



Bridging the evidence gap: expert consensus on management of SARS-CoV-2 acute infection and post-COVID-19 condition in immunocompromised patients

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The COVID-19 pandemic highlighted the inherent temporal disparity between the generation of reliable scientific evidence and the urgent clinical needs of patients, particularly those exhibiting significant, albeit less prevalent, comorbidities. This temporal lag frequently resulted in therapeutic decision-making under conditions of evidentiary scarcity. Immunocompromised individuals exhibit an elevated susceptibility to SARS-CoV-2 infection. However, the intersection of specific immunosuppressive comorbidities and COVID-19 is rarely characterized within COVID-19 research. This underrepresentation stems not only from the relatively low

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prevalence of these combined conditions but also from the inherent methodological complexities associated with conducting robust clinical investigations, particularly randomized controlled trials, within patient populations often characterized by high mortality rates and clinical heterogeneity.

In May 2023, WHO officially declared the end of the COVID-19 pandemic as a global health emergency, largely due to the widespread implementation of mass vaccination campaigns and the availability of effective medical therapies. Since then, the incidence of new COVID-19 cases has significantly declined worldwide, and guidelines developed during the pandemic have quickly become overly restrictive or outdated. Meanwhile, the dynamic evolution of clinical needs, particularly for immunocompromised individuals, has outpaced the generation of timely and high-quality evidence to inform optimal management strategies.

In this post-pandemic setting, clinicians frequently encounter complex decision-making scenarios in which current evidence offers limited direct guidance. Within ORCHESTRA ("Connecting European cohorts to increase common and effective response to SARS-CoV-2 pandemic"), a Horizon2020-funded project (<https://orchestra-cohort.eu/>) [1], a series of four Delphi survey were conducted to address critical knowledge gaps concerning COVID-19 management in key immunocompromised populations: solid organ transplants [2], hematologic malignancies [3], rheumatological diseases [4], and people with HIV [5]. The Delphi method is a well-established technique that employs iterative questionnaires with aggregated feedback from expert panellists to elicit informed opinion, particularly in areas characterized by evidence gaps. The main topics explored in these surveys included the identification of high risk for developing severe COVID-19, the diagnostic algorithms employed, the utilization of early antiviral therapy (including anti-spike monoclonal antibodies, remdesivir, nirmatrelvir/ritonavir, and molnupiravir), the interaction between COVID-19 and the relevant comorbidity, and post-COVID-19 condition (PCC). Notably, the

questions pertaining to PCC were standardized across all four Delphi surveys, and the findings have been published separately [6].

Drawn from international expertise, consensus was reached on 64 statements. They represent a collaborative synthesis of expert opinion supported by the available literature, offering practical guidance on key patient care areas in the selected immunocompromised populations.

A key insight derived from this experience was the reaffirmed importance of patient-centred care as the overarching guiding framework. Assessing the immediate risks for an individual patient—particularly when balancing the typically mild trajectory of SARS-CoV-2 infection against a pre-existing, clinically significant comorbidity—requires nuanced clinical judgment. This decision-making process involves the integration of numerous patient-specific variables that are best synthesized by the treating physician. In such complex scenarios, expert opinion—informed by literature and real-world clinical experience—plays a crucial role in outlining a range of reasonable, context-specific approaches rather than a single prescriptive pathway.

The second theme emerging from the survey is the recognition of increased risk of SARS-CoV-2 infection and severe COVID-19 that is still present in these immunocompromised patients. This increased vulnerability underscores the need to prioritize these populations in public health strategies, including resource allocation for vaccination campaigns, early antiviral treatment access, and targeted preventive interventions. At the individual patient level, it reinforces the importance of maintaining vigilant clinical follow-up, personalized risk assessment, and timely therapeutic decision-making to mitigate complications and improve outcomes.

Reflecting the survey's emphasis on patient-centred care and the need for targeted approaches in immunocompromised individuals, regarding the diagnostic process, it has been emphasized that both antigen and PCR-based tests maintain adequate positive predictive value in the current epidemiological scenario. Because of the lower incidence of COVID-19, testing should be limited to only symptomatic patients rather than universal screening at hospital admission.

The use of early antiviral therapy in clinical practice continues to be considered valuable by the panel, although its implementation remains constrained by several factors. Molnupinavir is not available in many countries right now, whereas the effectiveness of anti-spike monoclonal antibodies for prevention and treatment depends on the susceptibility of circulating variants. Remdesivir requires intravenous administration, posing logistical challenges, and the use of nirmatrelvir/ritonavir is frequently limited by drug–drug interactions. Nevertheless, specific prescribing patterns for early antiviral therapy appear to be emerging from expert experience: combination therapy has generally been avoided, and in severely immunocompromised patients—particularly those with B-cell depletion—the emerging clinical scenario of persistent COVID-19 symptoms has led to the practice of administering additional antiviral dosing. This trend highlights an important gap in the current evidence base and underscores the need for tailored therapeutic strategies in this high-risk population.

Temporary discontinuation of immunosuppressive agents—such as anti-CD20 monoclonal antibodies and antimetabolites—is generally recommended. Glucocorticoids, however, are typically excluded from this approach, as they remain the cornerstone of treatment in moderate to severe COVID-19. The timing of medical procedures in patients with COVID-19 has become more flexible, reflecting the increased manageability of the disease; short postponements are often sufficient, and extended delays are no longer routinely necessary in most clinical settings. In transplant settings, with the exception of lung grafts, SARS-CoV-2 positivity in donors is not considered a contraindication, and neither pre-emptive antiviral therapy nor alterations to induction immunosuppression are required.

Recommendations on PCC in immunocompromised patients remain limited. The ORCHESTRA panel experts identified chronic fatigue as the most frequent presentation of PCC in the target populations. Key risk factors for the development of PCC include severe acute COVID-19, older age, and female sex. In case of chronic fatigue or arthralgia of new onset, a diagnostic workup to rule out autoimmune disorders has been suggested. Preventive strategies—including full-course vaccination and timely antiviral therapy—should be strongly encouraged to reduce the risk of PCC in this vulnerable population.

Moving beyond the limitations of current evidence, this comprehensive effort, encompassing four distinct Delphi surveys, proactively addressed the urgent clinical needs of immunocompromised patients facing SARS-CoV-2 infection and its sequelae. The resulting consensus offers a valuable resource, empowering clinicians with expert-informed guidance to navigate the complexities of diagnosis, treatment, and long-term management in solid organ transplants, hematologic malignancies, rheumatological diseases, and people with HIV. The survey exercise not only provided practical recommendations but also helped to highlight critical gaps in the current evidence base. Notably, this approach not only addresses the immediate challenges of the recent pandemic but also provides a valuable framework for future pandemic preparedness plans, ensuring that the unique needs of immunocompromised individuals are proactively considered and addressed in evolving health crises. However, reliance on expert consensus alone is not sufficient in the long term. There remains a pressing need for more advanced, agile methodologies—capable of integrating real-world data, adaptive trial designs, and multidisciplinary input—to ensure that evidence keeps pace with emerging challenges and meets the nuanced needs of vulnerable patient populations.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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