Hypernatremia—A Manifestation of COVID-19: A Case Series

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We report for the first time therapy-resistant hypernatremia (plasma sodium concentration ≥150 mmol per liter) developing in 6 of 12 critically ill coronavirus disease 2019 (COVID-19) patients age 57–84 years requiring mechanical ventilation. There was no correlation between plasma sodium concentrations and sodium input. Plasma concentrations of chloride were elevated, those of potassium decreased. These findings are consistent with abnormally increased renal sodium reabsorption, possibly caused by increased angiotensin II activity secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–induced downregulation of angiotensin-converting enzyme 2 (ACE2) receptors. As hypernatremia was associated with increased length of intensive care unit stay, special attention should be paid to the electrolyte status of COVID-19 patients. (A&A Practice. 2020;14:e01295.)

GLOSSARY
ACE-I = angiotensin-converting enzyme inhibitor; ACE2 = angiotensin-converting enzyme 2; ARB = angiotensin receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; DRKS = Deutsches Register für klinische Studien (German Registry for Clinical Studies); EQUATOR = Enhancing the QUAlity and Transparency Of health Research; FIO₂ = fraction of inspired oxygen; ICU = intensive care unit; Pao₂ = partial pressure of oxygen; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SI = international system of units

While respiratory tract symptoms are usually the main manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection,1,2 numerous other pathologies have been reported. These include electrolyte disorders such as hypokalemia, hyponatremia, and hypocalcemia.3 During our treatment of patients with severe coronavirus disease 2019 (COVID-19), we observed the frequent development of therapy-resistant hypernatremia (plasma sodium concentration ≥150 mmol per liter). To the best of our knowledge, hypernatremia associated with COVID-19 has not previously been reported. Hypernatremia in patients treated in medical intensive care units (ICUs) varied between 6% and 26%.4 When sodium plasma concentrations exceeded 150 mmol per liter, the associated mortality rate was as high as 48%.4 In an attempt to identify the possible mechanism of the hypernatremias, we compared clinical and laboratory data of patients with and without hypernatremia.

This study was approved by the Ethics Committee of the University of Freiburg and registered with the Deutsches Register für klinische Studien (German Registry for Clinical Studies [DRKS]) under ID DRKS00021611. The Committee waived the need for written informed consent because all data had been acquired during routine care. This manuscript adheres to the applicable Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guideline.

CASE DESCRIPTIONS
We retrospectively analyzed the data of 12 consecutive patients with COVID-19 who had been treated in our ICU between March 25 and April 25, 2020. SARS-CoV-2 infection had been diagnosed by polymerase chain reaction testing of nasal or tracheal swabs. Patients were considered hypernatremic if plasma sodium concentration was ≥150 mmol per liter (reference range 135–145 mmol per liter). Data of clinical characteristics, laboratory results, medications, and fluid management were retrieved from electronic and paper records. We analyzed sex, age, comorbidities, body mass index (BMI), length of ICU stay, daily determined plasma concentrations of sodium, chloride, potassium, and creatinine; amount of enterally and parenterally administered fluids, type and amount of medications, urine output, and fluid balance. Perspiration was not considered in the fluid balance because assessment of amount and composition is unreliable, and because body temperatures were comparable between groups.5 Plasma concentrations and arterial partial pressure of oxygen (Pao₂) were determined by point-of-care-testing (ABL 825 Flex, Radiometer, Copenhagen, DK) or laboratory testing (Cobas 6000, Roche Diagnostics,
Urine was tested for protein by standard urine test strips analyzed by an automatic urine analysis system (CLINITEK Advantus, Siemens Healthcare, Munich, Germany). Sodium intake was calculated by adding up the sodium contents of enterally and parenterally administered fluids, and of medications and their solvents. As the number of patients was low, we refrained from statistical comparisons between groups.

Mechanical ventilation was initiated either shortly before ICU admission in the intermediate care unit or immediately after ICU admission. Once weaning from mechanical ventilation was completed, patients were transferred to the intermediate care unit. At ICU admission, demographic and clinical characteristics, and laboratory findings were grossly comparable between patients with and without hypernatremia (Table 1). Two patients of the group with hypernatremia, but none of the group without hypernatremia, had initial plasma sodium concentrations >145 mmol per liter.

During the ICU stay, hypernatremia was observed in 6 of the 12 patients. Median and maximal plasma sodium concentrations were considerably higher in patients with than in those without hypernatremia (Figure 1 and Table 2). There was no obvious relationship between plasma sodium concentration and sodium input (Figure 2). In patients with hypernatremia, total sodium input was roughly 40% lower than in patients without hypernatremia (Table 2). This was the result of our standard therapy for hypernatremia which consisted of avoidance of infusion of hyperchloremic, unbalanced solutions, infusion of free water containing solutions (eg, glucose 5% solution), enteral administration of free water, and intravenous administration of natriuretic diuretics (eg, spironolactone). In both groups, <10% of all administered fluids were sodium chloride–containing solutions.

Plasma chloride concentrations were higher and exceeded normal limits (reference range 95–109 mmol per liter).

### Table 1. Demographic, Clinical, and Laboratory Characteristics at Admission to the ICU

| Variables                          | Patients With Hypernatremia | Patients Without Hypernatremia |
|------------------------------------|-----------------------------|-------------------------------|
|                                    | n = 6                       | n = 6                         |
| Age, y                             | 69 (57–84)                  | 70 (54–80)                    |
| Sex, n                             | 4/2                         | 3/3                           |
| BMI, kg/m²                         | 30 (24–40)                  | 25 (22–48)                    |
| Chronic medications, n             |                             |                               |
| Total antihypertensives            | 7                           | 6                             |
| ACE-I                              | 2                           | 2                             |
| ARB                                | 1                           | -                             |
| Diuretic                           | -                           | 2                             |
| Antidiabetic                       | 3                           | 1                             |

| Comorbidities, n                   |                             |                               |
| Hypertension                       | 4                           | 4                             |
| Chronic heart disease              | 2                           | 3                             |
| Peripheral arterial disease        | 1                           | -                             |
| COPD                               | -                           | 2                             |
| Chronic renal insufficiency        | 2                           | -                             |
| Neurological disease               | 1                           | 2                             |
| Diabetes mellitus                  | 3                           | 4                             |
| Malignancy                         | 3                           | 2                             |

| Body temperature, °C              | 37.1 (36.4–38.5)            | 37.3 (36.4–38.0)              |
| PaO₂:FIO₂ ratio, mm Hg            | 178 (133–200)               | 166 (73–213)                  |

| Plasma concentrations             |                             |                               |
| Sodium, mmol/L                    | 139 (134–152)               | 137 (127–140)                 |
| Chloride, mmol/L                  | 107 (101–120)               | 104 (97–108)                  |
| Potassium, mmol/L                 | 3.8 (3.3–4.0)               | 4.1 (2.5–5.4)                 |
| Creatinine, mg/dL                 | 1.0 (0.63–2.19)             | 1.01 (0.62–1.72)              |
| Glucose mg/dL                     | 127 (122–210)               | 175 (110–249)                 |

Values are median (range), if not stated otherwise. SI conversion factors: To convert plasma sodium concentration to mmol/L, divide values by 23; plasma creatinine concentration to μmol/L, multiply values by 88.4; plasma glucose concentration to mmol/L, multiply values by 0.0555.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FIO₂, fraction of inspired oxygen; ICU, intensive care unit; PaO₂, partial pressure of oxygen; SI, international system of units.

Figure 1. Daily sodium and chloride plasma concentrations in patients with and without hypernatremia. Solid lines indicate median values; whiskers indicate ranges.
In all patients with, but in only 1 patient without hypernatremia (Figure 1 and Table 2). Standard therapy of hypernatremia did not appreciably lower plasma sodium concentrations. Plasma potassium concentrations (reference range 3.4–4.7 mmol per liter) in patients without hypernatremia (5 vs 2) reflects the higher incidence of hypernatremia in our patients. The considerably lower total sodium input in patients without hypernatremia (Figure 2) argue against iatrogenic hypernatremia in our patients. Despite administration of diuretics which increase sodium excretion, and despite administration of free water, plasma sodium concentrations remained elevated.

Although the overall severity of illness was comparable between groups, the ICU stay was considerably longer in patients with hypernatremia. Some of the latter died shortly after ICU admission, and some of them recovered relatively quickly allowing early discharge from the ICU to an intermediate care unit. By contrast, surviving patients with hypernatremia required prolonged mechanical ventilation. Possibly, the hypernatremia contributed to a prolonged requirement for mechanical ventilation, thereby retarding ICU discharge.

Elevated plasma creatinine concentrations in several patients of both groups, proteinuria in all but 1 patient, and need for dialysis in 1 patient of each group, reflect renal injury. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor which is highly expressed in the kidneys, specifically in the proximal tubule. Identification of SARS-CoV-2 ribonucleic acid (RNA) in the urine of an infected patient shows that the virus can enter the tubular fluid where it may bind to those ACE2 receptors in the proximal tubule. After binding, SARS-CoV-2 initially enters the cells together with the membrane receptor which is functionally removed from the external site of the membrane. Following endocytosis of the viral complex, surface ACE2 is further downregulated resulting in unopposed angiotensin II accumulation. Angiotensin II may further downregulate ACE2 expression, thereby retarding ICU discharge.

Table 2. Clinical, Laboratory, and Outcome Characteristics During ICU Stay

| Variables                  | Patients With Hypernatremia | Patients Without Hypernatremia |
|----------------------------|-----------------------------|-------------------------------|
|                            | n = 6                        | n = 6                          |
| Length of stay, d          | 19 (10–26)                  | 6 (4–9)                        |
| Deaths, n                  | 2                            | 3                              |
| Pao₂/Fio₂ ratio, mm Hg     | 205 (172–225)               | 155 (149–249)                  |
| Body temperature, °C       | 37.3 (37.0–38.1)            | 37.7 (36.5–38.5)               |
| Proteinuria, n             | 6                            | 5                              |
| Diaylasis, n               | 1                            | 1                              |
| Plasma concentrations      |                             |                                |
| Sodium, mmol/L             | 151 (149–154)               | 139 (132–142)                  |
| Chloride, mmol/L           | 150 (156–170)               | 143 (137–145)                  |
| Potassium, mmol/L          | 115 (109–120)               | 103 (101–113)                  |
| Chlortide, mmol/L          | 129 (114–134)               | 106 (104–117)                  |
| Creatinine, mg/dL          | 4.2 (3.8–4.6)               | 4.1 (3.5–5.4)                  |
| Glucose, mg/dL             | 1.56 (1.03–3.97)            | 1.68 (0.61–5.59)               |
| Fluid input, mL            | 2551 (1474–3486)            | 2208 (1789–3002)               |
| Total output, mg           | 2176 (1471–2813)            | 1506 (639–2219)                |
| Urine output, mL           | 2363 (1485–2708)            | 1317 (85–2017)                 |
| Fluid balance, mL          | 375 (−75 to 827)            | 790 (−194 to 2017)             |
| Sodium input, mg           | 4640 (2407–7101)            | 7196 (3430–8415)               |
| Sodium dose, mmol          | 26 (4–44)                   | 16 (1–31)                      |
| Daily diuretic dose, mg    | n = 5                       | n = 2                           |
| Furosemide                 | 27 (6–113)                  | 31 (4–120)                     |
| Torasemide                 | 1 (0–8)                     | n = 3                          |
| Spironolactone             | 70 (0–152)                  | 0 (0–13)                       |
| Hydrochlorothiazide        | 0 (0–7)                     | 0 (0–18)                       |
| Acetazolamide              | 44 (0–109)                  | n = 4                          |

Abbreviations: Fio₂, fraction of inspired oxygen; ICU, intensive care unit; Pao₂, partial pressure of oxygen; SI, international system of unit.

As the number of patients varied, the numbers of patients having received the respective medication are indicated as (n = ).

DISCUSSION

The main finding of this report is the observation of pronounced, difficult to treat hypernatremia in 6 of 12 patients with severe COVID-19. This is a higher incidence of hypernatremia than the previously reported one of 4%–26% in a medical ICU setting. Hypernatremia is usually caused by either a deficit of total body water or by an inappropriately high sodium input. In general, however, even during infusion of large amounts of sodium-containing solutions (as during treatment of acute hypovolemia), hypernatremia is infrequently observed and less pronounced. Lack of relationship between plasma sodium concentration and sodium input, and lower plasma sodium concentrations at comparable or even higher sodium input in patients without hypernatremia (Figure 2) argue against iatrogenic hypernatremia in our patients. The considerably lower total sodium input in patients with compared to those without hypernatremia reflects our practice to limit sodium input during hypernatremia. As all patients were consecutively cared for by the same health care team, treatment bias is also unlikely to have contributed to the frequent hypernatremias. Despite administration of diuretics which increase sodium excretion, and despite administration of free water, plasma sodium concentrations remained elevated.

ICU stay was longer (19 vs 6 days) in patients with compared to those without hypernatremia (Table 2). ICU mortality was comparable between groups. Following transfer to an in-hospital intermediate care unit or an outside hospital ICU, hypernatremia gradually resolved with improving overall condition.
These occurred, in fact, far more often in patients with than in those without hypernatremia, supporting the possibility of increased angiotensin II activity.

The lack of relationship between plasma sodium concentration and sodium input, the persistent hypernatremia despite targeted therapy, and the established binding of SARS-CoV-2 to the ACE2 receptor⁸ are consistent with unphysiologically increased renal sodium reabsorption caused by increased angiotensin II activity secondary to SARS-CoV-2 infection. Overall evidence is thus consistent with the possibility that the observed hypernatremias were a consequence of unphysiologically increased renal tubular sodium reabsorption. Although most demographic and clinical characteristics were comparable between both groups of patients, only half of them developed hypernatremia. This confirms the unpredictable and varying effects of infection with SARS-CoV-2 on organs and organ systems.

In conclusion, our findings suggest that hypernatremia is a further manifestation of COVID-19. The hypernatremia can be pronounced and almost resistant to standard therapy. Hypernatremia is generally associated with adverse outcome. In our patients, it was associated with increased length of ICU stay. Special attention should thus be paid to the electrolyte status of COVID-19 patients. The exact etiology of the hypernatremia remains to be determined.

DISCLOSURES

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REFERENCES

1. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323:2052–2059.

2. Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–1720.

3. Lippi G, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Ann Clin Biochem. 2020;57:262–265.

4. Lindner G, Funk GC. Hypernatremia in critically ill patients. J Crit Care. 2013;28:216.e211–216.e220.

5. Bates GP, Miller VS. Sweat rate and sodium loss during work in the heat. J Occup Med Toxicol. 2008;3:4.

6. Darmon M, Timsit JF, Francois A, et al. Association between hypernatraemia acquired in the ICU and mortality: a cohort study. Nephrol Dial Transplant. 2010;25:2510–2515.

7. Stelfox HT, Ahmed SB, Khandwala F, Zygun D, Shahpori R, Laupland K. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. Crit Care. 2008;12:R162.

8. Lan J, Ge J, Yu J, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020;581:215–220.

9. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020;46:586–590.

10. Battle D, Soler MJ, Sparks MA, et al; COVID-19 and ACE2 in Cardiovascular, Lung, and Kidney Working Group. Acute kidney injury in COVID-19: emerging evidence of a distinct pathophysiology. J Am Soc Nephrol. 2020;31:1380–1383.

11. Peng L, Liu J, Xu W, et al. SARS-CoV-2 can be detected in urine, blood, anal swabs, and oropharyngeal swabs specimens. J Med Virol. 2020:1–5.

12. Kai H, Kai M. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors—lessons from available evidence and insights into COVID-19. Hypertens Res. 2020;43:648–654.

13. Fountain J, Lappin S. Physiology, renin angiotensin system. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020.