REVIEW ARTICLE

Recommendations for the management of COVID-19 in patients with haematological malignancies or haematopoietic cell transplantation, from the 2021 European Conference on Infections in Leukaemia (ECIL 9)

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Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel virus that spread worldwide from 2019 causing the Coronavirus disease 19 (COVID-19) pandemic. SARS-CoV-2 infection is characterised by an initial viral phase followed in some patients by a severe inflammatory phase. Importantly, immunocompromised patients may have a prolonged viral phase, shedding infectious viral particles for months, and absent or dysfunctional inflammatory phase. Among haematological patients, COVID-19 has been associated with high mortality rate in acute leukaemia, high risk-myelodysplastic syndromes, and after haematopoietic cell transplant and chimeric-antigen-receptor-T therapies. The clinical symptoms and signs were similar to that reported for the overall population, but the severity and outcome were worse. The deferral of immunodepleting cellular therapy treatments is recommended for SARS-CoV-2 positive patient, while in the other at-risk cases, the haematological treatment decisions must be weighed between individual risks and benefits. The gold standard for the diagnosis is the detection of viral RNA by nucleic acid testing on nasopharyngeal-swabbed sample, which provides high sensitivity and specificity; while rapid antigen tests have a lower sensitivity, especially in asymptomatic patients. The prevention of SARS-CoV-2 infection is based on strict infection control measures recommended for aerosol-droplet-and-contact transmission. Vaccinations against SARS-CoV-2 has shown high efficacy in reducing community transmission, hospitalisation and deaths due to severe COVID-19 disease in the general population, but immunosuppressed/haematology patients may have lower sero-responsiveness to vaccinations. Moreover, the recent emergence of new variants may require vaccine modifications and strategies to improve efficacy in these vulnerable patients. Beyond supportive care, the specific treatment is directed at viral replication control (antivirals, anti-spike monoclonal antibodies) and, in patients who need it, to the control of inflammation (dexamethasone, anti-Il-6 agents, and others). However, the benefit of all these various prophylactic and therapeutic treatments in haematology patients deserves further studies.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel member of the Sarbecoviruses within the *Coronaviridae* family causing the Coronavirus disease 19 (COVID-19) that emerged in Wuhan, Hubei province of China in December 2019 [1, 2]. SARS-CoV-2/COVID-19 was declared a pandemic by the World Health Organization (WHO) on 11 March 2020 [2]. Since then, SARS-CoV-2/COVID-19 spread worldwide causing million deaths [3]. Patients diagnosed with haematological malignancies (HMs) and/or having undergone haematopoietic stem cell transplantation (HSCT) have been significantly affected by COVID-19 with an initial dramatic mortality rate [4, 5].

The epidemiology, clinical characteristics, diagnostic tools, treatments of COVID-19 in HMs were the topics discussed of 9th meeting of the European Conference on Infectious Disease in Leukaemia (ECIL 9), held virtually on 16–17 September 2021. The rationale and the final recommendations for the management of COVID-19 in HM patients approved at ECIL 9 are reported below.

METHODS

ECIL is a joint venture of four scientific organisations: the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation (IDWP-EBMT), the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG), the Immunocompromised Host Society (ICHS), and the European Leukaemia Net (ELN) that contribute to the scientific board. ECIL aim is to develop guidelines for the management of infections in haematology and haematopoietic stem cell transplant patients and, since 2005, a number of guidelines have been produced by eight editions of ECIL [https://ecil-leukaemia.com/en/resources/resources-ecil].

Literature search was performed on PubMed using key words: COVID-19 and haematology, lymphoproliferative and/or myeloproliferative disease, stem cell transplant, CAR-T, SARS-CoV-2/COVID-19 diagnosis, epidemiology, therapy, vaccination. Considering the rapid growth of COVID-19 literature, only the most relevant studies in English-language were considered. Unpublished data were reviewed if used by Food and Drug Administration or European Medicine Agency for authorisation of drugs and dosages and used only to support conditional recommendations. Preprints were considered but taken in account only if accepted after peer-review by Sept. 16th, 2021.

Grading of the quality of evidence and strength of recommendation were according to the European Society of Clinical Microbiology and Infectious Diseases system [6], showed in Table 1. The virtual meeting in September 2021 was attended by 32 infectious disease and haematology experts from ten European countries, Israel, and Brazil. In the plenary session, there was a first round where the literature analysis and guideline proposals were presented by the expert group and discussed with attendees to obtain a consensus, and a second round, where the revised guideline proposals were presented again to participants and voted for approval. The final slide set with recommendations was made publicly available on the ECIL website for 1 month (October 29th–November 30th, 2021) for comments or observations, and after that, the final approved slide set of recommendations were published on the website [https://ecil-leukaemia.com/en/resources/resources-ecil]. This is the written document of ECIL 9 consensus guidance of COVID-19 in HMs. The summary of recommendations for prevention, diagnosis, vaccination and treatment are shown in Table 2, while the final literature evaluation and comments are presented in the following paragraphs.

Table 1. Evidence-based medicine grading system according to the European Society for Clinical Microbiology and Infectious Diseases (ESCMID).

Strength of recommendation (SoR)	
Grade	Definition
A	ECIL strongly supports a recommendation for use
B	ECIL moderately supports a recommendation for use
C	ECIL marginally supports a recommendation for use
D	ECIL supports a recommendation against use
Quality of evidence (QoE)	
Level	Definition
I	Evidence from at least 1 properly designed randomised, controlled trial (orientated on the primary endpoint of the trial)
II	Evidence from at least 1 well-designed clinical trial (including secondary endpoints), without randomisation; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Added index for source of level II evidence	
Index	Source
r	Meta-analysis or systematic review of RCT
t	Transferred evidence, that is, results from different patient cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
a	Published abstract presented at an international symposium or meeting

EPIDEMIOLOGY

Patients with HMs are considered at increased risk of developing severe and life-threatening infections, because of acquired immunodeficiency and immunosuppressive treatments [4, 7]. A clear correlation between the type of HM and the incidence of COVID-19 has not yet been described in the literature, but current data indicate that lymphoproliferative disorders, in particular non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), and multiple myeloma (MM) are particularly associated with higher risk of SARS-CoV-2 infection. Various reports have been published on COVID-19 and HMs, but in most cases on small patient cohorts or specific malignancy, and only few multicentre larger reports [4, 7–15]. Most of these reports focused on the first wave of infection that occurred between March and May 2020 and therefore reflected what the trend of the pandemic was in those months when there were no effective therapeutic approaches. Epidemiological data from the first wave showed that the mortality rate among HMs was between 13.8 and 37%, with a high impact especially on patients with acute myeloid leukaemia (AML), NHL, and myelodysplastic syndromes (MDS). A multicentre survey (EPICOVIDEHA), which collected the data of more than 3800 cases diagnosed throughout 2020, including those of the second wave of pandemic between October and December 2020, showed that the initial death rate of 40.7% dropped significantly to 24.7% ($p < 0.0001$). This reduction in mortality is related to the rapid improvement of supportive care and the introduction of new therapeutic options [16]. This large survey also confirmed a particularly high mortality rate between 40–45% in patients with myeloid malignancies (mainly AML and MDS).

Mortality in patients undergoing HSCT (autologous or allogeneic) in the centres of European Group for Blood and Marrow Transplantation was about 25%, with no major differences

Table 2. Summary of ECIL 9 recommendations on prevention, diagnosis, vaccination and therapy for SARS-CoV-2/COVID-19 in oncohematological adult and paediatric patients.

Recommendations	Grading
SARS-CoV-2/COVID-19 prevention	
Hand hygiene, face mask, distancing, and ventilation of rooms are recommended in patients with HM.	AIIu
Caring for a SARS-CoV-2 positive HM patient requires the use of personal protective equipment by health personnel and isolation in single room.	AIIrtu
Placing a SARS-CoV-2 positive HM patient into positive pressure rooms is not recommended.	AIII
Routine deferral of chemotherapy in all asymptomatic SARS-CoV-2 positive HM patient is not advisable.	BIIu
Ensure the best possible treatment of underlying HM disease weighing individual patient related risks and benefits.	AIIu
Defer cellular therapy (HSCT, CAR-T) in HM patients with COVID-19.	AIIt
Defer cellular therapy (HSCT, CAR-T) in HM patients with asymptomatic SARS-CoV-2 infection or persistently shedding SARS-CoV-2 virus after a COVID-19 episode.	AIIu
Continue therapy with JAK2-inhibitors and TKI/BTKi.	AIII
Ensure clinical and virological resolution of COVID-19 episode before resuming chemotherapy.	AIItu
Adapt the treatment plan to reduce the visits to the hospital and the risk of SARS-CoV-2 exposure, i.e. telemedicine*, erythropoietin factors**	*AIII **BIII
Avoid using G-CSF out of recommended indications because of the risk of worse COVID-19 outcomes.	BII
SARS-CoV-2/COVID-19 diagnosis	
SARS-CoV-2 molecular NAT assays are recommended for diagnosis of HM and HSCT patients inside and outside of hospitals.	AII
SARS-CoV-2 molecular NAT assays should target at least two distinct viral gene sequences.	AIIt
Rapid antigen testing validated for circulating variants should be reserved for rapid point-of-care diagnosis*and be confirmed by molecular NAT assays**.	*AII **AII
Clinical virology laboratories need to document proficiency in external SARS-CoV-2 quality accredited programmes.	AII
Nasopharyngeal or naso-oropharyngeal swab are recommended to diagnose SARS-CoV-2 upper respiratory tract infections.	AII
Lower respiratory tract fluid sampling (tracheal aspirate, bronchoalveolar lavage) for SARS-CoV-2 is not recommended in HM and HCT patients with positive nasopharyngeal or naso-oropharyngeal swab molecular test, unless there are clinical indications for viral, bacterial, fungal, or parasitic infections in the lower respiratory tract.	AII
Lower respiratory tract fluid sampling (tracheal aspirate, bronchoalveolar lavage) is recommended in HM and HSCT patients with symptoms/signs of LRTI and negative nasopharyngeal or naso-oropharyngeal swab molecular test for SARS-CoV-2, to define the aetiology of LRTI.	AII
In symptomatic HM and HSCT patients with symptoms/signs of LRTI and negative SARS-CoV-2 molecular tests, diagnostic testing should be expanded to other pathogens.	AI
Testing for SARS-CoV-2 RNA in blood is not recommended for the initial diagnosis of SARS-CoV-2/COVID-19.	AI
SARS-CoV-2 infected HM and HSCT patients should be re-tested by molecular assays for decisions regarding deferral of haematological treatment and/or discontinuation of infection control measures.	AII
SARS-CoV-2 genome quantification of Ct-values >30 is associated with low/absent risk of transmission provided adequate sampling quality.	BII
SARS-CoV-2 antibody assays are not recommended to diagnose a new-onset acute SARS-CoV-2/COVID-19.	AII
Immunocompromised persons such as HM and HSCT patients may have mitigated antibody responses.	BII
Antibodies assay targeting N-protein can be considered to ascertain previous SARS-CoV-2 exposure.	AII
Antibodies assay targeting S-protein can be considered to ascertain vaccine response or previous exposure to SARS-CoV-2.	AII
SARS-CoV-2/COVID-19 vaccination	
Patients with HM should receive a full vaccination programme with the most immediately available locally approved vaccine, except in specific conditions where the expected response rate is very low.	AIIht
Considering the low response of HM patients to 1 dose, delaying the 2nd dose is not recommended unless mandated by the patient's individual situation.	BIItu
Whatever the actual measured vaccine response, HM patients should be informed of the ongoing risk of SARS-CoV-2/COVID-19 despite vaccination and adhere to the hygiene and social distancing recommendations of their community or country.	BIIt
The vaccination of the household contacts of haematology patients including children, according to the EMA approval for specific age groups, is strongly recommended.	AIIth
Due to the uncertainty of the antibody response persistence after vaccination, especially for patients on active treatment, HM and HSCT patients can receive a 3rd and 4th dose according to national guidelines.	not graded
HM patients with previous SARS-CoV-2/COVID-19 should be vaccinated with a full programme.	AIItu
	BIII

Table 2. continued

Recommendations	Grading
Patients who have been vaccinated before or during haematological treatment should be assessed 6 months after the end of treatment and re-vaccinated if they have low antibody titres.	
Considering the low rate and heterogeneity of the response in the different HM and therapies, vaccinated patients can be assessed for their antibody response 3–5 weeks after the last dose.	not graded
HSCT recipients should receive COVID-19 vaccine.	AIlut
Vaccination should preferably be initiated at least 6 months after HSCT if transmission of SARS-CoV-2 in the community is low.	BIlu
There is a risk for worsening/eliciting GVHD in allogeneic HSCT recipients. This risk needs to be considered when deciding about time for vaccination.	AIlu
Based on data from other vaccines, it is likely that immunity obtained from either pre-transplant SARS-CoV-2 infection or vaccination will be wiped out by the transplant procedure. However, no data currently exists regarding this issue. However, it seems logical from a risk/benefit assessment that such patients should have a full dose new vaccine schedule after transplantation.	BIII
HSCT patients with previous SARS-CoV-2/COVID-19 should be vaccinated with a full programme.	AIltu
There is no specific recommendation for vaccinating stem cell donors for any other purpose than protecting the donor. However, previous vaccination of the donor might reduce the risk to jeopardise the donation.	not graded
SARS-CoV-2/COVID-19 therapy	
In HM patients not immunised and at risk for severe COVID-19, pre-exposure prophylaxis is recommended with long-acting anti-SARS-CoV-2 monoclonal antibodies.	BIlt
In HM patients at high risk for COVID-19 progression (not vaccinated, vaccine non-responders or not expected to respond to vaccine) post-exposure prophylaxis is recommended with anti-SARS-CoV-2 monoclonal antibodies.	AIlt
In haematological patients with mild COVID-19, the following treatments are recommended: (a) anti-SARS-CoV-2 monoclonal antibodies (b) High titre convalescent plasma, (within 72 h from symptoms onset and anti-SARS-CoV-2 monoclonal antibodies not available) (c) Inhaled IFN b-1a (d) Molnupiravir (e) Remdesivir (f) ritonarvir/nirmatrelvir[a] (d) colchicine (in the absence of other therapeutic options) Dexamethasone should not be used to treat this phase of COVID-19	AIlt BIlt CIlt BIlt BIlt not graded CIlt AIlt
In HM patients with moderate COVID-19 (O_2 support, saturation >90%) or severe COVID-19 (saturation <90–94%%, respiratory rate >30/min) the following treatments are recommended, (a) Remdesivir (b) If patient seronegative, - casirivimab/imdevimab or - convalescent plasma (c) Dexamethasone (d) If worsening despite dexamethasone and present COVID-19- related inflammation, consider addition of the 2nd immunosuppressant: - anti-IL-6 (tocilizumab, sarilumab) - anti-IL1 (anakinra) - JAK –inhibitor (baracitinib/tofacinib)	BII t BII CIII AIlt BIII (moderate COVID-19) AIlt (severe COVID-19) BIlt CIlt CIlt
In patients with critical COVID-19 (ARDS, sepsis, septic shock, mechanical ventilation) (invasive or non-invasive) or vasopressor therapy, the following treatments are recommended (a) if seronegative, casirivimab/imdevimab in NIV (no data in IMV) (b) Dexamethasone (c) Remdesivir Add 2nd immunosuppressant, if COVID-19- related inflammation is present: - Anti-IL-6 (tocilizumab, sarilumab)	BIlt AIlt DIlt AIlt BIlt

ARDS acute respiratory distress syndrome, *ECIL* European Conference of Infections in Leukaemia, *HM* haematological malignancy, *SARS-CoV-2* severe acute respiratory syndrome Coronavirus-2, *HSCT* hematopoietic stem cell transplantation, *LRTI* lower respiratory tract infection, *Ct* cycle threshold, *EMA* European Medicine Agency, *NAT* nucleic acid test, *NIV* non-invasive ventilation, *IMV* invasive mechanical ventilation, *TKI* tyrosine kinase inhibitor, *BTKi* Bruton tyrosine kinase inhibitor.

[a] Data on ritonarvir-boosted nirmatrelvir were not available at the time of ECIL consensus voting (see manuscript text).

* or ** indicate the grading.

between patients treated with auto-HSCT and those treated with allo-HSCT [5].

In a population-based registry study in Spain, the risk factors associated with increased mortality in multivariate analysis were: age ≥60 years (hazard ratio, (HR) 3.17, 95% CI 1.25–8); diagnosis of AML when compared with non-Hodgkin lymphoma (HR 2.22, 95% CI 1.31–3.74); a 50% increased mortality in patients receiving conventional chemotherapy vs. no active therapy (HR 1.50, 95% CI 0.99–2.29) and treatment with monoclonal antibodies (HR 2.02, 95% CI 1.14–3.60) [9].

In a similar Italian study, four factor were associated with worse survival: older age (HR 1.06, 95% CI 0.60–1.24); progressive disease status (HR 2.10, 95% CI 1.41–3.12); type of HM (AML, indolent or aggressive non-Hodgkin lymphoma, plasma cell neoplasm), where

AML had the highest HR of 3.49 (95% CI 1.56–7.81); and severe or critical COVID-19 (HR 4.08, 95% CI 2.73–6.09) [4]. Similarly, a subsequent PETHEMA study, focusing on AML, confirmed that SARS-CoV-2 infection confers high mortality among these patients and establishing an association between mortality and age over 60 years (58.3% vs. 36.4%, $p = 0.043$), ≥2 lines of treatment (72.7% vs. 44.3%, p 0.020), active disease (62.5% vs. 29.4%, p 0.002) and pneumonia (61.2% vs. 22.7%, p 0.002) [17]. The EPICOVIDEHA survey also confirmed these results by showing that age, active haematological disease, AML, and MDS are the categories to be considered at greatest risk of death [16]. The factors that most influence the outcomes in HSCT patients are: older age; higher immunodeficiency scoring index group (based on neutrophils $<0.5 \times 10^9$/l, lymphocytes $<0.2 \times 10^9$/l, age ≥40 years, myeloablative conditioning, graft vs. host disease, use of steroids and HSCT < 30 days), and poor performance status [5, 18].

Children and adolescents were less affected than adults by COVID-19 pandemic. In a recent meta-analysis, incidence of severe COVID-19 and mortality were reported to be 0.28% and 3.3%, respectively, in the period of January 2020–October 2020 [19]. In a review of 220 published cases of SARS-CoV-2 infection during the first pandemic wave, 47% of patients were hospitalised, 10.3% required intensive care admission, and 4.9% died of COVID-19 [20]. In another multinational retrospective registry study of 124 paediatric haemato-oncological patients, the rate of severe/critical COVID-19 was 13%, intensive care admission 11%, and the mortality 3% [21]. Among 1301 patients reported by the Global Registry COVID-19 in Children Cancer, 67.4% were hospitalised, 19.9% had a severe or critical COVID-19, and 3.8% died of COVID-19. In this study, the risk factors for severe or critical COVID-19 included low-middle income country status, age of 15–18 years, lymphocyte count $\leq 0.3 \times 10^9$/l, neutrophil count $\leq 0.5 \times 10^9$/l, and infection during intensive chemotherapy treatment [22].

CLINICAL PRESENTATION

SARS-CoV-2 infection is defined by the detection of viral genome or antigen in the oral and respiratory fluids, or specific serum antibody regardless of symptoms or signs. COVID-19 defines the symptomatic form of SARS-CoV-2 infection. Clinical stages of COVID-19 in HM patients follow WHO criteria [23]. The most common symptom of COVID-19 in HM patients is fever (58.6–77%), followed by cough (41–67%), breathlessness (37–49.3%) and fatigue (20.3–50%). Atypical symptoms, such as diarrhoea, vomiting, loss of appetite and confusion, can also occur. A severe and critical clinical course is reported in 15.5%–52.4% and 6.9%–14% of patients, respectively. SARS-CoV-2/COVID-19 pneumonia requiring oxygen support, occurs in 57–67.7% of patients whereas the need for mechanic ventilation ranged between 6.9 and 17% [5, 9, 14, 16]. Imaging studies show (multi-)focal or diffuse unilateral or bilateral ground-glass opacities with or without additional consolidations.

Long-COVID (or post-acute COVID-19 syndrome) is a new syndrome defined by the persistence of symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of the acute phase. Main symptoms are fatigue, dyspnoea, cough, chest pain, sleep disturbance and declined quality of life. The prevalence of long-COVID in the general population ranges between 32.1 and 87.4% in the most relevant published studies [24–26], but only limited specific data about prevalence and risk factors in HM patients are available. A study in chronic myeloproliferative malignancy patients reported a prevalence of 32.1% with a median time of 6 months after the acute phase [27]. In paediatric patients, the incidence of long-COVID-19 was lower than adults (1.8% at week 8) [28] and the most frequent symptoms were headache (60–74%), fever (52–58%) and cough (42–49%); while the new syndrome, the "Multisystem Inflammatory Syndrome in Children (MIS-C)", occurring 3–6 weeks after SARS-COV-2 is less frequent than immunocompetent paediatric host [20, 22, 29, 30].

The key points of epidemiological and clinical presentation of SARS-CoV-2/COVID-19 in HM patients is shown in Table 3.

PREVENTION

The prevention of SARS-CoV-2/COVID-19 in HM patients is based on strict infection control measures recommended for aerosol-, droplet- and contact transmission that apply to the general population: hand hygiene, physical distancing, face masks and ventilation of rooms [31, 32]. HM patients diagnosed with SARS-CoV-2/COVID-19 should be placed in single rooms, avoiding positive pressure rooms, to prevent transmission. Health care workers in charge must wear protective equipment specifically, gloves, gowns, face shield, FFP2 mask, and practice careful disinfection of hands.

In patients with active cancer and asymptomatic SARS-CoV-2 infection, the deferral of chemotherapy is not advisable but the decision must weigh the individual risks and benefits considering the type of underlying HM, the type of chemotherapy or biological agents to administer, the intensity of treatment and the expected toxicity profile of the treatments [13, 33, 34]. On the other hand, non-chemotherapy target drugs such as JAK2-inhibitors and TKI/BTKi should not be discontinued, even in patients with COVID-19 [27, 35–38]. Deferral of cellular therapy such as HSCT or CAR-T is recommended in case of SARS-CoV-2 infection as well as in case of a persistent positivity after a COVID-19 episode, because all these conditions show a high propensity to progress to lower respiratory tract infection and, in turn, increase mortality [5, 12, 18, 34, 39]. Considering that a prolonged viral shedding has been observed in HM patients after COVID-19 [40], obtaining the SARS-CoV-2 negativity in nasopharyngeal swab (NPS) before continuing the

Table 3. Key points of literature review of COVID-19 epidemiology and clinical presentation in haematological malignancy patients.

• The severity and outcome of COVID-19 is worse in HM patients compared to the general population, with a significantly higher mortality rate.
• Low-dose chest CT is indicated in HM patients with symptoms consistent with LRTD.
• Among HM patients, the prevalence of COVID-19 is high in patients with lymphoproliferative diseases such as NHL, CLL and MM.
• High mortality rate is observed in COVID-19 patients affected by acute leukaemia and high risk-myelodysplastic syndromes, and in patients after HSCT and CAR-T therapy.
• In all subset of HM patients, older age, cardiovascular and metabolic comorbidities, and active or not controlled (i.e. not in remission) malignancy represents the main risk factors for mortality.
• Children with HM have a lower prevalence of COVID-19 and associated mortality than adults with HM.
• The type of clinical symptoms and signs of COVID-19 and long-COVID in HM patients is similar to that reported for the overall population

BA bronchoalveolar lavage, *CAR-T* chimeric-antigen receptor-T cells, *COVID-19* coronavirus 2019 disease, *CLL* chronic lymphocitic leukaemia, *CT* computed tomography, *HM* haematological malignancy, *HSCT* hematopoietic stem cell transplantation, *LRTD* lower respiratory tract disease, *NHL* non-Hodgkin lymphoma, *MM* multiple myeloma, *SARS-CoV-2* severe acute respiratory syndrome Coronavirus-2.

treatment and/or when accessing day-clinic or hospital is recommended to avoid nosocomial infections. Moreover, during the peak of pandemic, it is advisable to redefine the plan of cancer therapy to reduce the number of visits to the hospital [19] by using approaches like telemedicine or use of erythropoietin to reduce transfusion events in some patients [41]. In contrast, a more extensive use of G-CSF to shorten neutropenia is not recommended due to the risk of a worst outcome with COVID-19 [42].

DIAGNOSIS OF SARS-COV-2/COVID-19

The gold standard for the diagnosis of SARS-CoV-2 infection is the detection of viral RNA by nucleic acid testing such as reverse transcription-PCR (RT-PCR) which provides high sensitivity and specificity. By comparison, despite their operational advantages, rapid antigen tests (RATs) have a lower sensitivity requiring higher viral loads corresponding to RT-PCR cycle thresholds of ≤30 [43–45]. Since the majority of RATs detect the nucleocapsid (N) protein, a structural protein with less variation than the spike (S) protein, their performance seem to be only slightly reduced in case of the variant Omicron-BA.1 [46]. However, Omicron-BA.2 may not be detectable by certain RATs, causing an unacceptably high rate of false-negative results in point of care testing and affect infection control decisions (Hans Hirsch, personal communication).

For laboratory testing, the sampling obtained with NPS is considered the most appropriate, although associated with patient discomfort and requires trained personnel. Other sampling methods, such as combined NPS of both nares, or nasopharyngeal with oropharyngeal sampling, or saliva, sputum, and nasal sampling may be alternatives, especially in ambulatory care setting [47].

SARS-CoV-2 RNAemia is usually negative at the beginning of infection and, therefore, blood sampling is not useful for the initial diagnosis; on the other hand, the detection of SARS-CoV-2 RNAemia is a predictive factor for the persistence of symptoms beyond 28 days from the infection onset, especially in patients requiring hospitalisation for moderate-severe COVID-19 [48, 49].

Contagiousness of SARS-CoV-2 usually lasts average of 10 days from symptom onset in mild-moderate COVID-19, but can be longer (15 days) in severe/critical COVID-19 and immunocompromised patients; moreover, the viral viability have been documented up to 20 days from symptom onset. The persistence of RT-PCR positivity after 3 weeks from the initial positivity or the alternation of positive and negative RT-PCR tests in patients who recovered from COVID-19, has been explained by low viral loads, variability in sampling, and persistence of viral debris [50, 51].

The time needed to mount the IgG antibody response to SARS-CoV-2 is at least 10 days from RT-PCR positivity and can be longer in cases of milder COVID-19 or asymptomatic infection. For this reason, the assessment of SARS-CoV-2 serum antibody titres is not useful for diagnostic purposes, but can be a valid tool in epidemiological investigations of seroprevalence among different countries or populations, or to assess the duration of immunity induced by wild infection or the duration of vaccine antibody protection [52–54].

Considering the polyclonal antibody response of natural infection against spike surface proteins (including receptor binding domain proteins) and nucleocapsid proteins, the use of serological test specific for spike proteins or nucleocapsid protein can help distinguish between a previous exposure to infection or to a vaccine-spike-protein based response. The determination of antibody against nucleocapsid protein is also part of differential diagnosis of MIS-C [55–57].

Even though the overall mutation rate of coronaviruses is lower by 1–2 orders of magnitude compared to HIV or HCV, the high intra-host replication fitness and the high number of transmission and infection events determined the emergence of alpha, beta, delta and now Omicron variants within 2 years since the pandemic [58, 59]. These variants carry non-synonymous amino acid changes in the S-protein, which may alter the molecular architecture, optimise infection kinetics, and change antigenic properties. Thus, RNA-sequence-based and antigen-specific diagnostic assays based on the Wuhan-strain may be impaired. In addition, the performance of viral detection and antibody testing is dependent on the time after exposure and symptoms onset [52], whereby detection of viral antigen by nucleic acid testing decreases after 10 to 20 days post clinical and virological diagnosis [60], while SARS-COV-2 antibody response in blood increases.

In case of negative testing results, repeat testing as well as considerations regarding SARS-COV-2 variants or other community-acquired-respiratory-viral-infections due to influenza virus, respiratory syncytial virus, meta-pneumovirus, parainfluenza viruses and human coronaviruses may need to be considered [61].

VACCINES AND VACCINATION

Vaccines have proven to be a critical piece of our armamentarium against SARS-CoV-2. While multiple vaccines have advanced to the clinical setting, mRNA-based vectors (BNT162b2 and MRNA-1273) have been mostly used in immunosuppressed and HM patients [62]. Initial studies identified that while patients with solid tumours had high rates of seroconversion with COVID-19 vaccines, patients with HMs showed lower immunogenicity post vaccination. In addition, recently administered immunosuppressive therapies lead to lower responsiveness. The recent emergence of new variants probably requires updated vaccines and new vaccination strategies in HM patients.

Chronic lymphoproliferative disorders (CLP)

Patients with CLP have low antibody responses, especially those with CLL [63]. Several studies are consistent with response rate estimates of 35–75% in CLL [64–68] and 39–73% in NHL [66, 68, 69]. The main factors associated with poor responses were age over 70 years, decreased immunoglobulin levels, lymphopenia, anti-CD20 antibody administration within the last 6 to 12 months and use of Bruton Tyrosine Kinase inhibitors (BTKi) during the last 2 months. Most studies found better responses in treatment-naïve patients, followed by patients off-therapy and in complete remission, and the worst responses being in patients on treatment [65, 68, 70]. A main concern for patients, either on treatment or within at least 6 months off-treatment, showed very low responses between 0–17%, when treated with anti-CD20 antibodies [71–73]. Although several studies show that some T-cell response may be mounted despite the lack of antibody production, the protection offered by a pure cellular response is unknown. Furthermore, HM patients appear to be at higher risk of concordant low cellular and humoral responses after anti-CD20 antibodies, compared to vaccinated controls [72]. Therefore, these patients could benefit from other protective approaches such as the passive humoral protection with anti-spike monoclonal antibodies.

Patients with MM represent a heterogeneous group of patients. These patients can mount a measurable antibody response in 45–95% of the cases after 2 doses of mRNA vaccine [66, 74, 75], but with a very variable response according to given treatment. They have overall lower antibody titres than healthy controls [76]. The main factors impairing the response were older age, use of a daratumumab-based or belantamab mafadotin regimen, the number of previous lines of treatment, and low lymphocyte count [66, 75–77]. The vaccine response in patients with smouldering myeloma is better and patients with monoclonal gammopathy of undetermined significance respond similarly to healthy controls of the same age.

Limited data are available in patients with Waldenström's macroglobulinemia. In a series of 97 patients, the response rate

after 2 doses was 74.2% but no data are available on factors associated to response. Response in patients with Hodgkin lymphoma is close to that of healthy individuals [63, 66, 69].

In all these patients, it should be noted that even if the response rate may be close to healthy individuals of similar age, the antibody titres is always lower than in healthy controls. As expected, even in responding patients, the antibody titres decreased over time. In CLL, antibodies were still detectable 6 months after the second vaccine dose in 90.2% of 55 patients vs. 100% in controls, but with significantly lower antibody titres. Furthermore, patients on active treatment had a lower frequency of antibody persistence when compared to treatment-naïve patients or previously treated patients.

Due to the natural waning of antibody titres, a third dose is beneficial in healthy individuals. The benefit of a third vaccine dose has been investigated in haematology patients, mainly in CLL patients, although on limited numbers and with various times between the 2nd and the 3rd dose. In patients who did not respond to the initial regimen, the seroconversion rates after the 3rd dose was noted between 23–55% [66, 68, 78, 79]. These rates seem comparable after a homologous [66, 68, 79] or a heterologous [78] booster. Similar to the poor responses to the initial regimen, the on-therapy patients also had the poorest response to booster dose. In patients who had responded to the initial regimen and were still seropositive before the 3rd dose, almost all remained seropositive after the boost and even increased their antibody titres, although still lower than in healthy individuals [66, 79].

Chronic myeloproliferative neoplasms (CPMN)

Patients with CPMN generally develop robust vaccine responses (84–97%) close to healthy individuals of the same age range, albeit with potentially decreased antibody titres [63, 66, 80]. Factors correlating with decreased or absent response included ongoing chemotherapy, age and male sex, although this was not specific to CMN patients. While BCR-ABL tyrosine kinase inhibitors did not seem to impact response rate in these cohorts [81], the JAK-inhibitor ruxolitinib correlated with decreased or absent responses [63, 80].

Acute leukaemias

Although the data are very limited (two studies with 66 patients in total), patients with acute leukaemia seem to have vaccine response rates in the range of 80–91%, close to healthy individuals of the same age range, albeit with potentially decreased antibody titres. Factors potentially negatively influencing the response rate included ongoing chemotherapy (in particular with venetoclax) alongside age, male sex and LDH, though these factors were not necessarily specific to acute leukaemia patients [63, 66].

Safety data in non-transplanted haematology patients

Most studies show that the vaccine safety events were similar in non-transplanted haematology patients and in healthy individuals, both in frequency and type, and were mostly local (pain, redness, swelling) and rarely systemic (fatigue, headache, fever) [68, 76, 77, 82]. There are conflicting results on the association between vaccine response and adverse events [65, 68]. These data should, however, be interpreted with caution as safety data were not always collected or reported in observational or retrospective studies, and the size of the studies was much smaller than for healthy individuals.

Although many studies have been published, data may be difficult to interpret, due to different techniques to measure the responses, different definitions of being “on-therapy”, and limited information on whether the treatment of the underlying disease was postponed when performing the vaccination. After ECIL 9 meeting, during the Fall-Winter 2021–2022 season, a 3rd dose has been recommended in most European countries for immunocompromised patients starting from at least 4 weeks after the initial regimen, with a potential benefit to one third of the initial non-responders [83, 84]. Due to lack of significant safety reporting issues in this population, an additional booster dose at 3–6 months has been subsequently recommended in several countries for groups at high risk of severe-critical COVID-19 including immunocompromised subjects [85].

Allogeneic HSCT and CAR-T-cell therapy recipients

There have been several studies of varying designs performed in allogeneic HSCT patients for COVID-19 vaccine responses [82, 86–95]. The response rates (defined according to the authors of the papers) to two doses of mRNA vaccines have varied between 69 and 85%. These studies identified different risk factors for poor responses, most commonly showing that patients vaccinated earlier after HSCT [90–92, 96], those with lower lymphocyte counts or IgG levels [87, 89, 90, 92, 95], active GVHD and patients with ongoing or recently discontinued immunosuppression [88–90, 94, 95] had poorer responses. In patients post allogeneic HSCT, including those with chronic GVHD needing immunosuppression and those with previous poor serological responses, a robust polyfunctional, memory T-cell and serological immune responses induced after 2nd dose of vaccine has been reported [97], suggesting role of repeated vaccinations in these cohort to improve vaccine responsiveness. The data regarding CAR-T-cell patients is more limited. Three small studies have reported response rates between 0–36% [89, 93, 96].

The efficacy and safety of giving a 3rd dose is still limited. One study was performed in 42 HSCT patients who had responded poorly after the 2nd dose [98]. A 3rd dose resulted in a significant increase in SARS-CoV-2 antibodies, but only 48% reached the antibody levels the authors had defined as protective. No severe adverse event was noted. As a subset of a large cohort study, 181 patients received a 3rd dose at a median of 54 days after dose 2. Among 70 patients without a previous response, 41% mounted a detectable response. Furthermore, among 46% with a weak prior response, 85% achieved a good response, and finally in all 65 patients, who had a good response, the antibody level either increased or reached the highest antibody level of the used assay [91].

It is plausible that those who received COVID-19 vaccine before HSCT or CAR-T-cell therapy, the procedures will most likely wipe out all immune memory. In general, post-HSCT patients should be viewed as “never vaccinated” patients regardless of the pre-HSCT vaccination history of the patient or the donor. It is recommended that such individuals be re-vaccinated as if they have never received a COVID-19 vaccine. This is in accordance with the situation for other vaccines given pre-transplant and where post-transplant revaccination is recommended.

There is no data specifically addressing children or adolescents having undergone allogeneic HSCT or CAR-T-cell therapy. However, since studies show good safety of the mRNA vaccines in children from the age of 5 years, and although children less frequently get severe COVID-19, the EBMT registry has recorded a COVID-19 related mortality of ~10% [99], it is logical to vaccinate children after allogeneic HSCT and CAR-HCT or CAR-T-cell therapy with similar recommendations as in adults.

Safety information

Most reported studies show similar rates of side effects as in healthy controls. However, three studies have reported a risk for eliciting or worsening GVHD after COVID-19 vaccination of allogeneic HSCT recipients [86, 93, 96], while two studies did not report the occurrence or the recrudescence of GVHD after a 3rd dose of mRNA vaccine [98, 100].

Recommendations regarding vaccinations of non-transplanted and transplanted patients with HMs are shown in Table 2. Due to the limited available data, no recommendation can be given for patients having received CAR-T-cell therapy.

THERAPY

The pathogenesis of COVID-19 is characterised by an initial viral phase followed, in some patients, by a severe inflammatory phase [101]. This hyper-inflammatory state is the cause of high mortality rate in patients [101]. This hyper-inflammatory state is the cause of high mortality rate in subjects who develop it. Therefore, the treatment of SARS-CoV-2 infection is based on the initial control of the virus and/or subsequently, in patients who need it, on the control of hyper-inflammatory response.

The antiviral and anti-inflammatory therapies currently accepted as beneficial in the general population were assessed with focus on their efficacy, safety and potential benefit in HM/HSCT population. These therapies are showed in Table 4 and the recommendations are summarised in Table 2. Immunocompromised persons are at risk of a prolonged viral phase compared to typical 5–10 days reported in the general population, with some patients with HM/HSCT shedding infectious viral particles for months [40, 102, 103]. However, how frequently HM/HSCT [40, 102, 103]. However, how frequently HM/SCT subjects experience a prolonged viral phase remains undefined. Conversely, the inflammatory phase can be delayed, dysfunctional, weakened, or absent due to the underlying haematological disease and its treatment. Furthermore, the proportion of HM/SCT patients who develop hyper-inflammatory phase leading to respiratory failure and death is variable and depends on the ongoing patients' immunodeficiency and immunosuppression, together with other risk factors reported in the general population.

Therefore, due to the immunosuppression in HM/HSCT patients, the control of the virus becomes presumably very relevant. The usual timeline described in randomised controlled trials may not apply to HM/HSCT patients and a symptom-based categorisation rather than based on days from symptom onset should be adopted. As in immunocompetent patients, anti-inflammatory treatments are recommended in HM/HSCT patients when they present signs and symptoms of the inflammatory phase (e.g. presence of high levels of inflammation markers such as C-reactive protein and respiratory worsening).

TREATMENT OF VIRAL PHASE

Antivirals

Multiple randomised trials assessed remdesivir, a nucleoside analogue, active against SARS-CoV-2 virus for a reduction in mortality without finding statistically significant benefit [104–107]. However, in the main study that focused on time to recovery, comprised 80 cancer patients (8%), treatment with remdesivir did result in faster rates to recovery; the benefit was most pronounced in patients with low-flow O_2 requirements and in those with less than 10 days of symptoms, consistent with its impact mainly during the viral phase of the infection [104]. Additionally, in an observational study in 313 HM patients, remdesivir treatment was independently associated with lower mortality risk [108], and there was a non-statistically significant trend towards lower mortality in a study of 2186 adults with invasive cancer, including 470 with HMs [109]. A short course of remdesivir reduced the risk of progression to severe COVID-19/hospitalisation in symptomatic outpatients with COVID-19 (0.7% vs. 5.3%) [110]. Considering potentially higher impact of antiviral treatments in the immunocompromised compared to the general population, particularly with a prolonged viral phase, in addition to data on virological efficacy [33, 111] and overall good safety profile [104, 112], HM/HSCT patients may benefit from remdesivir treatment.

Molnupiravir, another nucleoside analogue active against SARS-CoV-2, showed lower rate of hospitalisation or death in a randomised trial in outpatients with mild/moderate COVID-19 (6.8% vs. 9.7%) and could be of benefit in HM/HSCT setting [113], although there are concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates.

Data on oral ritonavir-boosted nirmatrelvir, published after ECIL 9 meeting, showed lower rate of progression to hospitalisation or death (0.77% vs. 7.01%) in symptomatic, non-hospitalised, adult patients with COVID-19 [114]. This combination of antivirals could be beneficial in HM/HSCT patients, although attention to potential drug interactions through CYP3A inhibition should be considered.

Conversely, drugs with reported antiviral activity not confirmed in RCTs include (hydroxy-) chloroquine (CQ/HQ), lopinavir/ritonavir (LPV/r) and azithromycin, and there is also no sufficiently robust data to support the use of ivermectin, arbidol or favipiravir [115, 116].

Interferon (IFN)-beta

The rational for using IFN in COVID-19 patients relies on its potent antiviral and immunomodulatory functions [117], as well as the suppression by SARS-CoV-2 of interferon-β release in vitro [118] and interferon activity in patients who developed more severe disease [119]. Local concentrations and early administration are likely critical to its effect as recovery rate was higher in phase 2 randomised trials in adults (none of them with HM) treated with inhaled 6 MIU of interferon beta-1a [120], but no benefit was seen with systemic intravenous treatment with IFN b-1a in SARS-CoV-2 infection [107].

Anti-spike monoclonal antibodies

Several anti-spike protein monoclonal antibodies (anti-S MAbs), such as bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab or regdanvimab have been shown useful in reducing the rate of progression to severe COVID-19 or death in the general patient population with mild/moderate COVID-19, but at risk for severe COVID-19 [110, 121–126]. Although the number needed to treat to prevent one progression to severe COVID-19 or death was high (in the placebo arm this outcome was present in 4.6–8% of included patients), HM/HSCT patients who frequently fail to develop strong humoral response to the virus, may benefit most from Anti-S MAbs treatment.

As in the general population, the choice of the anti-S MAbs should be based on local availability, national approval and the updated epidemiology of circulating SARS-CoV-2 viral variants; since their activity might be affected by the specific mutations (e.g. sotrovimab is the only anti-S MAb to retain activity against the recent Omicron variant). A low rate of side effects, including infusion-related reactions, were reported in the pivotal trials [110, 121, 122, 125, 126].

The use of anti-S MAbs in patients with severe COVID-19 has been controversial, with initial trials halted due to the lack of benefit [127]. However, data from the RECOVERY trial documented the benefit of high dose casirivimab/imdevimab in the subgroup of 3153 hospital-admitted seronegative patients (day 28 mortality 24% vs. 30%, $p = 0.001$), while no benefit was reported in seropositive patients [128].

Convalescent plasma

The use of convalescent plasma (CVP) has been reported as beneficial in single arm trials, particularly if used early during the infection and with high titre of neutralising antibodies [129, 130]. However, RCTs and meta-analyses did not confirm higher rate of recovery or survival [131–134]. Few RCTs showed that an early administration (<72-h onset) of high-titre CVP reduced the progression to severe COVID-19 (16% vs. 31%) [135].

In observational studies and case reports/series in immunocompromised patients, including those with HM, a statistically significant benefit of CVP on clinical recovery and 30-day mortality was reported (13.3% vs. 24.8%, also after propensity score matching) [136]. Based on these data, and the reported safety of CVP treatment [132], if anti-S MAbs are not available, high titre CVP might be of benefit in seronegative immunocompromised

Table 4. Summary of ECIL-2021 recommendations on the treatment of SARS-CoV-2 infection and COVID-19 in haematology patients.

	Pre-exposure prophylaxis	Post-exposure prophylaxis	Mild COVID-19	Moderate COVID-19	Severe COVID-19	Critical COVID-19
COVID-19 signs or symptoms?	No	No	Mild or moderate, no dyspnoea, no need for COVID-19-related admission	Yes, clinical or radiological evidence of LRTD, O_2 saturation >90%, but hospitalised and receiving O_2	Yes, respiratory failure O_2 saturation <90% and/or RR > 30/min, but some studies considered severe if O_2 saturation <94% or <92%	ARDS, sepsis, septic shock, MV (invasive or non-invasive) or vasopressor therapy
Treatment	long-acting anti-SARS-CoV-2 Mabs (AZD7442) in non-immunised patients at risk for severe COVID-19	Anti-S MAbs in patients at high risk for COVID-19 progression (not vaccinated, vaccine non-responders or not expected to respond to vaccine)	Anti-S MAbs or High-titre CVP[a] or Inhaled IFN b-1a or Molnupiravir or Remdesivir or Ritonavir/nirmatrelvir Colchicine (in the absence of other therapeutic options) Dexamethasone not indicated	Remdesivir C/I or CVP if seronegative[a] Dexamethasone If worsening despite dexamethasone and present severe COVID-19-related inflammation[b], add the 2nd immunosuppressant anti-IL-6 (tocilizumab, sarilumab) or anti-IL1 (anakinra) or JAK–inhibitor (baracitinib/tofacinib)	If severe COVID-19- related inflammation present[b], add the 2nd immunosuppressant: Anti-IL-6 (tocilizumab, sarilumab) or anti-IL1 (anakinra) or JAK-inhibitor (baracitinib/tofacinib)	C/I if seronegative (in NIV, no data in MV) Dexamethasone Remdesivir not indicated If COVID-19-related inflammation present[b], add the 2nd immunosuppressant, Anti-IL-6 (tocilizumab, sarilumab)

Anti-S MAbs monoclonal antibodies against spike protein of SARS-CoV-2, *C/I* casirivimab/imdevimab, *CVP* convalescent plasma, *LRTD* lower respiratory tract disease, *MV* mechanical ventilation: *MIV* invasive, *NIV* non-invasive, *RR* respiratory rate.

[a]If Anti-S MAbs not available, preferably within 72 h from symptom onset.

[b]e.g. CRP >75 mg/dl in the absence of bacterial coinfection or other available inflammation parameters or scores (if not altered due to the underlying haematological disease). The effects of immunomodulatory therapies targeting COVID-19 on the course of disease in already immunosuppressed patients are poorly understood and deserve special consideration.

patients, particularly if administered early during the infection [135, 137].

Finally, based on the possibility of prolonged viral phase in HM/HSCT settings and after reviewing anecdotal evidence of efficacy of antiviral treatments, when given outside the timing of early infection (usually 10 days from the onset of symptoms in the general population), antiviral treatment might be useful in selected patients with prolonged viral replication in the course of SARS-CoV-2 infection [138–142]. However, the failure of remdesivir [143] and bamlanivimab [144] in HM/HSCT patients due to the emergence of mutations has been also reported.

Treatment of inflammatory phase

Steroid therapy, in particular dexamethasone 6 mg daily for 10 days in patients with O_2 therapy, showed a 3% reduction in mortality in the RECOVERY trial [145]. The results of this study confirmed the benefit of anti-inflammatory therapy in patients who develop inflammatory phase, as documented by the need for oxygen therapy; while there was detrimental effect observed when used in those with earlier viral phase and not needing O_2 administration [145]. Several doses and types of corticosteroids have been studied since, although 6 mg of dexamethasone had the most robust evidence [146]. No clear benefit of higher dose of steroids (dexamethasone 12 mg vs. 6 mg) has been shown [147].

Other immunosuppressive drugs, in particular anti-IL-6 monoclonal antibodies have been studied, and although initial randomised trials did not report clinical benefit [148–154], its benefit on clinical recovery was reported in one study [155], and two trials (in which over 80% patients received steroids) reported reduction in disease progression and mortality: day 28 mortality reduction from 35 to 31% in 4116 hospitalised patients with O_2 saturation <92% on room air and CRP ≥ 75 mg/l [156] and from 36 to 28% in 755 intensive care unit patients with high flow O_2, non-invasive or invasive mechanical ventilation [157]. Its benefit in severely and critically ill COVID-19 patients have also been confirmed in WHO network analysis [158].

Several other studies performed in the general population reported some benefit in clinical recovery rates but not on mortality with some other immunosuppressant drugs (usually given in association with steroids): baracitinib (plus remdesivir vs. placebo plus remdesivir) [159], oral tofacinib [160] and colchicine [161]. Anti-IL-1 treatment was shown effective only in a single trial, which identified the patients who could benefit from the therapy with high inflammatory state, based on elevated levels of soluble urokinase Plasminogen Activator Receptor levels (this was given in association with steroids in 89% of patients) [162].

Based on the current evidence and on the potential risks of using these treatments in immunocompromised HM/HSCT patients, we recommend using dexamethasone during the inflammatory phase of this disease (those with O_2 requirement and increased inflammatory markers), but without modifying the already active immunosuppressive treatments.

INTENSIVE CARE SPECIFICS

Since there are no dedicated trials in the HM/HSCT population, generally accepted measures of intensive care management should be followed. Appropriate management of infectious complications, including application of diagnostic algorithms in immunosuppressed patients with acute respiratory failure to rule out secondary infections, is mandatory [163].

ANTI-SPIKE MONOCLONAL ANTIBODIES AS PROPHYLAXIS

Anti-S MAbs (bamlanivimab and casirivimab/imdevimab) have been successfully used as post- exposure prophylaxis in household contacts and health care structures, with lowered rate of progression to COVID-19-related hospital admission or death [164, 165]. The half-

life of these MAbs require additional doses to be repeated 28 days after the first one. Anti-S MAbs (bamlanivimab and casirivimab/imdevimab) have been successfully used as post- exposure prophylaxis in household contracts and health care structures, with lowered rate of progression to COVID-19-related hospital admission or death [164, 165]. The half-life of these MAbs require additional doses administered after 28 days from the first one.

Data on pre-exposure prophylaxis with intramuscular administration of long-acting antibodies tixagevimab/cilgavimab (AZD7442) reported lower risk of developing symptomatic COVID-19 within the subsequent 6 months, with fewer SARS-CoV-2 related deaths (0 vs. 2 in placebo arm; 5197 participants, PROVENT study) [166, 167].

In conclusion, HM/HSCT might be at higher risk for severe or prolonged vial phase. Thus, antiviral treatment could be more beneficial than in the general population and required even later after the onset of infection. The benefit of various treatments in this population should be further studied to provide optimal individualised care plan for this difficult and heterogeneous patient population.

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AUTHOR CONTRIBUTIONS

SC and LP conceptualised and designed the project; SC, PL, MM, HHH, MVLT, CC, SM, VM, JS, FM, CB, FB, RCM, GB, HE, EA, JM, RFC and LP performed the literature search and wrote the initial draft of the paper; SC, PL, MM, HHH, MVLT, CC, SM, VM, JS, FM, CB, FB, RCM, GB, HE, EA, JM, RFC, and LP read and approved the final version of the manuscript; VM revised the English style of the manuscript; SC supervised the project and performed the final editing of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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