

## LETTERS TO THE EDITOR

**Clinical-scientific notes****Multifaceted persistent hypokalaemia in a patient with coronavirus disease 2019**

A 69-year-old woman with a 2-day history of fever, dry cough, sore throat, fatigue and diarrhoea was admitted in the Infectious Disease Unit in University Hospital of Ioannina in Greece after being confirmed positive for SARS-CoV-2. Previous medical history was unremarkable. On physical examination, temperature was 38.5°C, blood pressure 135/80 mmHg, pulse rate 99 b.p.m., respiratory rate 20/min and oxygen saturation 85% while the patient

was breathing ambient air. Bilateral crackles were evident on auscultation; chest X-ray showed basilar streaky opacities in both lungs. The patient was supplied with oxygen at a flow rate of 10 L/min with a Venturi face mask (FiO<sub>2</sub> = 50%) and treated with ceftriaxone (2 g once a day (q.d.)), azithromycin (500 mg q.d.) and hydroxychloroquine (400 mg twice a day (b.i.d.) for the first day and 200 mg b.i.d. afterwards), as proposed by Hellenic National Public Health Organisation.

Laboratory evaluation on day 1 showed increased inflammatory markers and persisting hypokalaemia (Table 1). Arterial blood gas test was consistent of both

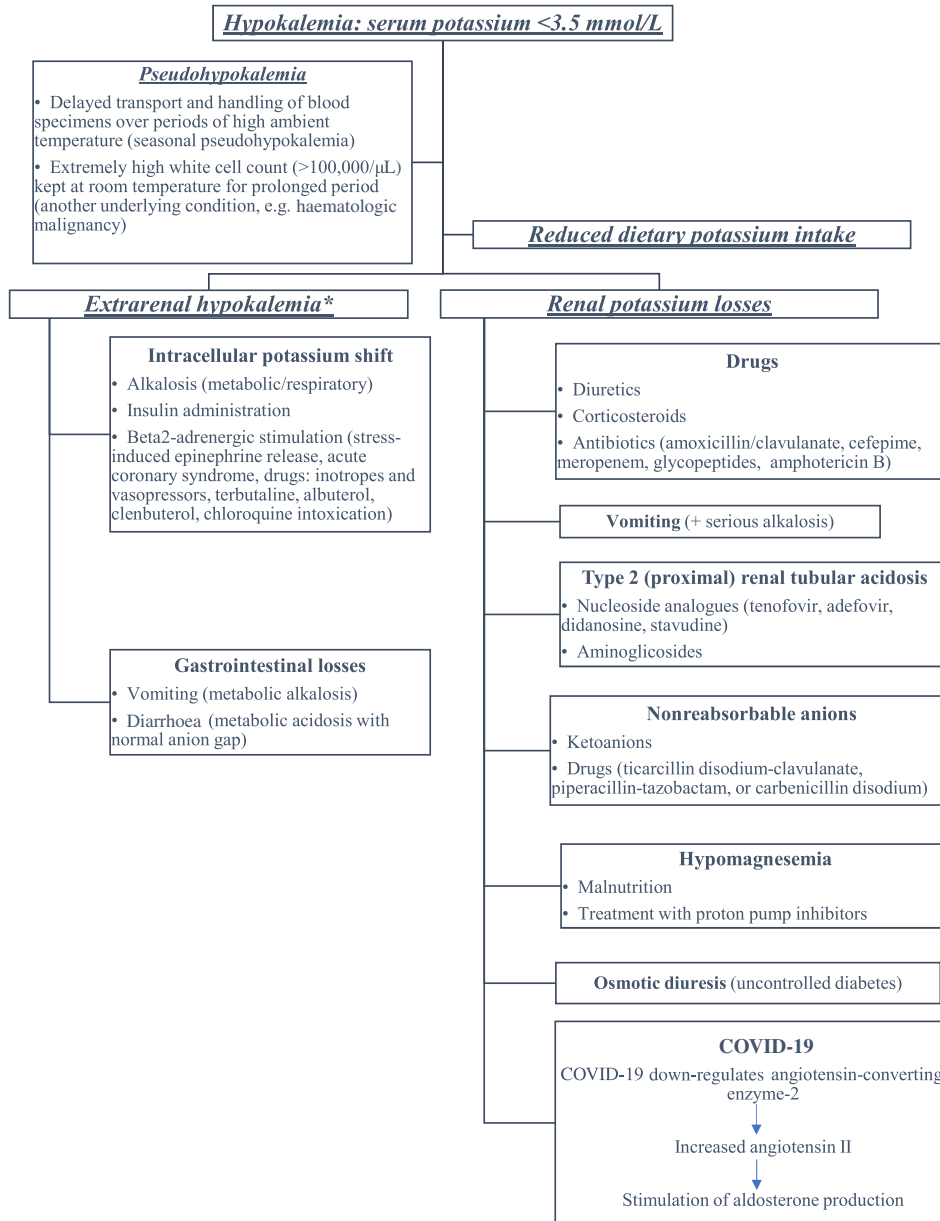
**Table 1** Clinical laboratory results

	Reference range	Day 1	Day 2	Day 3	Day 4	Day 5
Haematocrit (%)	41–53	38.7	37.9	38.6	37.9	42
Haemoglobin (g/dL)	13.5–17.5	13.2	13	13.3	12.7	13.9
White cell count (per $\mu$ L)	4500–11 000	5890	6250	6920	8180	8850
Absolute neutrophil count (per $\mu$ L)	1500–8000	4320	5060	5467	6500	6640
Absolute lymphocyte count (per $\mu$ L)	1000–4800	1180	820†	969†	1010	1450
Platelet count (per $\mu$ L)	150 000–400 000	262 000	299 000	312 000	375 000	465 000‡
International normalised ratio	$\leq$ 1.1	1.1	—	—	—	1.1
D-dimers ( $\mu$ g/mL)	<0.5	1.37‡	—	—	—	3.21‡
Fibrinogen (mg/dL)	200–400	684‡	—	—	—	786‡
Fasting plasma glucose (mg/dL)	70–125	92	96	85	95	85
Creatinine (mg/dL)	0.6–1.2	0.79	0.76	0.73	0.79	0.81
Urea (mg/dL)	11–54	19	16	19	19	19
Potassium (mmol/L)	3.5–5.3	2.9†	3.0†	3.4	3.9	3.8
Sodium (mmol/L)	136–146	137	138	136	137	137
Chloride (mmol/L)	98–106	103	105	103	107	108
Magnesium (mmol/L)	1.3–2.1	2.01	1.88	—	—	1.88
Alanine aminotransferase (U/L)	10–35	23	—	—	31	34
Aspartate aminotransferase (U/L)	10–35	29	—	31	32	34
Alkaline phosphatase (U/L)	30–125	52	—	—	—	—
Lactate dehydrogenase (U/L)	115–230	341‡	368‡	344‡	431‡	400‡
Total bilirubin (mg/dL)	0.1–1.1	0.7	—	0.8	0.8	—
Direct bilirubin (mg/dL)	0.01–0.2	0.2	—	0.31	—	—
Creatinine kinase (U/L)	25–160	36	45	193	51	48
High-sensitivity troponin (pg/mL)	0–11.6	5.8	5	5.3	4.3	4.2
Ferritin (mg/dL)	11–306.8	372‡	—	—	—	339‡
C-reactive protein (mg/L)	<6	80	75	78	81	91
pH	7.36–7.44	7.55‡	7.52‡	7.52‡	7.52‡	7.50‡
PO <sub>2</sub> (mmHg)§	$\geq$ 60	56.7†	58.5†	61.8	55.1†	70.4
PCO <sub>2</sub> (mmHg)	36–44	32†	32†	30.4†	25.4†	27.4†
HCO <sub>3</sub> (mEq/L)	21–27	30.4‡	28.1‡	26.8	25.4	24.8
Anion gap (mmol/L)	3–9	3.6	4.9	6.2	4.6	4.2
Lactate (mmol/L)	0.4–2	1	0.7	1	0.8	0.9

†The value in the patient was below normal.

‡The value in the patient was above normal.

§Oxygen was supplied by Venturi mask at a flow rate of 10 L/min (FiO<sub>2</sub> = 50%).



**Figure 1** Diagnostic approach of hypokalaemia in patients with coronavirus disease 2019 (COVID-19). \*Urinary potassium excretion <25 mmol per day or spot urine concentration <15 mEq/L or urine potassium-to-creatinine ratio <13 mmol/g indicate extrarenal potassium losses.

metabolic and respiratory alkalosis. Further assessment indicated increased renal excretion of potassium: urine potassium 60 mmol/L and urine potassium-to-creatinine ratio 38 mmol/g. For the treatment of hypokalaemia, potassium was administered intravenously via a peripheral line at a daily dosage of 80 mEq.

The following days, the patient remained febrile and stable without any signs of respiratory improvement, whereas she reported 1–2 diarrhoeas daily. After administering 400 mg tocilizumab on day 5, symptoms and laboratory improvement were noticed.

We were prompted to present this case by the results of a pre-printed retrospective study including 175 COVID-19 patients showing that 55% were diagnosed with hypokalaemia during their hospitalisation.<sup>1</sup> However, these findings were not confirmed by another study reporting mean potassium levels of 3.8 mmol/L (interquartile range: 3.5–4.2).<sup>2</sup> Considering the life-threatening risk of electrolyte abnormalities and especially hypokalaemia, it is useful to consider potential factors contributing to hypokalaemia in COVID-19 patients (Fig. 1). Delays regarding the handling of blood specimens might result in pseudohypokalaemia, especially in warm environments.<sup>3</sup> Lengthy


hospitalisations (~10 days) of SARS-CoV-2 patients might adversely affect potassium intake and lead to a negative imbalance.<sup>2,3</sup> COVID-19 symptoms, such as cough, dyspnoea and tachypnoea, could lead to respiratory alkalosis which lowers serum potassium by its intracellular shift, whereas diarrhoeas could increase potassium losses.<sup>2,3</sup> Cardiovascular complications of COVID-19, such as myocardial infarction or myocarditis, along with the infection-induced stress could increase intracellular potassium shift due to beta2-adrenergic stimulation.<sup>2-4</sup> Although septic shock is infrequent among patients with COVID-19 (~1%), it could be associated with extracellular volume depletion and metabolic alkalosis which increase both intracellular shift of potassium and renal loss.<sup>3</sup> Drug-induced hypokalaemia should always be considered in SARS-CoV-2 patients.<sup>3</sup> Inhaled beta2-adrenergic agonists and vasopressors, usually administered in those with respiratory infections and septic shock, increase beta2-adrenergic stimulation.<sup>3</sup> Chloroquine, used in treatment protocols against SARS-CoV-2, may be associated with severe hypokalaemia in case of intoxication.<sup>3,5</sup> Hypokalaemia induced by diuretics should be considered in hypertensive patients, while renal losses of potassium may be increased due to osmotic diuresis in those with poorly controlled diabetes.<sup>3</sup> Antibiotics, in particular piperacillin and ticarcillin, and nucleoside analogues may increase renal potassium losses.<sup>3</sup> However, remdesivir, a novel nucleotide analogue with *in vitro* activity against SARS-CoV-2 used as compassionate therapy, has not been connected with the development of hypokalaemia.<sup>5</sup> Finally, it has been pro-

posed that after the initial engagement of SARS-CoV-2 spike protein, there is subsequent down-regulation of ACE2 abundance on cell surfaces, leading to angiotensin II accumulation.<sup>6</sup> The latter could induce the secretion of aldosterone by the adrenal cortex, resulting in sodium reabsorption and potassium excretion from the collecting duct in kidney.

Although our patient presented with alkalosis and diarrhoea upon her admission, the analysis of her urine sample strongly indicated 'inappropriate' renal potassium losses. According to the diagnostic approach described above, the ACE2 theory supported her persistent hypokalaemia. It has been proposed that hypokalaemia could be a prognostic marker of the viral load and COVID-19 severity.<sup>1</sup> Of note, the variations of our patient's partial oxygen pressure paralleled those of potassium (Table 1). A keen eye and further investigation may confirm this relationship.

All things considered, hypokalaemia is of multifactorial origin in SARS-CoV-2 patients and may adversely affect outcome especially in those with pre-existing cardiovascular disease. Therefore, potassium levels should be monitored and restored to normal, especially in severely affected SARS-CoV-2 patients.

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