


## Case report

## Angioedema, ACE inhibitor and COVID-19

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Accepted 25 August 2020

**SUMMARY**

SARS-CoV-2, the virus responsible for COVID-19, binds to the ACE2 receptors. ACE2 is thought to counterbalance ACE in the renin-angiotensin system. While presently it is advised that patients should continue to use ACE inhibitors or angiotensin receptor blockers, questions still remain as to whether adverse effects are potentiated by the virus. Here, we report a case of a 57-year-old man, unknowingly with COVID-19, who presented to the emergency department with tongue swelling, shortness of breath and difficulty in speaking following 4 months taking benazepril, an ACE inhibitor. Finally, we also describe possible pathways that exist for SARS-CoV-2 to interact with the mechanism behind angioedema.

**BACKGROUND**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel lineage B betacoronavirus that emerged at the end of 2019.<sup>1</sup> It was identified as the pathogen that caused acute severe respiratory illness colloquially known as COVID-19.<sup>2</sup>

SARS-CoV-2 binds with high affinity to human ACE2 receptors,<sup>3</sup> possibly leading to its downregulation.<sup>4</sup> ACE2 is expressed broadly, including in the heart, kidneys and lungs.<sup>5</sup> ACE2-expressing cells are also found in oral tissue, especially in the epithelial cells of the tongue,<sup>6</sup> and it has been reported that SARS-CoV-2 was detected in resected tissue of the tongue and submandibular gland.<sup>7</sup>

Animal and human studies have shown that ACE inhibitors and angiotensin receptor blockers (ARBs) may modulate ACE2 expression.<sup>8</sup> Therefore, the implications of using these medications in a patient with COVID-19 may have previously unexpected consequences. Here, we report of a COVID-19-positive patient who was prescribed an ACE inhibitor and presented to the emergency department with angioedema, a potentially life-threatening adverse drug reaction of ACE inhibitors.

**CASE PRESENTATION**

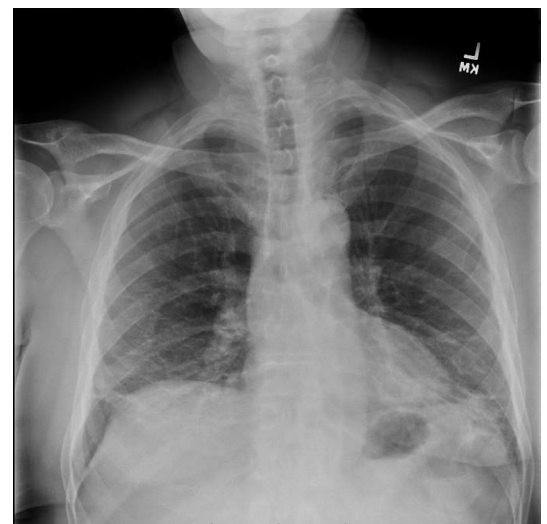
A 57-year-old man with a medical history of hypertension and type 2 diabetes mellitus presented in the emergency department with worsening swelling of the tongue, difficulty in speaking and shortness of breath since the morning. He was given multiple doses of intramuscular epinephrine in the prehospital setting with no change in symptoms. He had no associated pain, itchiness or rash, and he denied fever, nausea, vomiting, chest pain or cough. He reported not having any allergies or eating anything outside of his regular diet. The patient stated he began taking a new blood pressure medication,

benazepril, approximately 4 months ago. He had no personal or family history of facial or tongue swelling.

**INVESTIGATIONS**

On examination, the patient was afebrile and normotensive, with an oxygen saturation of 96% on room air. There was pronounced oedema involving the lingual mucosa and subcutaneous tissues of the perioral area without pain or pruritus. Cardiac auscultation revealed tachycardia without any pathological murmurs. Auscultation of the lungs revealed decreased breath sounds bilaterally with inspiratory effort, but no wheezing or crepitations. No jugular venous distention or lower limb swelling was appreciated. No urticarial eruption was noted throughout.

Laboratory tests revealed mild leucocytosis ( $10.8 \times 10^9/L$ ) with lymphopenia ( $800 \times 10^9/L$ ) and elevated high-sensitivity C-reactive protein (7.80 mg/dL), ferritin (866 ng/mL) and lactate dehydrogenase (1295 IU/L). D-dimer, C3 and C4 levels were not measured. Chest X-ray showed bilateral infiltrates in lung bases (figure 1), whereas CT impressions showed multifocal alveolitis in the periphery of the upper lobes bilaterally (not shown). CT imaging of the neck showed oedema along the prevertebral and submucosal tissues of the oropharynx and hypopharynx (figure 2), as well as in the submandibular area surrounding the submandibular glands. A nasopharyngeal swab was

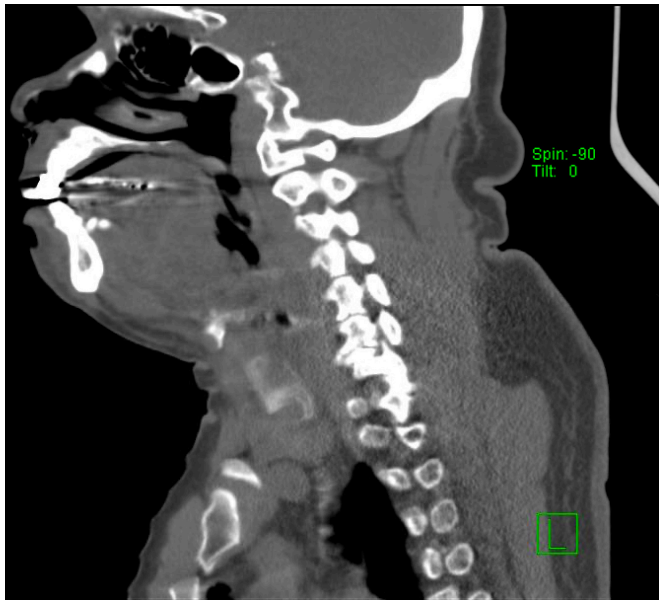


**Figure 1** X-ray of the chest in the posterior–anterior view.



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**To cite:** Grewal E, Sutarjono B, Mohammed I. *BMJ Case Rep* 2020;**13**:e237888. doi:10.1136/bcr-2020-237888



**Figure 2** CT of the head and neck in the sagittal view.

taken for COVID-19 assay by real-time PCR (Abbott Real-time SARS-CoV-2 PCR, M2000 platform; FDA, 2020).

### DIFFERENTIAL DIAGNOSIS

Anaphylaxis was our initial diagnosis of exclusion. Without positive clinical response following epinephrine administration, delay in considering alternative diagnoses may have led to a fatal outcome.<sup>9</sup> Other differential diagnoses chiefly included deep space abscess and hereditary or acquired angioedema. We considered infectious processes such as a lingual abscess,<sup>10</sup> or Ludwig's angina, a form of submandibular space infection arising from the odontogenic origin<sup>11</sup>; however, without fever, pain or specific fluctuant oedema, infectious processes were mostly ruled out. Trauma is a common cause of tongue swelling, particularly from epileptic tongue bites,<sup>12</sup> although the absence of personal history meant this was unlikely. Neoplasm was also a possibility, most commonly caused by oral squamous cell carcinoma of the tongue,<sup>13</sup> as was lingual thyroid, an abnormal mass of ectopic thyroid tissue normally seen in the base of the tongue from defects in embryogenesis.<sup>14</sup> The rapidity of symptom onset did not correspond to this picture. Rarer possibilities included submental haematoma, seen in anticoagulated patients,<sup>15</sup> and Melkersson-Rosenthal syndrome, which is normally accompanied by recurrent congenital facial nerve palsy.<sup>16</sup> Alternatively, other rare causes are tuberculosis of the tongue, which manifests in immunocompromised individuals,<sup>17</sup> and tertiary syphilis, which has been shown to invade the tongue in patients with chronic infection.<sup>18</sup>

Angioedema is the non-pruritic swelling of the deeper layers of the skin or mucosa, which can be fatal when it obstructs the airway.<sup>19</sup> Ultimately, in the absence of family history or repeated occurrence of angioedema, hereditary angioedema<sup>20</sup> was less likely. ACE inhibitor-associated angioedema was our primary diagnosis due to the recent use of ACE inhibitors in the last few months. However, during the height of the initial surge in New York City, we questioned whether SARS-CoV-2 could cause or at least potentiate angioedema. Other workup showed bilateral pulmonary infiltrates and elevated inflammatory markers with lymphopenia consistent with COVID-19 infection.

### TREATMENT

The decision to administer tranexamic acid in our patient with ACE inhibitor-induced angioedema was based on the evidence shown by a retrospective study in France.<sup>21</sup> Fresh frozen plasma, which has been shown to have success in treating ACE inhibitor-induced angioedema,<sup>22</sup> was prepared for the alternative measure.

In the emergency department, the patient's clinical presentation improved over 3 hours once tranexamic acid was given. Although the patient was able to talk, his voice was hoarse, and the decision was then made to admit the patient for airway monitoring. Intravenous diphenhydramine and famotidine were given, and benazepril was withheld.

### OUTCOME AND FOLLOW-UP

The angioedema resolved within 24 hours without further oropharyngeal swelling. Oxygen saturation was above 95% on room air despite suspicion for COVID-19. The patient was given oral diphenhydramine and famotidine to continue at home, whereas amlodipine was prescribed for hypertension in place of ACE inhibitors. He was also advised to follow-up with his primary care provider to modify his blood pressure medication. Soon after discharge, the patient's PCR result for COVID-19 returned positive.

### DISCUSSION

Currently, there is one other reported case of angioedema without urticaria in an ACE inhibitor user with COVID-19.<sup>23</sup> The presentation of this case report is similar to our own: non-pitting oedema of the lower face in the absence of pruritus, leucocytosis with relative lymphopenia, elevated inflammatory markers and resolution of symptoms within 48 hours, although the marked difference is the chronic use of ACE inhibitor, whereas our patient began his medication 4 months prior to admission.

The rapid improvement following tranexamic acid treatment in the emergency department validated our initial assessment of ACE inhibitor-induced angioedema. The development of angioedema is initiated by kallikrein, cleaving the active nonapeptide bradykinin from kininogen. Bradykinin generates nitric oxide and prostaglandins, which leads to vasodilatation and increased vascular permeability, particularly the postcapillary venules. Bradykinin is primarily degraded by ACE, neutral endopeptidase, aminopeptidase P, dipeptidyl peptidase IV and kininase I.<sup>24</sup> However, approximately 11% is converted into des-Arg<sup>9</sup>-bradykinin, which is cleaved by ACE2. ACE2 converts angiotensin II to its metabolite angiotensin-(1-7), which counterbalances ACE in the renin-angiotensin system,<sup>25</sup> opposing its effects of vasoconstriction, sodium retention and fibrosis.<sup>26</sup> Therefore, the theoretical downregulation of ACE2 by SARS-CoV-2 would lead to the elevated angiotensin II, creating an environment for a heightened level of bradykinin leading to angioedema.

The clinical presentation of patients with COVID-19 and ACE2 modulation are strikingly similar. For example, endotoxin inhalation in a mouse model causes a drastic reduction in pulmonary ACE2 activity, and the extended longevity of des-Arg<sup>9</sup>-bradykinin exacerbates lung inflammation,<sup>27</sup> with a presentation similar to acute respiratory distress syndrome (ARDS) as seen in patients with COVID-19. An impairment of cytokine degradation, evident by an increase in the level of C-reactive protein, has been implicated as being the primary mechanism of angioedema under the use of ACE inhibitor drugs,<sup>28</sup> which greatly resembles the dramatic release of proinflammatory cytokines caused

by SARS-CoV-2 infection.<sup>29</sup> C-reactive protein also stimulates interleukin-6.<sup>30</sup> Both C-reactive protein and interleukin-6 have been shown to be above the normal range in most patients with COVID-19<sup>31</sup> and C-reactive protein was shown to be elevated in both cases of angioedema in patients with COVID-19. Patients with COVID-19 also have markedly elevated plasma angiotensin II level that is linearly associated with viral load and lung injury.<sup>32</sup> Interestingly enough, the characteristic side effect of ACE inhibitor therapy, a dry cough, closely resembles the coughing in patients with COVID-19 as well.

It is difficult to elucidate whether the SARS-CoV-2 caused angioedema in both patients. It is possible that SARS-CoV-2 may be the trigger for angioedema when combined with the use of ACE inhibitors under a 'two-hit' mechanism. It has been documented that the addition of another medication can cause angioedema in individuals previously stable under ACE inhibitors. A common trigger is non-steroidal anti-inflammatory drugs, which may account for close to 50% of all ACE inhibitor-related angioedema.<sup>33</sup> Other medications, such as dipeptidyl peptidase IV inhibitors and mTOR inhibitors, are also associated with an increased incidence of angioedema with chronic use of ACE inhibitors.<sup>34,35</sup> With the use of omapatrilat, which concomitantly inhibits ACE as well as neutral endopeptidase, angioedema was observed at a rate threefold higher in comparison with enalapril during the OCTAVE trial.<sup>36</sup> Neutral endopeptidase is the inactivating enzyme for apelin.<sup>37</sup> Apelin, meanwhile, interacts with ACE2. Apelin is also normally cleaved and rendered inactivated by kallikrein.<sup>38</sup> Thus, these are examples of multiple pathways that may be prone to modification by SARS-CoV-2.

The existence of potential interactions creates more questions than answers. Future research should focus on acquiring levels of bradykinin and des-Arg<sup>9</sup>-bradykinin in order to determine if either of these compounds are influenced by SARS-CoV-2 infection. Icatibant, a competitive bradykinin B2 receptor antagonist, has been used for therapeutic management of ACE inhibitor-related angioedema with early use considered in severe cases.<sup>39</sup> C1-esterase inhibitor concentration (C1-INH) should also be investigated for its potential mechanism that may be vulnerable to SARS-CoV-2 infection, as its deficiency is known to cause the hereditary form of angioedema, where increasing its concentration may prove therapeutic.<sup>40</sup> Due to the emergent nature of ACE inhibitor-induced angioedema, we recommend a broader laboratory investigation as well as an exploration of treatment utilising icatibant or C1-INH concentrates.

Although it is unknown whether SARS-CoV-2 may cause angioedema, many avenues exist for possible interaction. In

accordance with current consensus,<sup>40–42</sup> we support the continuation of ACE inhibitor and ARB therapy during the pandemic and if infected with SARS-CoV-2. However, increased vigilance should be taken in patients who have sustained use of ACE inhibitors with elevated risk factors for contracting COVID-19, and we urge more research on the matter.

**Acknowledgements** Dedicated to the courageous staff at Brookdale University Hospital and Medical Center during the COVID-19 pandemic.

**Contributors** EG and BS contributed equally to this paper. IM provided patient management and edited the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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#### REFERENCES

- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;6736:30183–5.
- Joint mission report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). World Health organization, 2020. Available: <https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>
- Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol* 2020;5:562–9.
- Ciulla MM. SARS-CoV-2 downregulation of ACE2 and pleiotropic effects of ACEIs/ARBs. *Hypertens Res* 2020;43:1–2.
- Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;203:631–7.
- Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci* 2020;12:8.
- Guerini-Rocco E, Taormina SV, Vacirca D, et al. SARS-CoV-2 detection in formalin-fixed paraffin-embedded tissue specimens from surgical resection of tongue squamous cell carcinoma. *J Clin Pathol* 2020;jclinpath-2020-206635.
- de Maat S, de Mast Q, Danser AHJ, et al. Impaired breakdown of bradykinin and its metabolites as a possible cause for pulmonary edema in COVID-19 infection. *Semin Thromb Hemost* 2020. doi:10.1055/s-0040-1712960. [Epub ahead of print: 11 Jun 2020].
- Patel S, Mathew R, Bhoi S. Caution in diagnosing angioedema as anaphylaxis. *BMJ Case Rep* 2019;12:e230329.
- Schweigert J, Christian R, Kemp WL. Challenges in the diagnosis of a posterior lingual abscess, a potential lethal disorder: a case report and review of the literature. *Am J Forensic Med Pathol* 2020;41:64–6.
- Miller CR, Von Crowns K, Willoughby V. Fatal Ludwig's angina: cases of lethal spread of odontogenic infection. *Acad Forensic Pathol* 2018;8:150–69.
- Oliva M, Pattison C, Carino J, et al. The diagnostic value of oral lacerations and incontinence during convulsive "seizures". *Epilepsia* 2008;49:962–7.
- Marinelli LM, Chatzopoulos K, Marinelli JP, et al. Clinicopathologic predictors of survival in buccal squamous cell carcinoma. *J Oral Pathol Med* 2020. doi:10.1111/jop.13046. [Epub ahead of print: 25 May 2020].
- Noussios G, Anagnostis P, Goulis DG, et al. Ectopic thyroid tissue: anatomical, clinical, and surgical implications of a rare entity. *Eur J Endocrinol* 2011;165:375–82.
- Alamoudi U, Alsallumi Y, Rigby MH, et al. Spontaneous submental hematoma, a pseudo-Ludwig's phenomenon in 101-year-old patient: case report and literature review. *Int J Surg Case Rep* 2017;36:98–102.
- Nitter-Marszalska M, Krasnowska M, Solarewicz-Madejek K, et al. Restoration of facial lymphatic drainage in the course of disease. *Lymphology* 2010;43:34–41.
- Assante LR, Barra E, Bocchino M, et al. Tuberculosis of the tongue in a patient with rheumatoid arthritis treated with methotrexate and adalimumab. *Infez Med* 2014;22:144–8.
- Solis RN, Kuhn BT, Farwell DG. An unusual case of tertiary syphilis behaving like tongue squamous cell carcinoma. *J Investig Med High Impact Case Rep* 2018;6:232470961882035.

#### Learning points

- ▶ ACE inhibitor and angiotensinreceptor blocker therapy should be continued during the COVID-19 pandemic and if infected with SARS-CoV-2.
- ▶ Tranexamic acid and fresh frozen plasma are effective treatments for ACE inhibitor-induced episodes of angioedema during an urgent setting.
- ▶ Common causes of tongue swelling include anaphylaxis, angioedema, infection, trauma, neoplasm and ectopic thyroid tissue.
- ▶ SARS-CoV-2 has a high affinity to ACE2, which counterbalances ACE in the renin-angiotensin system.
- ▶ While bradykinin, which is thought to cause angioedema, is degraded by ACE, a portion is metabolised to des-Arg<sup>9</sup>-bradykinin, which is then degraded by ACE2.

- 19 Kim SJ, Brooks JC, Sheikh J, *et al.* Angioedema deaths in the United States, 1979-2010. *Ann Allergy Asthma Immunol* 2014;113:630-4.
- 20 Busse PJ, Christiansen SC. Hereditary angioedema. *N Engl J Med* 2020;382:1136-48.
- 21 Beauchêne C, Martins-Héricher J, Denis D, *et al.* Intérêt de l'acide tranexamique en traitement d'urgence de première intention des crises d'angioedème bradykinique sous IEC [Tranexamic acid as first-line emergency treatment for episodes of bradykinin-mediated angioedema induced by ACE inhibitors]. *Rev Med Interne* 2018;39:772-6.
- 22 Stewart M, McGlone R. Fresh frozen plasma in the treatment of ACE inhibitor-induced angioedema. *BMJ Case Rep* 2012;2012:bcr2012006849.
- 23 Cohen AJ, DiFrancesco MF, Solomon SD, *et al.* Angioedema in COVID-19. *Eur Heart J* 2020;ehaa452.
- 24 Cugno M, Nussberger J, Cicardi M, *et al.* Bradykinin and the pathophysiology of angioedema. *Int Immunopharmacol* 2003;3:311-7.
- 25 Turner AP, Hiscox JA, Hooper NM. Ace2: from vasopeptidase to SARS virus receptor. *Trends Pharmacol Sci* 2004;25:291-4.
- 26 Ferrario CM, Chappell MC, Tallant EA, *et al.* Counterregulatory actions of angiotensin-(1-7). *Hypertension* 1997;30:535-41.
- 27 Sodhi CP, Wohlford-Lenane C, Yamaguchi Y, *et al.* Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg<sup>9</sup> bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. *Am J Physiol Lung Cell Mol Physiol* 2018;314:L17-31.
- 28 Bas M, Hoffmann TK, Bier H, *et al.* Increased C-reactive protein in ACE-inhibitor-induced angioedema. *Br J Clin Pharmacol* 2005;59:233-8.
- 29 Mehta P, McAuley DF, Brown M, *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033-4.
- 30 Chen HM, Liao WS. Differential acute-phase response of rat kininogen genes involves type I and type II interleukin-6 response elements. *J Biol Chem* 1993;268:25311-9.
- 31 Chen N, Zhou M, Dong X, *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.
- 32 Liu Y, Yang Y, Zhang C, *et al.* Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 2020;63:364-74.
- 33 Kampitak T. Recurrent severe angioedema associated with imidapril and diclofenac. *Allergol Int* 2008;57:441-3.
- 34 Byrd JB, Touzin K, Sile S, *et al.* Dipeptidyl peptidase IV in angiotensin-converting enzyme inhibitor associated angioedema. *Hypertension* 2008;51:141-7.
- 35 Duerr M, Glander P, Diekmann F, *et al.* Increased incidence of angioedema with ACE inhibitors in combination with mTOR inhibitors in kidney transplant recipients. *Clin J Am Soc Nephrol* 2010;5:703-8.
- 36 Kostis JB, Packer M, Black HR, *et al.* Omapatrilat and enalapril in patients with hypertension: the omapatrilat cardiovascular treatment vs. enalapril (OCTAVE) trial. *Am J Hypertens* 2004;17:103-11.
- 37 Wang W, McKinnie SMK, Farhan M, *et al.* Angiotensin-Converting enzyme 2 metabolizes and partially inactivates pyr-apelin-13 and apelin-17: physiological effects in the cardiovascular system. *Hypertension* 2016;68:365-77.
- 38 Fischer C, Lamer T, Wang W, *et al.* Plasma kallikrein cleaves and inactivates apelin-17: palmitoyl- and PEG-extended apelin-17 analogs as metabolically stable blood pressure-lowering agents. *Eur J Med Chem* 2019;166:119-24.
- 39 Baş M, Greve J, Stelter K, *et al.* A randomized trial of icatibant in ACE-inhibitor-induced angioedema. *N Engl J Med* 2015;372:418-25.
- 40 Erickson DL, Coop CA. Angiotensin-Converting enzyme inhibitor-associated angioedema treated with C1-esterase inhibitor: a case report and review of the literature. *Allergy Rhinol* 2016;7:168-71.
- 41 European Medicines Agency. Latest data support continued use of ACE inhibitors and ARB medicines during COVID-19 pandemic. European medicines agency: science medicines health, 2020. Available: <https://www.ema.europa.eu/en/news/latest-data-support-continued-use-ace-inhibitors-arb-medicines-during-covid-19-pandemic>
- 42 National Institutes of Health. Considerations for certain concomitant medications in patients with COVID-19. NIH: COVID-19 treatment guidelines, 2020. Available: <https://www.covid19treatmentguidelines.nih.gov/concomitant-medications>

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