[22,23] Furthermore Tazobactam Argatroban Letaxaban Otamixaba MAFP Edoxaban Camostat Darexaban BIA 10-2474 are TMPRSS2 inhibitors^[24].

Several natural compounds have been identified as Nrf2 inducers, including ursodeoxycholic acid, sulforaphane, curcumin, resveratrol, Quercetin^[25]. Research has also identified niclosamide^[26], aspirin^[27], ezetimibe^[28], monoxidine^[29], nicorandil^[30], nitric oxide^[31], nifedipine^[32], statins^[33], verapamil^[34] as Nrf2 inducers.

Nsp1

Nsp1 interacts with host 40S ribosomal subunit that induces specifically host mRNA degradation and also inhibits type-I interferon production^[6]. The detailed screening results of Nsp1, Nsp3c, and ORF7a showed that a series of clinical drugs and natural products with anti-bacterial and anti-inflammatory effects exhibited relatively high binding affinity to these three target proteins, such as piperacillin, cefpiramide, streptomycin, lymecycline, tetracycline, platycodin D from *Platycodon grandifloras*, wogonoside from *Scutellaria baicalensis*, vitexin from *Vitex negundo*, andrographolide derivatives, and xanthones from *Swertia* genus^[6]. Only tenofovir, disoproxil, fumarate, and beclabuvir may bind to Nsp1^[6].

Nsp3

PLpro cleaves three sites at 181–182, 818–819, and 2763–2764 at the N-terminus and 3CLpro cuts at the other 11 sites at the C-terminus, and forming 15 non-structural proteins. Among them, Nsp3 contains multiple domains 6 including a segment of SARS unique domain and a deubiquitination and proteolytic enzyme PLpro. Nsp3 (Nsp3b,

Nsp3c, PLpro, and Nsp3e)^[6]. Nsp3c has ability to bind with host's ADP-ribose to help coronavirus resist host innate immunity⁴⁴. Our molecular docking results show that the potential targets of remdesivir is Nsp3b^[6]. Lopinavir's possible target is Nsp3b, Nsp3c, helicase, NRBD Our docking results showed that the possible targets of darunavir are Nsp3c, PLpro, E-channel or Spike proteins Docking results showed that the possible target of chloroquine is Nsp3b^[6] and that ritonavir's possible target is Nsp3c^[6].

Nsp5

The 3CLpro, also known as Nsp5, is first automatically cleaved from poly-proteins to produce mature enzymes, and then further cleaves downstream Nsps at 11 sites to release nsp9–Nsp16^[6]. 3CLpro directly mediates the maturation of Nsps, which is essential in the life cycle of the virus^[6] and several potential anti- SARS-CoV-2 3CLpro molecules have been found from medicinal plants^[4]. Mepacrine appears as the most powerful inhibitor among seven compounds studied here^[35].

Nsp7 Nsp8

Nsp8 can de novo synthesize up to 6 nucleotides in length, which can be used as a primer for Nsp12-RdRp RNA synthesis. Further, the Nsp7_Nsp8 complex increases the binding of Nsp12 to RNA and enhances the RdRps enzyme activity of Nsp12.

The docking results of arbidol with the possible drug targets of the new coronavirus showed that it may interact with Nsp7_Nsp8 complex, Nsp14, Nsp15, E-channel, or Spike^[6]. Docking results showed that the possible targets of darunavir are Nsp3c, PLpro, E-channel or Spike proteins^[6].

Nsp12

Nsp12, a conserved protein in coronavirus, is an RNA-dependent RNA polymerase (RdRp) and the vital enzyme of coronavirus replication/transcription complex. The RdRp domain of polymerase is located at the C-terminus and has a conserved Ser-Asp-Asp motif^[6]. Remdesivir (GS-5734), a nucleoside analogue, is an RdRp inhibitor^[6]. The genome encodes for the nsp12 protein, which houses the RNA-dependent-RNA polymerase (RdRP) activity responsible for the replication of the viral genome. Vitamin B12 (methylcobalamin) may bind to the active site of the nsp12 protein. A model of the nsp12 in complex with substrate RNA and incoming NTP showed that Vitamin B12 binding site overlaps with that of the incoming nucleotidemethylcobalamin binding may prevent association with RNA and NTP and thus inhibit the RdRP activity of nsp12. Overall, our computational studies suggest that methylcobalamin form of vitamin B12 may serve as an effective inhibitor of the nsp12 protein^[36]. Docking results showed that the possible target of chloroquine is Nsp3b or E-channel^[6].

Helicase (Nsp13)

Helicase (Nsp13) a highly conserved among coronaviruses multi-functional protein, includes N-terminal metal binding domain (MBD) (containing 26 cysteine residues to form a Zn²⁺ binding domain) and helicase domain (Hel). Nsp13 unravel double-stranded (ds) DNA and RNA along the 5'–3' direction^[37]. Having a crucial role for the replication of coronavirus. Research has reported as Nsp13 inhibitors with high mean force score anti-bacterial drugs (lymecycline, cefsulodine and rolitetracycline), anti-fungal drug itraconazole, anti-human immunodeficiency virus-1 (HIV-1) drug saquinavir, anti-coagulant drug dabigatran, and diuretic drug canrenoic acid

and research has also demonstrated that natural products, such as many flavanoids (α -glucosyl hesperidin, hesperidin, rutin, quercetagenin 6-O- β -D-glucopyranoside and homovitexin), xanthenes (3,5-dimethoxy-1-[(6-O- β -D-xylopyranosyl- β -D-glucopyranosyl)oxy]-9H-xanthen-9-one, kouitchenside H, kouitchenside A, 8,2-dihydroxy-3,4,5-trimethoxy-1-[(6-O- β -D-xylopyranosyl- β -D-glucopyranosyl)oxy]-9H-xanthen-9-one, kouitchenside D, 1-hydroxy-2,6-dimethoxy-8-[(6-O- β -D-xylopyranosyl- β -D-glucopyranosyl)oxy]-9H-xanthen-9-one and triptexanthoside D from *Swertia* genus, phyllaemblicin B and phyllaemblinol from *Phyllanthus emblica* have high binding affinity to this target^[6]. Furthermore a bismuth-mediated inhibition of the SCV helicase functions has been shown: The zinc ions bound to the MBD of SCV helicase were replaced by bismuth ions upon addition of bismuth compounds, resulting in dysfunction of the helicase^[37].

Nsp15

The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP1 5in MERS generating a mutant virus that developed ciclesonide resistance but no virus to mometasone resistance^[38].

Cytokines storm

Chloroquine (CQ) and hydroxychloroquine (HCQ) are 4-aminoquinoline derivatives^[2,6,9,11,14-16,18-19]. The major proposed immunomodulatory mechanisms of CQ and HCQ are the following: inhibition of cytokine production and release by T cells: IL-1, IL-2, IL-6, and IL-18, TNF- α and IFN- γ , reduced levels of chemokines, CCL2 and CXCL10, inhibition of micro-RNA expression, decreased TH17-related cytokines, increased in Treg activity and upregulated levels of IFN- α and IL-2 and IL-10, inhibition of cytotoxic T cell and self-reactive CD4+ lymphocyte activities, decreased DNA, RNA and protein synthesis in thymocytes^[39,55]. Systemic corticosteroids have broad-spectrum actions on the immune system that may suppress the exuberant systemic inflammatory response but corticosteroid use was prolonged SARS-CoV-2 RNA shedding as observed in SARS and MERS infections^[39]. A high dose of Intravenous immunoglobulin (IVIg) administered at the appropriate point could successfully block the progression of the disease cascade and improve the outcome of COVID-19^[39,40]. JAK inhibitors Tocilizumab, sarilumab, siltuximab are IL-6 antagonists^[39]. JAK2 inhibitor Fedratinib is a promising IL-6 IL-17antagonist^[41]. Both IL-1 β and IL-18 fuel cytokine storm and MAS and IL-1 cytokines (except IL-18) can be successfully inhibited by anakinra^[39]. Clinical use of traditional Chinese medicine has been also proposed^[42]. The protective effects of *N*-acetylcysteine (NAC) have been documented in experimental and clinical acute lung injury as interleukin-8-(IL-8)secretion inhibitor^[43]. as well as the IL-12 production inhibition by 1,25- dihydroxyvitamin D3^[44]. Dapsone, belongs to a class of drugs known as sulfones, suppresses production of specific cytokine signatures as IL1 α , IL8, IL1 β , IL6, and IL8 and tumor necrosis factor- α ^[45]. Mizolastine was associated with early phase reduction of cyotkine levels of IL1, IL6, and TNF- α . Fexofenadine significantly inhibited IL6 and TNF α ^[46]. and significantly increase the anti-inflammatory IL-10 concentrations^[47]. Mavrilimumab is a GM-CSF inhibitor^[39]. Mycophenolate mofetil (MMF), has strong immunosuppressant effects^[39].

Coagulation diseas

Cytokines storm also lead to sepsis induced coagulopathy^[48]. and Heparin^[49]. and LMWH^[50] have decreased mortality in sepsis induced coagulopathy (SIC) in COVID-19^[49-51].

Convalescent plasma or immunoglobulins^[29,52] have been used as a last resort to improve the survival rate of patients with SARS whose condition continued to deteriorate despite treatment with pulsed methylprednisolone^[52]. Risks of passive administration of convalescent sera exist including those trasfusion associated infectious transmissions and reactions. Moreover in this case clinicians should be aware of the risk of transfusion-related acute lung injury (TRALI)^[53] and the risk-benefit assessment should be made^[53].

Nicotine and nicotinic orthosteric and/or allosteric agents

In conclusion, we propose, and try to justify, the hypothesis that nAChRs play a critical role in the pathophysiology of SARS-CoV-2 infection and as a consequence propose nicotine and nicotinic orthosteric and/or allosteric agents as a possible therapy for SARS-CoV-2 infection. Interestingly, ivermectin, which has been recently shown to inhibit the replication of SARS-CoV-2 in cells in vitro, is a positive allosteric modulator of a7 nAChR^[54].

Stem Cell Therapy

As an important member of the stem cell family, mesenchymal stem cells (MSC) have powerful anti-inflammatory and immunoregulatory functions in addition to their potential for self-renewal and multi-directional differentiation reducing the occurrence of cytokine storms and can also relieve ARDS, and can regenerate and repair damaged lung tissue and resist fibrosis opening new therapeutic anti-COVID-19 pathways^[55].

Vaccine

Worldwide there is a great expectancy of a vaccine. In this context perplexing concern regards possible antibody dependent enhancement (ADE) of SARS-CoV-2 and the potential role of Th17 responses on eosinophilic immunopathology (EI) development^[56].

siRNA based therapy, TGF- β blockade therapy,H2S-producing compounds, statins, interferon beta-1b

Future studies are needed to examine the efficacy of siRNA^[57], of TGF- β function blockade^[58] the application of a harmless H2S donor (sodium thiosulfate)^[59], adjunctive immunomodulatory statins action^[60,61] and of interferon beta-1b alone or in combination with other drugs^[62] as anti COVID-19 therapy.

Phisicians should be aware of the risk of COVID-19 Drug Interactions also on QTc^[18] including of the risk of Genetic Susceptibility for COVID-19-Associated Sudden Cardiac Death^[67-69], of the toxicity^[70], and of the cardiovascular effects^[71] and drug interactions of several covid-19 Covid therapies^[72] including those between Statins and Antiviral Agents for COVID-19 Treatment^[61]. Remarkable, most available statins are substrate for the cytochrome P450 (CYP) system, especially 3A isoenzymes and P-glycoproteins (P-gp) while Protease inhibitors (e.g., lopinavir, darunavir) and their pharmacokinetic enhancers (ritonavir and cobicistat) are potent inhibitors of both CYP3A and P-gp, and their concomitant administration can results in markedly increased statin exposure and adverse effects^[61]. Research has recommended the monitoring of cardiac rhythm,QT, laboratory examination including electrolytes^[73], cardiac function and myocardial injury and providing to consequential other cardiovascular drugs and supports¹ together current cardioprotective therapies^[1]. Faced with COVID-19 emergency, I think that the use of verified repurposed drugs remains as an important opportunity of treatment although it will require certainly further evaluation as well as further studies are needed about nonsteroidal antiinflammatory drugs (NSAIDs),about inhibitors of mRNA translation and predicted regulators of the Sigma1 and

Sigma2 receptors^[74], and about drugs targeting RNA cap 2'-O-MTase nsp16/nsp10 protein complex thus blocking virus immune evasion^[75]. Several clinical trials have already been conducted or are currently ongoing evaluating drugs^[76] and it will be important to helping treat COVID-19 patients^[72]. The world is desperately waiting for an effective and safe therapy for Covid-19 in the hope that an equally effective and safe vaccine will soon arrive.

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