Hematopoietic stem cell transplantation for autoimmune diseases in the time of COVID-19: EBMT guidelines and recommendations

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Received: 28 February 2021 / Revised: 17 April 2021 / Accepted: 21 April 2021 / Published online: 24 May 2021 © The Author(s) 2021. This article is published with open access

Abstract
Coronavirus disease-19 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), represents one of the biggest challenges of 21st century, threatening public health around the globe. Increasing age and presence of co-morbidities are reported risk factors for severe disease and mortality, along with autoimmune diseases (ADs) and immunosuppressive treatments such as haematopoietic stem cell transplantation (HSCT), which are also associated with adverse outcomes. We review the impact of the pandemic on specific groups of patients with neurological, rheumatological, and gastroenterological indications, along with the challenges delivering HSCT in adult and pediatric populations. Moving forward, we developed consensus-based guidelines and recommendations for best practice and quality of patient care in order to support clinicians, scientists, and their multidisciplinary teams, as well as patients and their carers. These guidelines aim to support national and international organizations related to autoimmune diseases and local clinical teams delivering HSCT. Areas of unmet need and future research questions are also highlighted. The waves of the COVID-19 pandemic are predicted to be followed by an “endemic” phase and therefore an ongoing risk within a “new normality”. These recommendations reflect currently available evidence, coupled with expert opinion, and will be revised according to necessary modifications in practice.

Introduction
Since the onset of the COVID-19 pandemic [1], various reports detail its clinical manifestations and outcomes [2–6]. Delivery of HSCT requires maintenance of a complex infrastructure, quality assured according to a range of accreditation standards, and severely impacted during the pandemic. Under normal circumstances, autologous and allogeneic HSCT are performed in patients with severe ADs after careful balance of benefits and risks, with consideration of other non-transplant treatment options [7–10]. The majority of such patients have chronic diseases, which impact on quality of life and may shorten life expectancy. Transplant regimens used in autologous HSCT for ADs are generally more immunosuppressive than those used for other indications [8], and patients often receive immunomodulatory treatments prior and after HSCT. Immunocompromised patients are at elevated risk of complications from SARS-CoV-2 [11–17]. However, it remains uncertain whether conventional immunosuppressive treatments, glucocorticoid usage, and/or targeted-biologic disease modifying therapies (DMTs), are advantageous or detrimental [18].

As a basis for our guidelines and recommendations, we appraise the impact of the pandemic on patients with ADs,
including non-HSCT treatments, along with the challenges delivering HSCT during the initial waves of the COVID-19 pandemic. The current phase of the COVID-19 pandemic is predicted to be followed by an “endemic” phase and therefore an ongoing risk within a “new normality”. There is therefore a need within the community for guidelines to restart HSCT programs, whilst maintaining quality and cautiously balancing risks and benefits against alternative treatment options in each AD. These guidelines and recommendations should be read in conjunction with general and AD-specific guidelines from European Society for Blood and Marrow Transplantation (EBMT) [19, 20]. They aim to provide useful information and general principles for national and international organizations and local clinical teams across relevant AD specialties whilst complementing guidelines and recommendations issued by other specialist societies.

**Methods**

The recommendations (Tables 1–3) provided in this “living document” reflect currently available evidence, COVID-related guidelines regularly updated by EBMT [20], relevant AD specialists and HSCT societies, policies and procedures produced by national authorities as well as local and institutional policies, coupled with expert opinion from an international multidisciplinary team (MDT). Evidence was sourced from PubMed searches of original observations and key reviews, including the previous EBMT guidelines [7, 8, 19–21], and, where relevant, recent congress presentations.

As per other EBMT guidelines and recommendations, level of evidence for the efficacy of autologous HSCT in ADs is systematically classified in three categories of recommendations where HSCT should be considered (S/CO/GNR—see Tables 2 and 3, and related footnotes) [7, 21]. Strength of evidence supporting the assignment of a particular category of recommendations is graded (levels I, II, and III) based on consideration of health benefits, side effects, and risks and balanced against the non-HSCT options. Clinical priority, as determined by a relevant MDT [22], has been classified as high, intermediate, or low, while the COVID-19 Alert Level [23, 24] as very low, low, moderate, high, or very high (see Tables 2 and 3, and related footnotes).

**Preliminary analysis of the impact of COVID-19 outbreak on HSCT programs for ADs**

Across the EBMT registry, we investigated the impact of the COVID-19 outbreak on transplant activity for ADs. When the transplant activity for ADs during the pandemic was compared with the corresponding time in 2019, a total of 116 patients received an autologous HSCT between March and December 2020, while 242 patients received autologous HSCT the previous year in the same time frame (Fig. 1). Compared to 2019, transplant activity for ADs decreased by 52%. Nevertheless, indications remained unchanged with multiple sclerosis (MS) and systemic sclerosis (SSc) comprising 80% of transplants in ADs reported to the EBMT in 2020, being HSCT an integral and standard-of-care part of their treatment algorithms [21].

**General recommendations for restarting HSCT program in ADs**

All AD patients considered for HSCT should be carefully discussed at the local MDT meeting, with input from HSCT and AD specialists and consideration of alternative treatments [20]. If HSCT treatment is in the best interests of patients, established treatment protocols for AD should be followed, as per guidelines and evidence-based appraisals.

The ongoing learning curve will need to be extended into longer-term modifications in clinical practice, with the “restoration and recovery” or “reset” periods, during which SARS-CoV-2 minimization can be completed, aiming to overcome any further “resurges” and peaks. Consequently, HSCT programs must be ready to rapidly adapt to this change following the course of the pandemic and be able to prioritize the process of delivering HSCT according to clinical urgency [25], depending on virus, hospital, patient, and HSCT-related factors (Table 1) [22, 25].

Nurses have a key role in explaining all the related precautions, including strict adherence to local policies relating to visiting. Clear written information for patients and caregivers should be provided, including measures to minimize the risk of infection, and need for a dedicated caregiver, having low risk of SARS-CoV-2 exposure, in the first months after HSCT. Patients intending to travel abroad for HSCT should consider carefully what arrangements are in place to minimize the risk but also the provision of care post discharge, especially if there are any potential travel restrictions between the country of treatment and their home.

Since the COVID-19 situation varies substantially between and within countries, we recognize that centers are mandated to follow guidelines, policies, and procedures decided by national authorities as well as local and institutional policies. Special consideration should be made when the home base or country of the patient is different from the HSCT center, where R numbers [26] and clinical practice, including in relation to precautions, may differ. As such arrangements will be individualized, there is a recommendation that patients are systematically discussed by and between MDTs at both sites, and, after the HSCT procedure, there is a clear communication between the
Summary of general recommendations [19, 20, 22, 25, 91].

Table 1 Summary of general recommendations [19, 20, 22, 25, 91].

| Key factors       | Recommendations                                                                                                                                  | Remarks                                                                                   |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Virus-related     | • Surveillance of the local prevalence of virus in the community.                                                                               | • In the event of “resurges” and peaks or local outbreaks, it is likely that HSCT for AD  |
| factors           | • Continuous updating of the reproduction number “R” [26], reflecting the infectious potential of the disease.                                   | may again need to stop.                                                                     |
|                   | • Tracing of the national and regional alert status.                                                                                             | • Patients and families need to be counseled about the possibility of short notice          |
|                   |                                                                                                                                                | cancellation of their planned HSCT.                                                        |
|                   |                                                                                                                                                | • The key epidemiological parameters are the “R” rate, and the growth rate of the          |
|                   |                                                                                                                                                | epidemic [26].                                                                             |
|                   | • In the event of “resurges” and peaks or local outbreaks, it is likely that HSCT for AD may again need to stop.                                |                                                                                           |
|                   | Hospital-related                                                                                                                                  |                                                                                           |
| factors           | • Availability of IPC and PPE, COVID-19 vaccination³ for the staff.                                                                             | • In many countries HSCT follows established pathway for adult elective care but patients  |
|                   | • Testing and tracing of staff and patients (prior to mobilization and transplant).                                                            | may also need to access services urgently.                                                  |
|                   | • Ability to create COVID secure facilities with clear pathways to separate patients from those that may have COVID.                             | • Where possible and clinically appropriate there should be separated care pathways for      |
|                   | • Adequate supportive services for the HSCT program including ICU beds.                                                                           | urgent and planned care, to eliminate the risk of nosocomial infection. Staff looking      |
|                   | • Suitable isolation facilities including single rooms with en suite facilities and for patients that tested positive for SARS-CoV-2 rooms with   | after COVID-19-positive patients should not be involved in face-to-face care of             |
|                   |    negative pressure or neutral pressure if this is not possible.                                                                               | negative recipients.                                                                        |
|                   | • Backlog of patients with hematological malignancies who will take priority.                                                                     | • Most hospitals have developed physically separate defined zones and cohorted staffing   |
|                   | • Discussing patients being considered for HSCT in appropriately constituted MDTs meeting; established treatment protocols for AD should be    | (reduced movement between COVID protected and non-protected areas).                         |
|                   |    followed; mobilization with Cy provides additional disease control and requires consideration [7, 8].                                         |                                                                                           |
|                   | • Visitors should generally not be admitted to transplant wards, except a single caregiver with negative swab for children.                    | • Risk minimization for other viral outbreaks is recommended, e.g., compliance of HCW      |
|                   | • Ability to create COVID secure facilities with clear pathways to separate patients from those that may have COVID.                             | with seasonal influenza vaccination.                                                        |
|                   | • Adequate supportive services for the HSCT program including ICU beds.                                                                           | • Methods for communication between recipients, family members, and HCW such a            |
|                   | • Suitable isolation facilities including single rooms with en suite facilities and for patients that tested positive for SARS-CoV-2 rooms with   | video calls should be supported.                                                           |
|                   |    negative pressure or neutral pressure if this is not possible.                                                                               | • Risk minimization for other viral outbreaks is recommended, e.g., compliance of HCW      |
|                   | • Backlog of patients with hematological malignancies who will take priority.                                                                     | with seasonal influenza vaccination.                                                        |
|                   | • Discussing patients being considered for HSCT in appropriately constituted MDTs meeting; established treatment protocols for AD should be    | • Methods for communication between recipients, family members, and HCW such a            |
|                   |    followed; mobilization with Cy provides additional disease control and requires consideration [7, 8].                                         | video calls should be supported.                                                           |
|                   | • Visitors should generally not be admitted to transplant wards, except a single caregiver with negative swab for children.                    | • Risk minimization for other viral outbreaks is recommended, e.g., compliance of HCW      |
|                   | • Ability to create COVID secure facilities with clear pathways to separate patients from those that may have COVID.                             | with seasonal influenza vaccination.                                                        |
|                   | • Adequate supportive services for the HSCT program including ICU beds.                                                                           | • Methods for communication between recipients, family members, and HCW such a            |
|                   | • Suitable isolation facilities including single rooms with en suite facilities and for patients that tested positive for SARS-CoV-2 rooms with   | video calls should be supported.                                                           |
|                   |    negative pressure or neutral pressure if this is not possible.                                                                               | • Risk minimization for other viral outbreaks is recommended, e.g., compliance of HCW      |
|                   | • Backlog of patients with hematological malignancies who will take priority.                                                                     | with seasonal influenza vaccination.                                                        |
|                   | • Discussing patients being considered for HSCT in appropriately constituted MDTs meeting; established treatment protocols for AD should be    | • Methods for communication between recipients, family members, and HCW such a            |
|                   |    followed; mobilization with Cy provides additional disease control and requires consideration [7, 8].                                         | video calls should be supported.                                                           |
|                   | • Visitors should generally not be admitted to transplant wards, except a single caregiver with negative swab for children.                    | • Risk minimization for other viral outbreaks is recommended, e.g., compliance of HCW      |
|                   | • Individual risk/benefit assessment and ability to give fully informed consent.                                                                   | with seasonal influenza vaccination.                                                        |
| Patient-related    | • Ability to self-isolate, PPE compliance, home infrastructure to allow self-isolation, and agreement to comply with need to self-isolate.         | • Methods for communication between recipients, family members, and HCW such a            |
| factors           | • Financial factors pertinent to the need to work from home for the first months following HSCT.                                                  | video calls should be supported.                                                           |
|                   | • Post-transplant recovery and rehabilitation may be facilitated at home via telehealth [22, 92, 93], enabling early discharge from hospital if the    | • Risk minimization for other viral outbreaks is recommended, e.g., compliance of HCW      |
|                   |    patient can be safe and well-supported at home.                                                                                             | with seasonal influenza vaccination.                                                        |
| HSCT-related       | • Consideration within the MDTs.                                                                                                                | • Methods for communication between recipients, family members, and HCW such a            |
| factors           | • Potential recipients should self-quarantine at home for 14 days and be swabbed                                                              | video calls should be supported.                                                           |
|                   | • Although in a general HSCT context consideration of a modified mobilization procedure, such G-CSF alone, may be appropriate to avoid immunosuppression [22]. |                                                                                           |
| Key factors                                                                 | Recommendations                                                                                     | Remarks                                                                                                                                                                                                 |
|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| [20] (ideally within the 48 h and by molecular testing) prior to mobilization | Potential recipients should not be transferred to the transplant ward and should not                | in most AD protocols mobilization, the additional use of Cy provides additional disease control and may prevent disease flares. Cryopreservation is recommended.                                               |
| and transplant [20, 22].                                                  | commence conditioning until a negative swab result has been reported.                               | • Treatment in a clinical study, if available, should always be considered.                                                                                                                             |
| • In case when potential recipient tests positive for SARS-CoV-2, any     | In patients with mild or asymptomatic SARS-CoV-2 infection, deferral of at least 14 days after the first negative swab and symptoms clearance is required,        | • Immunosuppressed patients can have a prolonged SARS-CoV-2 shedding (weeks or months), and recurrence of symptoms has been reported in a patient who became severely immunocompromised. |
| transplant procedure (i.e., mobilization, collection, conditioning regimen) should be deferred [20]. | with an additional negative swab before the start of conditioning. Similar minimum timeframes are advised from the time of last contact with a known COVID-positive contact. Deferral of HSCT for at least 3 months is recommended in patients with moderate/severe COVID-19. | • In the post-transplant period, patients with fever should be swabbed for SARS-CoV-2 as part of the workup for investigation of infection [7, 22, 91, 95]. All swabs should include testing for other respiratory viral pathogens [19]. Discussion of treatment for SARS-CoV-2 infection is beyond the scope of these guidelines but should follow the latest evidence available in local treatment guidelines and the responsibility of an expert in treating SARS-CoV-2 infection, yet with involvement of AD expert as the leading experts for the immunosuppressive therapy. |

**Table 1 (continued)**

| AHSCT autologous hematopoietic stem cell transplantation, ADs autoimmune diseases, IPC infection prevention and control, PPE personal protective equipment, COVID Coronavirus disease, ICU intensive care unit, SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2, ATG anti-thymocyte globulin, GVHD graft-versus-host disease, HCW healthcare workers, Cy cyclophosphamide, MDTs multidisciplinary teams. |

*The protective role of active immunization might be limited in case of extensive circulation of viral strain with certain mutations.

COVID-19 Alert Level [23, 24]—Level 1 (very low): COVID-19 is not known to be present; Level 2 (low): infection is present but the number of cases and transmission rate are low (R [26] below 1, growth rate [26] below 0 and average weekly number of new cases of <20 per 100 000 population); Level 3 (moderate): infection is epidemic in the general population but transmission is not high or rising exponentially (R [26] below 1, growth rate [26] below 0 and average weekly number of new cases of 20 or more per 100 000 population); Level 4 (high): infection is epidemic in the general population; transmission is high or rising exponentially (R [26] above 1 and growth rate [26] above 0); Level 5 (very high): as Level 4 but with material risk of healthcare services being overwhelmed.

Post-transplant immune reconstitution [40, 96, 97] HSCT in ADs enables the regeneration of a new and non-disease-mediating immunity 40. The post-HSCT period is usually divided into the (1) pre-engraftment period (day 0 to days 15–45), (2) immediate post-engraftment period (engraftment to day +100), and (3) late post-engraftment period (days +100 to +365). In general, the neutrophil count recovers 2–3 weeks after HSCT. Recovery of B cells, natural killer (NK) cells, and CD8+ T cells is normally achieved in the first few weeks to 6 months, whereas CD4+ T-cell reconstitution is usually slower, where replenishment in adults may require up to 2 years post-HSCT [98, 99]. During the pre-engraftment period, the risk of opportunistic infection varies depending on the conditioning intensity (myeloablative or reduced intensity) [7, 40, 97]. In the post-engraftment period, the immune system is generally well-reconstituted and recovered in autologous HSCT recipients. Moreover, the degree of immune recovery (e.g, serum IgG concentrations > 4 g/L and CD4+ count >200 cells/μL) is associated with clinical outcomes, thus minimizing the risk of infection and healthcare attendance [40, 97, 100].
Considerations and recommendations for HSCT in neurologic autoimmune diseases

Immune-mediated neurological disorders (IMNDs) affect the central and the peripheral nervous systems resulting in a range of diseases including MS, neuromyelitis optica spectrum disorder (NMOSD), stiff person spectrum disorder, myasthenia gravis, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), autoimmune encephalopathies, and others [27].

The limited available evidence suggests that IMNDs and their treatments affect the susceptibility to or the severity of COVID-19. Patients with MS have increased risk of several types of infections compared to the general population particularly if they are on B-cell depleting therapies, such as rituximab [28, 29]. An earlier study from Italy reported on 232 MS patients from 38 centers with confirmed or suspected COVID-19 [30], did not show any significant association between previous DMT exposure and COVID-19 severity. Of those patients, 223 had mild, 4 had severe, and 6 had critical infection.

In a registry-based study of 347 patients with MS, age, EDSS score, and obesity were found to be independent risk factors for severe COVID-19, although no association was found between DMTs exposure and COVID-19 severity [31]. Another study suggested that the incidence of COVID-19 in MS patients was not more than that of the general population; transmission is high or rising exponentially (R [26] above 1 and growth rate [26] above 0); Level 5 (very high): as Level 4 but with material risk of healthcare services being overwhelmed.

Table 2 Summary of recommendations for autologous HSCT in neurologic autoimmune diseases in the time of COVID-19.

| Clinical priority [22] | Strength of evidence and recommendations [7] | Maximum COVID-19 Alert Level [23, 24] | Minimum setting required [7] |
|-----------------------|---------------------------------------------|---------------------------------------|-----------------------------|
| Highly active relapsing remitting MS failing DMTs | S/I | 1 | 4 | Registry |
| Aggressive MS not previously treated with a full course of DMT | CO/II | 1 | 3 | Registry |
| Progressive MS with active inflammatory component | CO/II | 2 | 2 | Registry |
| Progressive MS without active inflammatory component | GNR/III | N/A | N/A | N/A |
| Pediatric MS | CO/II | 1 | 3 | Registry |
| Treatment-resistant CIDP | CO/II | 2 | 2 | Registry |
| Treatment-resistant NMOSD | CO/II | 1 | 3 | Registry |
| Treatment-resistant SPSD | CO/II | 2 | 2 | Registry |
| Rare IMNDs and treatment-resistant systemic ADs | CO/II | 2 | 2 | Registry |

Strength of evidence of clinical efficacy [7]—Grade I: evidence from at least one well-executed randomized trial, Grade II: evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies, Grade III: evidence from opinions of respected authorities based on clinical experience. Recommendations[7]: S standard of care, CO clinical option, GNR generally not recommended.

Clinical priority (as determined by a relevant multidisciplinary team) [22]—1: high, delaying the HSCT procedure presents a high risk of disease progression, morbidity or mortality; 2: intermediate, there is a risk of disease progression or clinical complications if HSCT is delayed significantly, 3: low, the risk of disease progression or clinical complications if HSCT is significantly delayed is low.

COVID-19 Alert Level [23, 24]—Level 1 (very low): COVID-19 is not known to be present; Level 2 (low): infection is present but the number of cases and transmission rate are low (R [26] below 1, growth rate [26] below 0 and average weekly number of new cases of less than 20 per 100 000 population); Level 3 (moderate): infection is epidemic in the general population; transmission is not high or rising exponentially (R [26] below 1, growth rate [26] below 0 and average weekly number of new cases of more than 20 per 100 000 population); Level 4 (high): infection is epidemic in the general population; transmission is high or rising exponentially (R [26] above 1 and growth rate [26] above 0); Level 5 (very high): as Level 4 but with material risk of healthcare services being overwhelmed.

Setting [7]—prospective studies: randomized controlled trials (RCTs) and other clinical trials, including RAM-MS, STAR-MS, NET-MS, COAST, BEAT-MS, or prospective non-interventional studies (NIS) including OMST [6]. Registry: reporting data to EBMT registry (or equivalent international registry, e.g., CIBMTR).

HSCT autologous hematopoietic stem cell transplantation, MS multiple sclerosis, DMT disease modifying therapies, CIDP chronic inflammatory demyelinating polyradiculoneuropathy, NMOSD neuromyelitis optica spectrum disorder, SPSD stiff person spectrum disorder, IMNDs immune-mediated neurological disorders, ADs autoimmune diseases, CIBMTR Center for International Blood and Marrow Transplant Research, N/A not applicable.
had con

Global Data Sharing Initiative [34], clinician-reported data associated to alemtuzumab and cladribine treatments. In the MS major symptoms suggestive of COVID-19, mainly asso-
ciata

scores appear to be an MS-speci-

cial ventilation compared to all other DMTs. A number of phase II non-randomized trials have also shown its safety and ef-
cacy in treatment-

women aged 18 years or older and meeting the diagnostic criteria for rheumatic and musculoskeletal diseases, RMDs rheumatic and musculoskeletal diseases, SSc systemic sclerosis, SLE systemic lupus erythematosus, RA rheumatoid arthritis, JIA juvenile idiopathic arthritis, CIBMTR Center for International Blood and Marrow Transplant Research, N/A not applicable.

Strength of evidence of clinical efficacy [21]—Grade I: evidence from at least one well-executed randomised trial, Grade II: evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies, Grade III: evidence from opinions of respected authorities based on clinical experience. Recommendations [21]: S standard of care, CO clinical option, GNR generally not recommended.

Clinical priority (as determined by a relevant multidisciplinary team) [22]—(1) high, delaying the HSCT procedure presents a high risk of disease progression, morbidity, or mortality, (2) intermediate, there is risk of disease progression or clinical complications if HSCT is delayed significantly, (3) low, the risk of disease progression or clinical complications if HSCT is significantly delayed is low.

COVID-19 Alert Level [23, 24]—Level 1 (very low): COVID-19 is not known to be present; Level 2 (low): infection is present but the number of cases and transmission rate are low (R [26] below 1, growth rate [26] below 0 and average weekly number of new cases of <20 per 100,000 population); Level 3 (moderate): infection is epidemic in the general population but transmission is not high or rising exponentially (R [26] below 1, growth rate [26] below 0 and average weekly number of new cases of 20 or more per 100,000 population); Level 4 (high): infection is epidemic in the general population; transmission is high or rising exponentially (R [26] above 1 and growth rate [26] above 0); Level 5 (very high): as Level 4 but with material risk of healthcare services being overwhelmed.

Setting—prospective studies: randomized controlled trials (RCTs) and other clinical trials, or prospective non-interventional studies (NIS). Registry: reporting data to EBMT registry (or equivalent international registry, e.g., CIBMTR).

HSCT autologous hematopoietic stem cell transplantation, RMDs rheumatic and musculoskeletal diseases, SSc systemic sclerosis, SLE systemic lupus erythematosus, RA rheumatoid arthritis, JIA juvenile idiopathic arthritis, CIBMTR Center for International Blood and Marrow Transplant Research, N/A not applicable.

population, but the risk of hospitalization in these patients was higher than estimated for the disease [32]. The prevalence and impact of COVID-19 across Europe were assessed in the 399 patients with MS taking part in the RADAR-CNS programme [33]; of those 21.8% reported major symptoms suggestive of COVID-19, mainly associated to alemtuzumab and cladribine treatments. In the MS Global Data Sharing Initiative [34], clinician-reported data from 21 countries on 1540 patients in which 776 (50.4%) had confirmed COVID-19, and confirmed that older age, progressive MS, and higher EDSS scores were associ-

ated with higher frequencies of severe outcomes. Anti-CD20 DMTs, ocrelizumab, and rituximab were positively associated with hospital and ICU admission and the need for artificial ventilation compared to all other DMTs.

Therefore, patients with MS seem to be affected by the same risk factors as the general population, high EDSS scores appear to be an MS-specific risk factor and the majority of DMT treatment does not seem to be associated with a particularly poor prognosis.

Data related to other IMNDs are limited. CARE-MG registry reported worsening of myasthenic control requiring rescue therapy in the setting of COVID-19 in 36 of 91 patients. Complete recovery or discharge to home was reported in 39 (43%) patients whereas 22 (24%) patients died due to COVID-19 [35]. The clinical course and outcome of patients with COVID-19 and NMOSD seem to be variable [36–38] and also exacerbations of CIDP have been reported [39].

The use of autologous HSCT in the treatment of IMNDs is expanding and becoming increasingly evidence-based [7, 40–42]. Recently, the first phase III randomized controlled trial [41] in MS has demonstrated its efficacy in patients with active relapsing remitting disease failing standard DMTs. A number of phase II non-randomized trials have also shown its safety and efficacy in treatment-
resistant CIDP [43], SPS [44], and NMOSD [45], whilst definitive data are less readily available [7, 27, 42, 46]. The conditioning regimens usually employed in neurological ADs range from high-dose cyclophosphamide and the combination of BCNU, Etoposide, ARA-C and Melphalan, both associated with serotherapy with either anti-thymocyte globulin (ATG), rabbit or horse, or monoclonal antibodies targeted to lymphocyte subsets, such as alemtuzumab or rituximab [7]. The different intensity of the regimens results in corresponding degrees of immunosuppression. In any case, with any type of regimen, a patient would be considered at high risk in case of SARS-CoV-2 infection [39, 47, 48].

The most appropriate choice of conditioning regimen should be addressed for each individual patient, after a careful assessment of diagnosis, disease stage, and overall clinical condition at baseline. Therefore the use of this treatment should be restricted to patients with a clear risk/benefit ratio based on treatment-resistant disease entity, according to the level of evidence for autologous HSCT.
efficacy in this particular disease, defined clinical priorities [22], and local COVID-19 Alert Levels (Table 2) [23].

All treatment-related decisions should be made by MDTs and patients should be treated within clinical trials if available or as part of well-defined registry studies to allow longitudinal collection of efficacy and safety data of the various treatment options. Patients with severe comorbidities known to be associated with poor COVID-19 outcomes should not be considered for HSCT during the pandemic.

Considerations and recommendations for HSCT in rheumatic diseases

The COVID-19 pandemic has considerable impact on different aspects of the management of patients with rheumatic and musculoskeletal diseases (RMDs). Chronic suppression of immune functions, both with synthetic or biologic DMTs, is the cornerstone of treatment in those indications [49–53]. Alongside, autologous HSCT has emerged as an established treatment option for some indications where effective drug therapy is not available, even in the biological era. Particularly, three randomized controlled trials (ASSIST, ASTIS and SCOT) have demonstrated the superiority of HSCT compared to monthly IV bolus of cyclophosphamide in patients with early rapidly progressive SSc in terms of event-free and overall survival, improvement of skin fibrosis, and evidence for benefits on pulmonary function [54–56]. SSc is now considered a standard indication for autologous HSCT [21, 57]. Other diseases in which the use of HSCT is supported by evidence from non-randomized controlled trials and is regarded as treatment option include systemic lupus erythematosus (SLE), vasculitides, polymyositis/dermatomyositis, and both rheumatoid and juvenile idiopathic arthritis [21].

Chronic use of DMTs may be associated with an increased risk of infection-related morbidity and mortality in RMDs [58, 59]. However, despite this notion, accumulating data from larger case series, national and international registries suggest that patients with RMDs neither have an increased risk of developing SARS-CoV-2 infection nor do they have a worse prognosis compared to the general population [60–63]. Only RMD patients on high-dose corticosteroids, but not methotrexate and biologic DMTs, non-steroidal anti-inflammatory drugs and antimarial drugs had a higher risk of SARS-CoV-2 infection or hospitalization [60–62, 64, 65]. However, recent data from the French RMD COVID-19 cohort including 694 adults indicated for the first time an increased risk for severe infection in patients receiving mycophenolate mofetil or rituximab [65]. Conversely, RMD patients on a background tumor necrosis factor (TNF) inhibitor had an adjusted 60% reduction in risk of hospitalization [62], and recently the FDA authorized the emergency use of baricitinib in certain hospitalized patients with COVID-19. Overall, risk factors for more severe COVID-19 in RMD patients include older age and comorbid conditions [65]. The only rheumatic disease diagnosis with odds of hospitalization significantly different from other RMDs seems to be SLE. Data from the Global Rheumatology Alliance (GRA) Registry indicated that lupus patients were at 80% increased risk of hospitalization [62]. Patients with SSc are largely underrepresented in international COVID-19 registries and their risk during COVID-19 pandemic is evaluated incompletely. Nevertheless, first single-center studies and personal observations indicated that incidence of confirmed SARS-CoV-2 infections was low and severe complications, including death, were rare. Only one death and 11 infections related to COVID-19 have been reported among 526 Italian SSc patients [66]. Overall, 390 (10.5%) died out of 3729 RMD patients included in the GRA physician COVID-19 registry [67]. Provisional recommendations for the management of RMD patients were published based on expert consensus from international task forces of the EULAR [68] and ACR [69]. Both recommendations strongly suggest continuing the DMTs treatment in RMD patients who do not have suspected or confirmed COVID-19. In addition, management of RMD patients following SARS-CoV-2 exposure and documented infection, and the use of immunosuppressive drugs, should be multidisciplinary, discouraging the off-label use of DMTs outside the context of clinical trials [68].

The use of HSCT in RMDs must be carefully weighed against the risk of the procedure, should be based on the strengths of evidence per indication and ideally performed as part of a clinical study. Particularly, access to intensive care medicine and resources for appropriate screening procedures, including the recommended cardiopulmonary screening assessments for SSc patients should be available [63]. Appropriate candidates for autologous HSCT during COVID-19 pandemic should therefore be those with high clinical priority, reflected by life-threatening and otherwise refractory courses of the disease, i.e., unresponsiveness or lack of tolerability to standard or alternative DMTs therapies, in which delaying the HSCT procedure may be associated with a high risk of disease progression, morbidity, or mortality (Table 3).

In summary, continuation with autologous HSCT for RMD patients during COVID-19 pandemic can be recommended, presupposing a risk adjustment according to local SARS-CoV-2 infection rates and medical resources, strengths of evidence of HSCT per indication, lack of alternative therapies and adoption of a prioritization process, delivering HSCT based on clinical urgency.
Considerations and recommendations for gastrointestinal diseases

In gastroenterology, the main area application of autologous HSCT has been in inflammatory bowel diseases (IBDs), particularly Crohn’s disease (CD) [9, 10]. Although the COVID-19 pandemic has led to substantial concerns for patients with IBDs, as a high proportion of them receive immuno-suppressive therapies [70], similar COVID-19 rates and no increased mortality have been reported as compared to the general population [71–73]. Corticosteroids may pose significant risk to IBD patients with COVID-19 [72]. In addition, recent results demonstrated that thiopurine treatment, either as monotherapy or in combination with TNF inhibitors, was associated with increased risk of severe COVID-19 [74, 75]. Anti-TNF therapy, anti-integrins, and anti-IL12/23 have not been associated with increased mortality [71, 73].

Recommendations in the management of IBD suggest that medical treatments should be re-evaluated in SARS-CoV-2-positive patients and corticosteroid therapy should be re-evaluated regardless of symptoms. A goal should be to treat active disease and maintain remission, while adopting the same protective measures as the general population. In addition, nonurgent surgeries and endoscopic procedures should be postponed [76]. The use of autologous HSCT should be restricted to patients with a clear risk/benefit ratio, according to strengths of evidence of HSCT per indication, clinical priorities [22], and local COVID-19 Alert Levels (Table 4) [23].

Considerations and recommendations for pediatric population

Only limited data are available on risks of HSCTs in pediatric ADs [76, 77] during the COVID-19 outbreak [30]. There was no significant association between previous DMTs and COVID-19 severity in children [77]. Therefore, children post-HSCT for ADs usually have a story of intensive immunosuppression and are at potential risk during the COVID-19 outbreak [13]. A rapid global response for children with cancer was published [78]. Feasibility of HSCT for pediatric ADs during the COVID-19 outbreak was demonstrated, provided there is the availability of hospital resources. Therefore, during the pandemic outbreak, the indication for HSCT in children with ADs must be restricted to patients with a clear risk/benefit ratio [78]. In children, it could be severe “malignant” forms of neurological ADs, severe progressive systemic diseases, CD, and immune cytopenias.

Considering the better outcomes of HSCT in children during the COVID-19 outbreak, a less restrictive approach could be applied [79]. As patients with pediatric ADs are mostly transplanted in the same departments as patients with malignancies, priority must be given to these children followed by patients with severe ADs [78]. Centers must be very careful using immunotherapy such as ATG as well as monoclonal antibodies [80]. Preferably, only one parent or guardian, identified as the primary caregiver, and with a recent negative swab for SARS-CoV-2, may be present in the room with a pediatric patient, requesting a visitor exception to the local care team.

Special recommendations for vaccinations

The response to the pandemic includes efforts to develop safe and effective vaccines [81] with an unprecedented urgency and large-scale investment of human and financial resources [82]. All the main arms of the immune response are involved in the generation of protective immunity to SARS-CoV-2: innate immune responses as well as adaptive immunity, including humoral and T-cell responses. SARS-CoV-2 has the ability to suppress innate immune responses [81]. Antibody responses to the Coronavirus spike (S) protein develop during COVID-19 infection in the majority of subjects [83]. Emerging evidence indicates that T-cell mediated immunity may be critically important against COVID-19 [81, 84, 85]. Collectively, these data suggest that individuals with compromised innate or adaptive immunity may not only be at risk of more severe COVID-19 disease but also at higher risk of lacking protective immunity from infection or vaccination.

The guidelines of the 2017 European Conference on Infections in Leukaemia provide general recommendations for vaccination in HSCT recipients [86]. Recently, EBMT has provided specific COVID-19 vaccine recommendations [20]. The vaccines against COVID-19 currently approved for use in EU, following review by EMA, can be grouped in two platforms: recombinant replication-defective viral-vectorized vaccines and mRNA-based vaccines [20, 81]. No evidence is published to inform us on the safety and efficacy of any COVID-19 vaccine in HSCT recipients. Based on inferences from other current evidence [20, 87, 88], we suggest that live-attenuated COVID-19 vaccines or vectored by live-attenuated viruses should be contraindicated in HSCT recipients. For all other COVID-19 vaccine types, we suggest that vaccination could be considered from 3 months after HSCT. Follow-up after vaccination is therefore important. Continued precautions should be taken based on the pandemic situation in the society [20, 89]. Individuals vaccinated before HSCT will almost certainly lose protective immunity after HSCT and may require revaccination. Clinical trials in HSCT patients are needed to establish the safety and immune response of vaccines against COVID-19.
Data reporting

Routine data reporting should continue into the EBMT registry, and, alongside, we strongly encourage center participation in the ongoing EBMT-wide prospective survey on the impact of COVID-19 in HSCT recipients [19].

Clinical trials

With respect to clinical trials, special consideration should be made by trial management groups, oversight committees, sponsors, and local principal investigators in the best interests of patients in relation to the trial protocol and recruitment during the pandemic [90]. Even so, clinical trials provide a means of actively monitoring the impact of the COVID-19 pandemic on outcomes.

Quality and accreditation

In EBMT, quality in HSCT and cellular therapy is assured through JACIE accreditation, which has been central to EBMT recommendations for HSCT in ADs [8]. Elsewhere, equivalent quality assurance is provided by FACT, based on harmonized FACT—JACIE standards. Therefore, we recommend that HSCT procedure should only be carried out in experienced centers with an active accreditation by JACIE or FACT [7].

As the situation may change over time, the current statements should be reviewed at regular intervals and read in conjunction with general EBMT guidelines [20] on the COVID-19 pandemic, which are continually updated [20], along with local and national guidance.

Conclusions

Although current evidence suggests that HSCT is a valid treatment option in the management of selected patients with ADs, its intense immunosuppression could expose to increased risks during the current COVID-19 pandemic [13, 47, 48]. Therefore, the use of autologous HSCT during the pandemic should be restricted to AD patients with a clear risk/benefit ratio based on disease entity, level of evidence for HSCT efficacy in this setting, defined clinical priorities [22], and local COVID-19 Alert Levels (Tables 2–4) [23]. All patients being considered for HSCT should be discussed in appropriately constituted MDT meetings (including transplant and disease specialists) with individual assessment of risks and benefits of HSCT as best as possible and considering the current and predicted

### Table 4: Summary of recommendations for autologous HSCT in IBDs in the time of COVID-19.

|                      | Strength of evidence and recommendations [21] | Clinical priority [22] | Maximum COVID-19 Alert level [23, 24] | Minimum setting required [8] |
|----------------------|-----------------------------------------------|------------------------|----------------------------------------|------------------------------|
| Crohn’s disease      | CO/II                                         | 1                      | 3                                      | Registry                    |
|                      |                                               | 2                      | 2                                      |                              |
| RCD II               | CO/II                                         | 1                      | 3                                      | Registry                    |
|                      |                                               | 2                      | 2                                      |                              |

Strength of evidence of clinical efficacy [21]—Grade I: evidence from at least one well-executed randomised trial, Grade II: evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies, Grade III: evidence from opinions of respected authorities based on clinical experience. Recommendations [21]: S standard of care, CO Clinical option, GNR generally not recommended.

Clinical priority (as determined by a relevant multidisciplinary team) [22]—(1) high, delaying the HSCT procedure presents a high risk of disease progression, morbidity or mortality, (2) intermediate, there is risk of disease progression or clinical complications if HSCT is delayed significantly, (3) low, the risk of disease progression or clinical complications if HSCT is significantly delayed is low.

COVID-19 Alert Level [23, 24]—Level 1 (very low): COVID-19 is not known to be present; Level 2 (low): infection is present but the number of cases and transmission rate are low (R [26] below 1, growth rate [26] below 0 and average weekly number of new cases of <20 per 100,000 population); Level 3 (moderate): infection is epidemic in the general population but transmission is not high or rising exponentially (R [26] below 1, growth rate [26] below 0 and average weekly number of new cases of 20 or more per 100,000 population); Level 4 (high): infection is epidemic in the general population; transmission is high or rising exponentially (R [26] above 1 and growth rate [26] above 0); Level 5 (very high): as Level 4 but with material risk of healthcare services being overwhelmed.

Setting—prospective studies: randomized controlled trials (RCTs) and other clinical trials, or prospective non-interventional studies (NIS). Registry: reporting data to EBMT registry (or equivalent international registry, e.g., CIBMTR).

HSCT autologous hematopoietic stem cell transplantation, IBD inflammatory bowel diseases, RCD refractory celiac disease, CIBMTR Center for International Blood and Marrow Transplant Research, N/A not applicable.
geographical variations in the pandemic related to transplant center, referral center, and home locality of the patient (which may be different). HSCT programs must be ready to rapidly adapt to change following the course of the pandemic. Updates of this COVID-19-specific guidance will be incorporated within updates to recommendations from EBMT for specific ADs.

Acknowledgements The authors contribute this article on behalf of Autoimmune Diseases Working Party (ADWP) of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT (JACIE). We acknowledge the ADWP for support in working party activities and outputs; Infectious Diseases Working Party (IDWP) and Pediatric Working Party (PWP); and all EBMT member centers and their clinicians, data managers, and patients for their essential contributions to the EBMT registry. The EBMT Autoimmune Diseases Working Party (ADWP) included: Raffaella Greco (Chair), Tobias Alexander (Secretary), John Snowden (Chair April 2016 to May 2020), Manuela Badoglio (Study Coordinator), Myriam Labopin (Statistician) and actively participating clinicians; Mario Abinun, Shashikant Apte, Renate Arnold, Claudia Boglione (EBMT Nurses Group representative), Charlotte Brierley, Joachim Burman, Cristina Castilla-Llorente, Nichola Cooper, Giulia Daghia, Thomas Daikeler, Nicoletta del Papa, Jeska de Vries-Bouwstra, Dominique Farge, Jurgen Finke, Hans Hagglund, Chris Hawkey, Jörg Hennes, Falk Hiepe, Helen Jessop (EBMT Nurses Group representative), David Kiely, Majid Kazmi, Kirill Kirgizov, Ellen Kramer (also representing the EBMT Patient Advocacy Committee), Gianluigi Mancardi, Zora Marjanovic, Roland Martin, Thierry Martin, David Ma, John Moore, Paul Miller, Paolo Muraro, Maria-Carolina Oliveira, Alexey Polushin, Francesco Onida, Belinda Simoes, Mathieu Puyade, Igor Resnick, Elena Ricart, Montserrat Rovira, Riccardo Saccardi, Muhammad Saif, Joanna Sakellari, Basil Sharrack, Emilian Snarski, Hans Ulrich Scherer, Claudia Sossa, Barbara Withers, Nicolo Wulffraat, Elena Zaccara. The EBMT JACIE Committee included: Kim Orchard (Chair), John Snowden, Riccardo Saccardi, Franco Bambi, Fermin Sanchez-Guijo, Nina Worel. The EBMT Paediatric Diseases Working Party included: Persis Amrolia, Marc Ansari, Adriana Balduzzi, Selim Corbacioglu (Chair), Arnaud Dalassier, Jean-Hugues Dalle, Cristina Heredia Diaz, Tobias Feuchtinger, Franco Locatelli, Giovanna Lucchini, Jaques-Emmanuel Gilimard, Marta Gonzalez Vincent, Rupert Handgretinger, Katharina Kleinschmidt (Secretary), Anita Lawitschka, Antonio Perez Martinez, Christina Peters, Vanderson Rocha, Annalisa Ruggeri, Petter Sedlaczek, Peter Svec, Jacek Toporski, and Akif Yesilipek. The EBMT Infectious Diseases Working Party (IDWP) included: Iris Agreiter, Mahmoud Aljurf, Ana Sofia Almeida, Dina Averbuch (Secretary), Sherif Badawy, Gregorx Basak, Amer Bejtinaheh, Haydee Bernhard, Roni Bitterman, Ola Blennow, Nicole Bijlevens, Alessandro Busca, Jun Cai, Mansour Ceesay, Simone Cesaro, Benhur Cetin, Teresa Daniela Clerici, Patrizia Comoli, Catherine Cordonnier, Consoelo Corti, Elisabeth de Kont, Rafael de la Camara (Chair), Joanna Drezd-Sokowska, Jaroslav Dybko, Hermann Einsele, Dan Engelbard, Idefonso Espigado, Jose-Maria Fernandez-Navarro, Irene Garcia-cadenas, Lidia Gil, Marta Gonzalez Vincent, Andreas Groll, Hans Hirsch, Stefan Klein, William Kruger, Lalit Kumar, Arjan Lankster, Amanda Le Bougeois, Caroline Lindehans, Per Ljungman, Jose Lopez, Maria Teresa Lupo Stanghellini, Nuria Martinez-Cibrian, Rodrigo Martino, Michael Mclinger, Varun Mehra, Patentia Mensah-Glansonska, Malgorzata Mikulska, Ilana Oren, Amit Patel, Mehrdad Payandeht, Katia Perrucco, Anna Pieczonka, Agnieszka Piekarzka, Jose Luiz Pinana, Miguel Perales, Regina Pirumova, Christine Robin, Montserrat Rovira, Martin Schmidt-Hieber, Laura Scott, Liat Shargian, Peter Shaw, Emilnar Snarski, Maria Stoumoulos, Ian Styczynski, Maria Suarez-Lledo, Daniel Teschner, Gloria Tridello, Gauran Trikha, Rosario Varela, Lourdes Vazquez, Anke Verlinden, Sebastian Voigt, Jacek Wachowiak, Kate Ward, Alienor Xhaard, Nabil Yafour.

Author contributions The authorship group includes active representatives of the ADWP, IDWP, PWP, and JACIE, including representatives from the EBMT, Nurses Group and Patient Advocacy Committee. RG, JAS, and TA led on concept, design, coordination, and data analysis, provided expert and analytical feedback and were involved in reviewing, writing, and editing the manuscript. All authors contributed to the acquisition, analysis of data and interpretation of information, writing sections of the manuscript. BS led the section on immune-mediated neurological diseases and devised the risk-level assessment. PAM made substantial contributions to aspects on immune reconstitution and vaccinations. The experts on this panel are active members of the EBMT and national links for the main countries contributing to the registry. All co-authors were involved in drafting the paper, revising it critically, and approval of the submitted and final versions. The EBMT provided resources via the working parties, data office, and registry. Other than EBMT support there is no funding body supporting these guidelines, commercial, or otherwise.

Compliance with ethical standards

Conflict of interest RG discloses honoraria for speaking from educational events supported by Biotest, Pfizer, and Magenta. JAS declares honoraria for speaking at educational events supported by Jazz, Gilead, Janssen, Mallinckrodt, Actelion, an advisory board by MEDAC, and is a member of IDMC for a trial supported by Kiadis Pharma. TA declares travel grants from Neovii and study support from Amgen. PAM discloses travel support and speaker honoraria from unrestricted educational activities organized by Novartis, Bayer HealthCare, Bayer Pharma, Biogen Idec, Merck-Serono, and Sanofi Aventis. He also discloses consulting to Magenta Therapeutics and Jasper Therapeutics. PL reports grants and other from MSD, outside the submitted work. The other authors declare no competing interests.

Ethics approval This review, guideline and recommendations, and registry data analysis were approved, led, and supported by the Autoimmune Diseases Working Party (ADWP) and have been endorsed by the Pediatric (PWP) and Infectious Disease Working Parties (IDWP), Nurses Group (NG) of the European Society for Blood and Marrow Transplantation (EBMT), and the Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and EBMT (JACIE).

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