

Klinefelter syndrome—Considerations in management during the SARS-CoV-2 pandemic

To the Editor,

The current unprecedented severe acute respiratory syndrome coronavirus 2 pandemic (SARS-CoV-2) has presented a multitude of challenges to healthcare systems and led to disease-specific management recommendations, with several published in this journal. We would like to highlight such considerations for patients with Klinefelter syndrome (KS). Whilst we are not aware of a specific study addressing SARS-CoV-2 in a KS population, its associated features have been independently linked to increased susceptibility to infection and managing this constellation of risks warrants discussion.

Men appear more susceptible to severe SARS-CoV-2 infection, though the precise mechanisms are debated. Hypogonadism is of course the cardinal feature of KS and several parallel lines of evidence support the notion that low testosterone can increase susceptibility to SARS-CoV-2 infection. For example, older men with hypogonadism have an increased incidence of acute respiratory distress syndrome, respiratory failure and mortality following influenza and testosterone replacement has been shown to reduce airway inflammation in asthma.¹ It has been suggested that the immunomodulatory effect of testosterone in counteracting the damaging cytokine surge in SARS-CoV-2 infection might be lost in low testosterone states.¹ An opposing view is that patients with KS and a relatively low testosterone environment may be relatively protected against SARS-CoV-2 infection. Testosterone increases transcription of transmembrane protease serine 2 (TMPRSS2) allowing viral entry into host cells and it may limit the immune response to acute infection by reducing eosinophil and neutrophil action.¹ Further, the additional X chromosome could carry the benefits of an equivalent number of X-linked immune-related genes as women, who are relatively protected.² To add further complexity, a more recent study has suggested that the overall androgenicity of an individual, characterised by polymorphism in the X-linked androgen receptor gene, rather than androgens alone, may be more important. Longer alleles in the polyQ tract were associated with reduced receptor functionality and worse outcomes in SARS-CoV-2.³

KS is associated with an increased risk of cardiovascular disease and an adverse metabolic profile including abdominal adiposity, metabolic syndrome and type 2 diabetes mellitus. Diabetes and SARS-CoV-2 share a common pathogenic pathway and a large meta-analysis of patients with SARS-CoV-2 has demonstrated that diabetes was associated with an increased risk of severe infection and mortality,⁴ compounding the risk for patients with KS.

KS and SARS-CoV-2 infection have also both been associated with an increased risk of venous thromboembolism. Hypogonadism, obesity, insulin resistance and inherited thrombophilia are cited as risk factors. Polycythaemia secondary to testosterone therapy may theoretically exacerbate this risk, but this has not been demonstrated clinically. We suggest a low threshold for considering thromboembolic disease in the deteriorating patient and for potentially extending the period of thromboprophylaxis following SARS-CoV-2 infection.

At the present time, KS-associated infertility is managed by attempted spermatozoa retrieval using testicular extraction of sperm (TESE) yielding successful retrieval rates of 20%–66%. Though there is currently little data in men recovering from SARS-CoV-2 and the long-term effects on spermatogenesis and fertility, several factors are worth considering. The virus may have a detrimental effect on spermatogenesis given potential increased exposure of the testes to the virus via the highly expressed angiotensin-converting enzyme 2 and TMPRSS2. In addition, increased incidence of microthrombosis and disseminated intravascular coagulation associated with SARS-CoV-2 infection may further impair fertility potential. These factors, along with potential delays to surgical intervention due to the pandemic may generate anxiety for patients and their families.

KS is associated with a complex range of cognitive difficulties affecting learning, auditory processing, speech, language and social communication along with an increased risk of autistic traits. This can contribute to anxiety, depression and low confidence in social settings which is exacerbated by the restrictions imposed by the pandemic. In our experience, patients describe increased levels of stress caused by current social restrictions and report increased feelings of isolation, fear and rumination about virus transmission and anxiety about news coverage. Mask-wearing can make communication such as interpreting cues from facial expressions and identifying the tone of voice even more challenging. Interestingly, noncompliance with SARS-CoV-2 regulations by others has also been highlighted as a significant cause of increased anxiety and potential conflict. Baseline psychosocial comorbidities can disrupt understanding of conversations about health and limit engagement with health providers. Reduced clinical interactions and changes in format have disrupted routines and, along with a lack of integrated specialised psychological services, puts further strain on the therapeutic relationship, with potential long-lasting implications for engagement with health services.

Effective management of KS requires a multidisciplinary approach from an early age.⁵ The outpatient KS service at our institution,

'KF-Xtra', provides multidisciplinary, holistic care for patients and their families, with support from paediatric, endocrinology, andrology, fertility and psychology colleagues. Clinics have been modified to run remotely with telephone and video calls, however, we aim to provide continuity with the same staff. We have adapted the service to address specific concerns relating to the pandemic such as safety and compliance with the regulation in the home, school and workplace as well as managing feelings of isolation and anxiety. Elements of medical monitoring (e.g., biochemical monitoring for testosterone and metabolic assessments) have been deferred or devolved to local primary care services.

Population-based studies in KS subjects to define the specific risk posed by the SARS-CoV-2 virus and mechanistic studies to understand the aetiological factors involved would be of interest. We do not advocate changes in therapy based on theoretical risks or benefits in the absence of clear data, however, physicians need to be aware of the complex interplay of risk factors alongside psychosocial challenges in KS to provide effective treatment and support. Whilst the current pandemic has limited the provision of routine healthcare, it has unexpectedly presented an opportunity to innovate and trial new models of healthcare delivery. Flexible multidisciplinary input, delivered across various platforms and tailored to the individual patient is crucial to provide holistic care in this cohort.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

SQ: Detailed literature review and main author of manuscript. JF: Contributed to 20% of manuscript writing, particularly regarding psychological and social impact of KS. PS: Reviewed and edited urology aspect of manuscript. GB: Reviewed and edited manuscript. US: Conceived of concept for literature review, assisted with literature review and detailed revision and editing of manuscript.

DATA AVAILABILITY STATEMENT


Data sharing is not applicable to this article as no new data were created or analysed in this study.

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