

References

1. Batarseh E, Kersten BP, Pinelo AC, Nadler JN, Schwartz SA. Angioedema in African American patients hospitalized for COVID-19 [letter]. *Am J Respir Crit Care Med* 2020;202:1581–1584.
2. Cohen AJ, DiFrancesco MF, Solomon SD, Vaduganathan M. Angioedema in COVID-19. *Eur Heart J* 2020;41:3283–3284.
3. Messerole E, Peine P, Wittkopp S, Marini JJ, Albert RK. The pragmatics of prone positioning. *Am J Respir Crit Care Med* 2002;165:1359–1363.
4. George G, Awhad SA, Thampi SM, Philip MA. Isolated lower lip edema: a rare complication of prone positioning. *J Anaesthesiol Clin Pharmacol* 2017;33:274–275.
5. Majluf-Cruz A, Nieto-Martínez S. Long-term follow up analysis of nadroparin for hereditary angioedema: a preliminary report. *Int Immunopharmacol* 2011;11:1127–1132.
6. Hippensteel JA, LaRiviere WB, Colbert JF, Langouët-Astrié CJ, Schmidt EP. Heparin as a therapy for COVID-19: current evidence and future possibilities. *Am J Physiol Lung Cell Mol Physiol* 2020;319:L211–L217.

Copyright © 2021 by the American Thoracic Society



Reply to Chan and Majluf-Cruz

From the Authors:

We wish to reply to the letter by Chan and colleagues that comments on our previous report regarding angioedema and coronavirus disease (COVID-19) (1).

Risk Factors for Angioedema

Multiple risk factors are believed to increase the incidence of ACE (angiotensin-converting enzyme) inhibitor (ACEI)-induced angioedema through various pathways, including polymorphisms in the genes encoding NEP and APP, medications that inhibit DPP4, and autoantibodies against C1-INH.

Onset of Angioedema

Although we hypothesize similarities between ACEI-induced angioedema and COVID-19-associated angioedema, there is a wide window for the development of angioedema after the onset of COVID-19 symptoms and it can still be related to the kallikrein-kinin system for the following reasons:

First, the timeline for COVID-19 phases and clinical manifestations continues to evolve because of complex multisystem activities. Studies have noted that the onset of the COVID-19 hyperinflammatory state has ranged between 2 and 5 weeks (2).

Second, the presentation of ACEI-induced angioedema can range between weeks and months after starting and discontinuing the medication. Thus, we can anticipate a similar variability in angioedema onset in patients hospitalized for COVID-19 (3).

Third, ACE2 does not inhibit BK but mainly inhibits DABK and Lys-DABK, which are downstream in the systemic and tissue kallikrein pathway, leading to a later onset in their signaling activity.

Fourth, BK binds primarily to $\beta 2R$, which is expressed on endothelial cells and does not rely on the inflammatory cascade to induce angioedema. In contrast, DABK and Lys-DABK bind primarily to $\beta 1R$, which is only upregulated in the setting of inflammation. Therefore, accumulation of DABK and Lys-DABK would not induce angioedema until the establishment of the inflammatory state.

Proning and Angioedema

Regarding proning the patients, patients 1, 2, and 3 developed angioedema 6–7 days after the last time they were proned. Patient 4 was never proned. The swelling involved the whole face, tongue, lips, upper airway edema, and laryngeal edema. For those patients who were proned, they were positioned in reverse Trendelenburg position when proned. Therefore, proning was not believed to be related to angioedema.

Role of C1-INH in Angioedema Associated with ACE2 Dysregulation

Although the patient with angioedema described by Cohen, referenced in our original letter, had an elevated functional concentration of C1-INH, it may not necessarily prevent angioedema. This is evidenced by data showing that many patients with ACEI angioedema do not respond to C1-INH concentrate. Also, C1-INH is a potent inhibitor of BK release from HMWK (high-molecular-weight kininogen) but it does not directly affect the metabolism of LMWK (low-molecular-weight kininogen) to Lys-BK and subsequently to Lys-DABK, which can precipitate angioedema in the setting of dysfunctional ACE2. However, it is important to note that the rapid improvement in the patient's angioedema may be related to the inactivation of BK by the elevated C1-INH concentration

Regarding the issue of LMWH enhancing C1-INH activity, Chan and colleagues raise an interesting point. All of our patients were on deep venous thrombosis prophylaxis; two were receiving heparin and two were receiving LMWH. Current literature suggests that autoimmune phenomena may be increased during COVID-19 and in the post-COVID-19 syndrome (4). Consequently, one can speculate that autoantibodies to C1-INH can develop during COVID-19, increasing the risk of angioedema. Thus, the suggestion by Chan and colleagues to use LMWH to augment the activity of C1-INH bears consideration and could become a potential

Ⓐ This letter is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Author Contributions: A.C.P. and V.V. collected clinical and demographic data. E.B. drafted and edited the manuscript. E.B., B.P.K., V.V., J.N.N., and S.A.S. critically edited the manuscript. J.N.N. and S.A.S. were senior investigators on the manuscript. All authors revised and contributed to the final version.

Originally Published in Press as DOI: 10.1164/rccm.202012-4365LE on December 22, 2020

treatment for COVID-19–associated angioedema in combination with β 1R and β 2R blockade. Furthermore, LMWH might become the preferred anticoagulant in patients with COVID-19 with angioedema and hypercoagulability concerns.

Recently Published Similar Cases

At this time, we have noted several publications associating facial, tongue, eye, and lips swelling with COVID-19; however, none of them made a definitive association with race (5–8).

Conclusions

With the second wave of increase in cases of COVID-19, we can anticipate additional reports of angioedema in patients with COVID-19. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Einass Batarseh, M.D.*
University at Buffalo
Buffalo, New York

Brian P. Kersten, Pharm.D.
Buffalo General Medical Center
Buffalo, New York

Anna C. Pinelo, M.D.
Vincent Vertalino, M.D.
Jamie N. Nadler, M.D.
Stanley A. Schwartz, M.D., Ph.D.
University at Buffalo
Buffalo, New York

ORCID IDs: 0000-0001-8707-8801 (E.B.); 0000-0003-4807-6699 (B.P.K.); 0000-0002-8664-1380 (S.A.S.).

*Corresponding author (e-mail: einass.batarseh@gmail.com).

References

- Batarseh E, Kersten BP, Pinelo AC, Nadler JN, Schwartz SA. Angioedema in African American patients hospitalized for COVID-19 [letter]. *Am J Respir Crit Care Med* 2020;202:1581–1584.
- Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. *Mod Pathol* 2020;33:2128–2138.
- Dasgupta SK, Rivera S, Thiagarajan P. Lisinopril-induced angioedema in a patient with plasma prekallikrein deficiency. *TH Open* 2020;4:e33–e35.
- Cañas CA. The triggering of post-COVID-19 autoimmunity phenomena could be associated with both transient immunosuppression and an inappropriate form of immune reconstitution in susceptible individuals. *Med Hypotheses* 2020;145:110345.
- Abasaeeed Elhag SA, Ibrahim H, Abdelhadi S. Angioedema and urticaria in a COVID-19 patient: a case report and review of the literature. *JAAD Case Rep* 2020;6:1091–1094.
- Adeliño R, Andrés-Cordón JF, Aracelis De La Cruz Martínez C. Acute urticaria with angioedema in the setting of coronavirus disease 2019. *J Allergy Clin Immunol Pract* 2020;8:2386–2387.
- Azmy V, Benson J, Love K, Steele R. Idiopathic nonhistaminergic acquired angioedema in a patient with coronavirus disease 2019. *Ann Allergy Asthma Immunol* 2020;125:600–602.
- Grewal E, Sutarjono B, Mohammed I. Angioedema, ACE inhibitor and COVID-19. *BMJ Case Rep* 2020;13:e237888.

Copyright © 2021 by the American Thoracic Society



Apparent Increase in Chronic Obstructive Pulmonary Disease Mortality Is Likely an Artifact of Changes in Documentation and Coding

To the Editor:

As the developers of the Centers for Medicare and Medicaid Services' Chronic Obstructive Pulmonary Disease (COPD) Hospital Mortality and Readmission measures, we read with interest the recent paper by Neira and colleagues (1). The authors document a substantial increase in 30-day mortality for patients hospitalized for COPD between the years 2006–2010, 2010–2014, and 2014–2017, corresponding with the period before, in the run-up to, and after the implementation of Medicare's Hospital Readmissions Reduction Program. Over this same period, 30-day readmission rates were observed to decline, raising concerns that hospital efforts intended to prevent readmissions might have inadvertently led to harm. As part of their analysis, the authors estimate that some 1,196 deaths might be attributable to this federal program.

Although unintended consequences of the Hospital Readmissions Reduction Program are one potential explanation for the apparent increase in 30-day mortality, our own analysis of Medicare claims data for this same period suggests that the increase was an artifact of recent changes in hospital documentation and coding practices. In 2016, hospitals received updated coding instructions for cases in which a patient is admitted for a COPD exacerbation complicated by pneumonia. In such instances, hospitals were guided to use COPD—rather than pneumonia—as the principal diagnosis (2). Within the span of 1 year, we observed a large increase (both in absolute and relative terms) in patients entering the COPD Measure Cohort who carried a secondary diagnosis of pneumonia. Between 2015–2016 and 2016–2017, the COPD cohort grew by approximately 47,000 cases, a figure almost entirely accounted for by an additional 48,000 cases with pneumonia who previously would have been counted in the pneumonia measure (Figure 1).

†This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgem@thoracic.org).

The authors are supported by the Centers for Medicare and Medicaid Services to develop and maintain outcome measures for chronic obstructive pulmonary disease and pneumonia.

Originally Published in Press as DOI: 10.1164/rccm.202009-3697LE on November 9, 2020