COVID-19 and Cushing's syndrome: recommendations for a special population with endogenous glucocorticoid excess

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Over the past few months, COVID-19, the pandemic disease caused by severe acute respiratory syndrome coronavirus 2, has been associated with a high rate of infection and lethality, especially in patients with comorbidities such as obesity, hypertension, diabetes, and immunodeficiency syndromes.[1]

These cardiometabolic and immune impairments are common comorbidities of Cushing's syndrome, a condition characterised by excessive exposure to endogenous glucocorticoids. In patients with Cushing's syndrome, the increased cardiovascular risk factors, amplified by the increased thromboembolic risk, and the increased susceptibility to severe infections, are the two leading causes of death.[2]

In healthy individuals in the early phase of infection, at the physiological level, glucocorticoids exert immunoenhancing effects, priming danger sensor and cytokine receptor expression, thereby sensitising the immune system to external agents.[3] However, over time and with sustained high concentrations, the principal effects of glucocorticoids are to produce profound immunosuppression, with depression of innate and adaptive immune responses. Therefore, chronic excessive glucocorticoids might hamper the initial response to external agents and the consequent activation of adaptive responses. Subsequently, a decrease in the number of B-lymphocytes and T-lymphocytes, as well as a reduction in T-helper cell activation might favour opportunistic and intracellular infection. As a result, an increased risk of infection is seen, with an estimated prevalence of 21–51% in patients with Cushing's syndrome.[4] Therefore, despite the absence of data on the effects of COVID-19 in patients with Cushing's syndrome, one can make observations related to the compromised immune state in patients with Cushing's syndrome and provide expert advice for patients with a current or past history of Cushing's syndrome.

Fever is one of the hallmarks of severe infections and is present in up to around 90% of patients with COVID-19, in addition to cough and dyspnoea.[1] However, in active Cushing's syndrome, the low-grade chronic inflammation and the poor immune response might limit febrile response in the early phase of infection.[2] Conversely, different symptoms might be enhanced in patients with Cushing's syndrome; for instance, dyspnoea might occur because of a combination of cardiac insufficiency or weakness of respiratory muscles.[2] Therefore, during active Cushing's syndrome, physicians should seek different signs and symptoms when suspecting COVID-19, such as cough, together with dysgeusia, anosmia, and diarrhoea, and should be suspicious of any change in health status of their patients with Cushing's syndrome, rather than relying on fever and dyspnoea as typical features.

The clinical course of COVID-19 might also be difficult to predict in patients with active Cushing's syndrome. Generally, patients with COVID-19 and a history of obesity, hypertension, or diabetes have a more severe course, leading to increased morbidity and mortality.[1] Because these conditions are observed in most patients with active Cushing's syndrome,[2] these patients might be at an increased risk of severe course, with progression to acute respiratory distress syndrome (ARDS), when developing COVID-19. However, a key element in the development of ARDS during COVID-19 is the exaggerated cellular response induced by the cytokine increase, leading to massive alveolar–capillary wall damage and a decline in gas exchange.[5] Because patients with Cushing's syndrome might not mount a normal cytokine response,[4] these patients might parodoxically be less prone to develop severe ARDS with COVID-19. Moreover, Cushing's syndrome and severe COVID-19 are associated with hypercoagulability, such that patients with active Cushing's syndrome might present an increased risk of thromboembolism with COVID-19. Consequently, because low molecular weight heparin seems to be associated with lower mortality and disease severity in patients with COVID-19,[6] and because anticoagulation is also recommended in specific conditions in patients with active Cushing's syndrome,[7] this treatment is strongly advised in hospitalised patients with Cushing's syndrome who have COVID-19. Furthermore, patients with active Cushing's syndrome are at increased risk of prolonged duration of viral infections, as well as opportunistic infections, particularly atypical bacterial and invasive fungal infections, leading to sepsis and

Panel: Risk factors and clinical suggestions for patients with Cushing's syndrome who have COVID-19

Reduction of febrile response and enhancement of dyspnoea
Rely on different symptoms and signs suggestive of COVID-19, such as cough, dysgeusia, anosmia, and diarrhoea.

Prolonged duration of viral infections and susceptibility to superimposed bacterial and fungal infections
Consider prolonged antiviral and broad-spectrum antibiotic treatment.

Impairment of glucose metabolism (negative prognostic factor)
Optimise glycaemic control and select cortisol-lowering drugs that improve glucose metabolism.

Hypertension (negative prognostic factor)
Optimise blood pressure control and select cortisol-lowering drugs that improve blood pressure.

Thrombosis diathesis (negative prognostic factor)
Start antithrombotic prophylaxis, preferably with low-molecular-weight heparin treatment.

an increased mortality risk,[2] and COVID-19 patients are also at increased risk of secondary bacterial or fungal infections during hospitalisation.[1] Therefore, in cases of COVID-19 during active Cushing's syndrome, prolonged antiviral treatment and empirical prophylaxis with broad-spectrum antibiotics[1,4] should be considered, especially for hospitalised patients (panel).

Surgery represents the first-line treatment for all causes of Cushing's syndrome,[8,9] but during the pandemic a delay might be appropriate to reduce the hospital-associated risk of COVID-19, any post-surgical immunodepression, and thromboembolic risks.[10] Because immunosuppression and thromboembolic diathesis are common Cushing's syndrome features,[2,4] during the COVID-19 pandemic, cortisol-lowering medical therapy, including the oral drugs ketoconazole, metyrapone, and the novel osilodrostat, which are usually effective within hours or days, or the parenteral drug etomidate when immediate cortisol control is required, should be temporarily used.[9] Nevertheless, an expeditious definitive diagnosis and proper surgical resolution of hypercortisolism should be ensured in patients with malignant forms of Cushing's syndrome, not only to avoid disease progression risk but also for rapidly ameliorating hypercoagulability and immunospuppression;[9] however, if diagnostic procedures cannot be easily secured or surgery cannot be done for limitations of hospital resources due to the pandemic, medical therapy should be preferred. Concomitantly, the optimisation of medical treatment for pre-existing comorbidities as well as the choice of cortisol-lowering drugs with potentially positive effects on obesity, hypertension, or diabates are crucial to improve the eventual clinical course of COVID-19.

Once patients with Cushing's syndrome are in remission, the risk of infection is substantially decreased, but the comorbidities related to excess glucocorticoids might persist, including obesity, hypertension, and diabetes, together with thromboembolic diathesis.[2] Because these are features associated with an increased death risk in patients with COVID-19,[1] patients with Cushing's syndrome in remission should be considered a high-risk population and consequently adopt adequate self-protection strategies to minimise contagion risk.

In conclusion, COVID-19 might have specific clinical presentation, clinical course, and clinical complications in patients who also have Cushing's syndrome during the active hypercortisolaemic phase, and therefore careful monitoring and specific consideration should be given to this special, susceptible population. Moreover, the use of medical therapy as a bridge treatment while waiting for the pandemic to abate should be considered.

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*Rosario Pivonello, Rosario Ferrigno, Andrea M Isidori, Beverly M K Biller, Ashley B Grossman, Annamaria Colao
rosario.pivonello@unina.it

Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università Federico II di Napoli, Naples 80131, Italy (RP, RF, AC); UNESCO Chair for Health Education and Sustainable Development, Federico II University, Naples, Italy (RP, AC); Department of Experimental Medicine, Sapienza University of Rome – Policlinico Umberto I – COVID Hospital, Rome, Italy (AMI); Neuroendocrine and Pituitary Tumor Clinical Center, Massachusetts General Hospital, Boston, MA, USA (BMKB); Centre for Endocrinology, Barts and the London School of Medicine, Queen Mary University of London, London, UK (ABG); and Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK (ABG)

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