Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation

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Graft-versus-host disease (GVHD) is a major factor contributing to mortality and morbidity after allogeneic stem-cell transplantation. Because of the small number of results from well designed, large-scale, clinical studies there is considerable variability in the prevention and treatment of GVHD worldwide. In 2014, to standardise treatment approaches the European Society of Blood and Marrow Transplantation published recommendations on the management of GVHD in the setting of HLA-identical sibling or unrelated donor transplantation in adult patients with haematological malignancies. Here we update these recommendations including the results of study published after 2014. Evidence was searched in three steps: first, a widespread scan of published trials, meta-analyses, and systematic reviews; second, expert opinion was added for specific issues following several rounds of debate; and third, a refined search to target debated or rapidly updating issues. On the basis of this evidence and the 2014 recommendations, five members of the EBMT Transplant Complications Working Party created 38 statements on GVHD prophylaxis, drug management, and treatment of acute and chronic GVHD. Subsequently, they created the EBMT GVHD management recommendation expert panel by recruiting 20 experts with expertise in GVHD management. An email-based, two-round Delphi panel approach was used to manage the consensus. Modified National Comprehensive Cancer Network categories for evidence and consensus were applied to the approved statements. We reached 100% consensus for 29 recommendations and 95% consensus for nine recommendations. Key updates to these recommendations include a broader use of rabbit anti-T-cell globulin; lower steroid doses for the management of grade 2 acute GVHD with isolated skin or upper gastrointestinal tract manifestations; fluticasone, azithromycin, and montelukast should be used for bronchiolitis obliterans syndrome; and the addition of newer treatment options for resteroid-refractory acute and chronic GVHD. In addition, we discuss specific aspects of GVHD prophylaxis and management in the setting of haploidentical transplantation and in paediatric patients, but no formal recommendations on those procedures have been provided in this Review. The European Society of Blood and Marrow Transplantation proposes to use these recommendations as a basis for the routine management of GVHD during stem-cell transplantation.

Introduction

One of the main clinical challenges of allogeneic stem-cell transplantation is its inherent treatment-associated morbidity and mortality, with graft-versus-host disease (GVHD) as a major contributing factor. Because of the small number of results from well designed, large-scale, clinical studies, there is considerable variability in the management approaches for GVHD worldwide. No standard clinical definitions exist detailing how to measure response to treatment and outcome in patients with GVHD, which is a major hurdle to the effective implementation of useful interventional studies and prevents progress in the field.

To address this medical need and to harmonise clinical practice, a European Society of Blood and Marrow Transplantation (EBMT) and European Leukaemia Net working group published recommendations on the management of GVHD in 2014.[1] A follow-up study showed that these recommendations influenced clinical standard procedures in EBMT centres.[2] However, clinical implementation is still suboptimal and the follow-up study identified some weaknesses in the previous recommendations.[2] Since then, important studies have been published that have influenced the management of GVHD prophylaxis and therapy. Thus, EBMT decided to update the 2014 GVHD recommendations. Like the previous guidelines,[1] the present recommendations exclusively apply for the most common allogeneic transplant settings. We focus on allogeneic stem-cell transplantation in adult patients with standard risk haematological malignant disease using an HLA-matched sibling or unrelated donor and bone marrow or peripheral blood as stem-cell source. There are divergent views concerning paediatric transplantations, haploidentical transplantations, and mismatched unrelated donor transplantations—for which recommendations on GVHD management have not be provided; however, specific aspects of GVHD management in the haploidentical setting and in paediatric transplantation have been included in this Review.

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Methods

Consensus approach

As a first step, the EBMT Transplant Complications Working Party (TCWP) created a task force consisting of five senior haematologists with expertise in the management of GVHD: TR (Coordinator of first version on GVHD recommendations), MM (Expert in in evidence-based medicine and the consensus processes), NK (EBMT President), GB (TCWP chairperson), and OP (TCWP GVHD subcommittee chairperson). The task force created 38 statements to guide standard GVHD prevention and treatment practice after transplantations from a matched sibling (including 9/10 HLA-matched donors) or a matched unrelated donor (10/10 HLA-matched) at a standard risk of malignant disease. The task force created the EBMT GVHD managment recommendation expert panel by recruiting 20 European GVHD management experts. The choice of who to recruit to the panel was made based on their role within this field in Europe, reflected by their contributions to the field, such as publications, presentations at conferences, and other research activities. In addition, the task force recruited GVHD experts from several countries and centres to increase the general applicability of the recommendations.

The 38 statements developed by the task force underwent a consensus process according to the Delphi consensus protocols. Multiple iterative rounds (two rounds for the present study) of questioning are required, comments on each statement being collected by a methodologist (MM). Consensus was achieved when 80% of the panellists agreed with a statement. Statements that did not achieve consensus were modified and resubmitted in further rounds until a consensus was reached. The recommendations that did not reach a final consensus were cancelled. Consensus for each statement after first and second Delphi round and the reasons for disagreement are included in the appendix (pp 1–3).

Evidence review

Evidence was searched in three steps: the first step was a widespread scan of published trials, meta-analyses, and systematic reviews; the second step was to add the opinions from the experts for each of the debated issues; and the third step was a refined search to target highly debated or rapidly updating issues.

During the first search, in June, 2018, the methodologist enquired EMBASE, PubMed, and the Cochrane Library (appendix p 4). The search was aimed at identifying published randomised trials on GVHD prophylaxis and treatment, and newly published clinical trials, meta-analyses, and systematic reviews on this topic. Studies addressing non-malignant conditions and those specifically focusing on children were excluded. The retrieved evidence was connected to each of the primarily proposed recommendations (first round): the panellists were provided with references and synthetic issues, including the study design, outcomes assessed, and substantial differences and consistency between the studies.

The panellists were asked to provide additional evidence for each statement by specifying the study design (ie, large retrospective studies) and level of evidence. In March, 2019, the methodologist (MM) performed a second search of evidence for any debated recommendations (eg, for implementation of post-transplantation cyclophosphamide as a preparative regimen) to support an evidence-focused discussion.

Categories of evidence and consensus

The National Comprehensive Cancer Network classification of evidence and consensus was modified replacing category 3 recommendations (not approved) by category 2C recommendations (not directly supported by evidence). Recommendations are therefore classified into one of four groups. Category 1 recommendations are based upon high-level evidence (eg, randomised trials or meta-analyses) and achieved 100% consensus. Category 2A recommendations are based upon lower-level evidence (eg, smaller randomised trials) and had 100% consensus. Category 2B recommendations are based upon lower-level evidence and 80–100% consensus after the second round of comments. Category 2C recommendations are not supported by direct evidence, rather included in published and adopted clinical protocols.

Definitions

To define acute GVHD during the consensus process, we used the criteria established by the Mount Sinai Acute GvHD International Consortium (MAGIC) group.[3–5] To define chronic GVHD, we used the National Institutes of Health (NIH) 2014 criteria.[4–6] Steroid resistance and dependence in acute GVHD and chronic GVHD was defined as described in the EBMT–NIH–Center for International Blood and Marrow Transplant Research (CIBMTR) Task Force position statement.[5] Paediatric patients were defined by a maximum age of 17 years.

Consensus recommendations

Based on previous EBMT GVHD management recommendations[1] and on all available relevant published data, the task force designed 38 recommendation statements. These statements were sent to the expert panel. After two rounds of commenting and editing, the panel achieved either 95% or 100% consensus for every recommendation. 95% consensus indicates that 19 out of 20 panellists agreed to the given statement. The following sections summarise some prominent and new aspects of the recommendations.

Prophylaxis of GVHD

The updated recommendations suggest that rabbit anti-thymocyte globulin or anti-T-lymphocyte globulin (ATG) should be used for GVHD prophylaxis in patients undergoing matched-unrelated donor allogeneic stem-cell

transplantation and in patients undergoing matched-related donor allogeneic stem-cell transplantation at a high risk of GVHD. The recommendations supporting a broader use of ATG are based on high-level evidence publications that show reduced chronic GVHD in matched-unrelated donor transplantation[7–9] and in matched-related donor allogeneic stem-cell transplantation (table 1).[9,24–26]

The panellists regarded prophylaxis with calcineurin inhibitors ciclosporin or tacrolimus as roughly equivalent in GVHD. This recommendation is based on solid evidence from randomised trials and several retrospective controlled studies showing similar GVHD and survival outcomes with tacrolimus (plus methotrexate) versus ciclosporin (plus methotrexate).[13–19] However, the task force and the panellists acknowledge that the frequency of ciclosporin use in Europe was historically higher and a smaller fraction of centres currently uses tacrolimus.

On the basis of high-level evidence, the panel recommended the use of methotrexate in combination with a calcineurin inhibitor in patients who received myeloablative conditioning before allogeneic transplantation to avoid or mitigate GVHD. Meta-analyses and retrospective studies reported higher grade 3–4 GVHD prevalence following prophylaxis with mycophenolate mofetil and calcineurin inhibitors compared with treatment with methotrexate and a calcineurin inhibitor.[20,23,27] Of note, similar GVHD 2–4 and survival outcomes were reported following prophylaxis with a regimen including methotrexate and a calcineurin inhibitor compared with a mycophenolate mofetil and a calcineurin inhibitor regimen.[20–22] By contrast, the evidence level for recommendations on mycophenolate mofetil versus methotrexate in dose-reduced conditioning or non-myeloablative conditioning is low. Comparative evidence for mycophenolate mofetil versus methotrexate is absent in this setting. However, according to common practice the panel recommends a mycophenolate mofetil regimen in patients receiving non-myeloablative conditioning and dose-reduced conditioning.

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See **Online** for appendix

Drug management during prophylaxis of GVHD

The level of evidence for each recommendation on drug management is low, mainly because comparative analyses are absent. However, on the basis of common

	Percentage approval (%)	Evidence and consensus category	Comments
Patients undergoing matched related donor or matched unrelated donor allogeneic transplant should receive GVHD prophylaxis with a calcineurin inhibitor plus an antimetabolite*	100	1	Reduction of acute GVHD with methotrexate plus ciclosporin *vs* ciclosporin alone in several trials[10–12]
Tacrolimus or ciclosporin can be used in the setting of sibling or matched unrelated donor transplants. The choice should be made based on experience at the centre (eg, ciclosporin is the standard calcineurin inhibitor adopted in most European centres)	100	1	Similar GVHD and survival outcomes are achieved with tacrolimus plus methotrexate *vs* ciclosporin plus methotrexate in randomised trials and several retrospective, controlled studies[13–19]
Methotrexate is the recommended antimetabolite for patients receiving MAC	100	1	Meta-analyses and retrospective studies reported similar grade 2–4 GVHD prevalence and survival rates with methotrexate plus calcineurin inhibitor *vs* mycophenolate plus calcineurin inhibitor;[20–23] however, higher prevalence of grade 3–4 GVHD were reported with mycophenolate[20–23]
Mycophenolate mofetil can be used instead of methotrexate for patients receiving MAC in case of contraindications to methotrexate or for those patients who need rapid engraftment (eg, those with aspergillosis)	100	2A	Meta-analyses and retrospective studies reported similar grade 2–4 GVHD prevalence and survival rates with methotrexate plus calcineurin inhibitor *vs* mycophenolate mofetil plus calcineurin inhibitor;[20–23] however, higher prevalence of grade 3–4 GVHD were reported with mycophenolate mofetil[20–23]
Mycophenolate mofetil is the recommended antimetabolite for patients receiving non-MAC conditioning and RIC	100	2A	Common practice based on the initial developed protocol.[10] Comparative evidence for mycophenolate mofetil *vs* methotrexate in the non-myeloablative conditioning setting does not exist
rATG (Thymoglobulin [Sanofi, Paris, France] or Grafalon [Neovii, St Gallen, Switzerland]) is recommended for preventing GVHD in patients undergoing matched unrelated donor allogeneic stem-cell transplantation†	100	1	The incidence and severity of chronic GVHD was reduced in clinical trials in allogeneic stem-cell transplant recipients treated with rATG or Grafalon as part of the conditioning regimen[7–9]
rATG can also be recommended for preventing GVHD in patients undergoing MRD allogeneic peripheral blood allogeneic stem-cell transplantation; rATG is recommended for patients who are at a high risk of GVHD	95	2B	Reduction of chronic GVHD in randomised studies and retrospective analyses[9,24–26]

Evidence category assessed by modified National Comprehensive Cancer Network criteria. GVHD=graft versus host disease. MAC=myeloablative conditioning. RIC=reduced-intensity conditioning. rATG=rabbit anti-thymocyte globulin. *In children (<18 years) many centres use calcineurin inhibitor as a single agent; this is discussed in the paediatric transplantation section. †In children (<18 years) many centres use rATG in matched unrelated donor allogeneic stem-cell transplant; this is discussed in the paediatric transplantation section.

Table 1: **Recommendations for the prophylaxis of GVHD**

practice and expert opinion the panel reached a high level of consensus regarding recommendations on drug management.

An area of controversial discussion in allogeneic stem-cell transplantation is the target serum concentration of calcineurin inhibitor. Therefore, we provide formal recommendations for ciclosporin, which is preferentially used in Europe as GVHD prophylaxis, based on retrospective studies showing that ciclosporin concentrations in the first 4 weeks after the transplant were associated with an increased frequency of acute GVHD.[28–31] We recommend careful monitoring with a standard laboratory assay and a ciclosporin target serum concentration of 200–300 µg/L in the first 4 weeks after the transplant to efficiently prevent acute GVHD. Subsequently, ciclosporin target concentrations should be balanced between GVHD and relapse risks. In standard GVHD risk HLA-matched transplantation, the recommended ciclosporin target concentration range until 3 months after transplantation is 100–200 µg/L; this target concentration exclusively refers to a two daily dose administration setting. When a continuously infusion schedule is used, higher target ciclosporin concentrations are needed (table 2).[19,40]

Another area of controversy is the schedule of calcineurin inhibitor and mycophenolate mofetil tapering. In standard risk recipients of allogeneic stem-cell transplantation with haematological malignancies, improved outcomes were observed in patients who completed calcineurin inhibitor tapering by 6 months, reflecting the current practice in Europe. However, early calcineurin inhibitor tapering (eg, by 60 days) improved outcomes in patients at a high-risk of leukaemia.[34,35,41] Therefore, we recommend that the duration of ciclosporin or tacrolimus prophylaxis be 6 months. Dose tapering of these drugs needs to be adjusted according to each patient's risk of relapse, T-cell chimerism, and the presence or absence of GVHD. The dose is tapered from 3 months onwards if no GVHD is present. Faster tapering is recommended if the risk of relapse is high and if a bone marrow graft is provided, especially if complete donor chimerism is reported. The dose is not tapered while signs of acute or chronic GVHD, with the exception of mild cutaneous acute GVHD, are present. In cases of persistent disease or relapse and no GVHD, ciclosporin or tacrolimus dose can be tapered slowly in small increments. We do not recommend the use of a combination of calcineurin inhibitors because not enough clinical data are available to support this approach. Similarly, clinical data and experience are not sufficient to recommend the use sirolimus as part of the prophylactic regimen.

The most common duration of mycophenolate mofetil prophylaxis is about 30 days in matched-related donors and 2–3 months in matched-unrelated donor transplants; however, treatment duration needs to be adapted according to the patient's risk of relapse and of developing GVHD (ie, sex mismatch and dose of infused T cells). In cases of persistent disease or relapse and no GVHD, an earlier stop of mycophenolate mofetil could be considered.

Finally, the type, dose, and duration of ATG treatment is a matter of ongoing controversy in allogeneic stem-cell transplantation because they have not been sufficiently addressed in clinical studies. On the basis of available evidence, we recommend either Grafalon (Neovii, St Gallen, Switzerland) or Thymoglobulin (Sanofi, Paris, France) as GVHD prophylaxis.[7,8,24,25,38] Regarding the total dose, we recommend ATG (Grafalon) in adults with 30 mg/kg for matched-related donor and 60 mg/kg for matched-unrelated donor transplants. However, use of lower doses (15–30 mg/kg) has been reported to be effective in non-randomised studies. The recommended total dose of ATG ranges from 2·5–5 mg/kg in matched-related donor to 4·5–6 mg/kg in matched-unrelated donor transplants—higher doses are associated with a higher risk of infectious complications.[9,38,39] The timing and duration of ATG administration might also affect its efficacy. However, because no reliable study data exist, we refrained from giving formal recommendations on the timing of ATG administration.

Treatment of acute GVHD

A randomised controlled trial, published in 2017, showed more infections and no advantage regarding development of grade 3–4 acute GVHD when grade 1 acute GVHD was treated.[42] This panel acknowledges these important results and recommends initiation of systemic treatment exclusively for acute GVHD of grade 2 or higher (table 3). Furthermore, the panel has added the recommendation that grade 2 acute GVHD with isolated skin or upper gastrointestinal tract manifestations can be treated with lower steroid doses, such as 1 mg/kg per day methylprednisolone or prednisone. A retrospective analysis and a randomised trial reported the efficacy of a 1·0 mg/kg per day prednisone dose in this context.[42,46] The randomised trial,[45] published in 2015, assigned 102 patients with grade 2 acute GVHD with isolated skin or upper gastrointestinal tract manifestations to receive either 0·5 or 1·0 mg/kg prednisone; the trial showed that 0·5 mg/kg prednisone doses were as effective as 1·0 mg/kg at inducing remission.[45]

An obvious matter of debate in the community is the choice of second-line therapy in cases of steroid-resistance GVHD. However, not enough data from well designed studies are available to be able to compare the efficacies of the different second-line treatment options. Consequently, no standard second-line treatment exists for acute GVHD, with available second-line options including alemtuzumab, α1-antitripsin, basiliximab, cellular therapies (eg, mesenchymal cells and regulatory T cells), daclizumab, extra-corporal photopheresis, faecal microbiota transplantation, JAK inhibitors

	Percentage approval (%)	Evidence and consensus category	Comments
Ciclosporin regimen is usually initiated on the day before the infusion of the graft. The drug is given in two daily doses or as a 24 h infusion. The recommended initial dose is 3 mg/kg per day intravenously	95	2B	Ciclosporin is historically started 1 day before the transplant; however, an earlier start could potentially reduce acute GVHD[12,28,32]
Ciclosporin concentration should be carefully monitored. When using the two daily doses regimen the target concentration in the first weeks post-transplant should be 200–300 µg/L to efficiently prevent acute GVHD	100	2A	Retrospective studies showed that higher ciclosporin concentrations in the first weeks post-transplant were associated with a lower frequency of acute GVHD[28–31]
Subsequently ciclosporin target concentrations should be balanced between the risk of developing GVHD and relapsing. In most patients, the recommended ciclosporin target concentration until 3 months post-transplantation is 100–200 µg/L*	95	2C	This recommendation is based on common practice and expert opinion
Ciclosporin concentrations should be monitored with whole blood sampling for 12 h after a dose, sampling from the lines used for ciclosporin infusion should be avoided	100	2A	Minimal variability in ciclosporin blood concentration exists between 4 h and 12 h[33]
Ciclosporin doses should be adapted to avoid toxicity (renal insufficiency, microangiopathy, and neurological problems) according to institutional guidelines	100	2C	This recommendation is based on common practice and expert opinion
The standard duration of ciclosporin prophylaxis is 6 months; however, it needs to be adjusted to the risk of relapse, chimerism, and presence or absence of GVHD. If no GVHD is reported, ciclosporin dose is tapered from 4 months until the regimen is stopped. Faster tapering is recommended if the risk of relapse is high and a bone marrow graft is provided, especially if complete chimerism is reported. The dose is not tapered if there are signs of acute GVHD or chronic GVHD with the exception of mild cutaneous acute GVHD. In cases of persistent disease or relapse and no GVHD, ciclosporin dose can be carefully tapered†	100	2A	Earlier ciclosporin tapering is feasible in patients with high risk leukemia.[34,35] One study reported very early cyclosporin tapering starting at day 30 with the aim to discontinue ciclosporin by day 60.[34]
Methotrexate is given as a bolus intravenous injection. In MAC transplants initial methotrexate dose is 15 mg/m² given on the first day after the transplant; however, lower doses of methotrexate have also been reported in reduced-intensity transplants. In MAC transplants, two additional doses of 10 mg/m² are given on day 3 and 6 after the transplant, an additional dose at 11 days after transplant can be administered. Lower doses are usually administered in reduced-intensity transplants on 3 and 6 days after the transplant	100	2A	This recommendation was developed on the basis of standard practice based on a seminal randomised trial[12]
On the basis of expert opinion, we recommend leucovorin rescue after prophylactically given methotrexate; however, no definite evidence supports leucovorin rescue for preventing methotrexate toxicity or enhancing methotrexate efficacy	100	2A	This recommendation is based on standard practice and expert opinion
The leucovorin regimen is usually started 24 h after each dose of methotrexate; on the first day after the transplant the leucovorin should be three 15 mg doses every 6 h, the dose should then increase to four 15 mg doses every 6 h after methotrexate doses 3, 6, and 11 days after the transplant; leucovorin should be administered by intravenous injection	100	2A	This recommendation is based on standard practice and expert opinion
Mycophenolate mofetil should be administered intravenously or orally in three 10–15 mg/kg daily doses; the dose should be adapted according to toxicity	100	2A	Mycophenolate mofetil half-life is >12 h; therefore, at least three daily doses are necessary. Three 15 mg/kg doses were most effective in prevention of GVHD[17,36,37]
Mycophenolate mofetil administration is usually started 1 day after the transplant, and the prophylaxis regimen most commonly lasts about 30 days in matched related donor transplants and 2–3 months in matched unrelated donor transplants; however, duration needs to be adapted to risk of relapse and of GVHD (eg, regimen length is dependent on sex mismatch and dose of infused T cells); in case of persistent disease or relapse and no GVHD, an earlier stop of mycophenolate mofetil can be considered	95	2B	This recommendation is based on standard practice and expert opinion
The recommended total dose of rATG Grafalon (Neovii, St Gallen, Switzerland) in adults is 30 mg/kg for matched related donor and 60 mg/kg for matched unrelated donor transplants; however, use of lower doses (15–30 mg/kg) has been shown to be effective in non-randomised studies.	95	2B	Clinical studies assessing the efficacy of ATG as GVHD prophylaxis have not addressed optimal dosing. Therefore, the dosing recommendations are largely based on expert opinions;[7,8,24,25,38] however, the optimal dosing has not been addressed in those studies
The recommended total dose of rATG Thymoglobulin (Sanofi, Paris, France) ranges from 2·5 to 5 mg/kg in matched related donor and 4·5 to 6 mg/kg in matched unrelated donor transplants: higher doses are associated with a higher risk of infectious complications	100	2A	This recommendation is based on evidence from randomised[9] and non-randomised studies[38,39]

Evidence category by modified National Comprehensive Cancer Network criteria. GVHD=graft-versus-host disease. MAC=myeloablative conditioning. rATG=rabbit anti-thymocyte globulin. *In children (<18 years) with malignant diseases many centres discontinue calcineurin inhibitors until 100 after the transplant. Discussed in the paediatric transplantation section. † In children (<18 years) with allogeneic stem-cell transplant for non-malignant diseases a longer duration of calcineurin inhibitor is often applied. Discussed in the paediatric transplantation section.

Table 2: **Recommendations for drug management during prophylaxis of GVHD**

	Percentage approval (%)	Evidence and consensus category	Comments
The decision to initiate treatment for acute GVHD is based on clinical signs; biopsies before initiation of treatment are recommended, but the decision to treat should not be delayed until after histology reporting	100	2C	This recommendation is based on standard practice and expert opinion
Systemic treatment is initiated for grade 2 or higher acute GVHD	100	1	More infections and no advantage regarding development of grade 3–4 acute GVHD when grade 1 acute GVHD was treated in a randomised trial[42]
First-line treatment of acute GVHD is methylprednisolone with an initial dose of 2 mg/kg per day; prednisone in a dose of 2·0–2·5 mg/kg per day is regarded as equivalent to methylprednisolone to the 2 mg/kg per day dose	100	1	A meta-analysis of 7 randomised trials reported a 14% decrease in the survival of patients receiving additional immunomodulating agents (eg, mycophenolate mofetil, ATG, infliximab, and anti-IL2 antibody) besides steroids;[43] higher doses of methylprednisolone (10 mg/kg per day) did not improve outcomes when compared with standard 2 mg/kg per day doses[44]
Grade 2 acute GVHD with isolated skin or upper gastrointestinal tract manifestations can be treated with lower steroid doses, such as 1 mg/kg per day methylprednisolone or prednisone	100	1	Retrospective analyses and a randomised trial showed efficacy of 1·0 mg/kg per day prednisone[45,46]
No reduction in the prednisolone dose is recommended during the first 7 days after the transplant, but parenteral steroids can be stopped, and oral steroids can be used until all signs of acute GVHD have disappeared. Tapering of the dose is a slow, response dependent process: in cases of complete response, steroid dose should be gradually reduced to 10% of the initial dose over a period of approximately 4 weeks. In cases of steroid-resistant GVHD, long-term use of steroids might cause major complications; therefore, second-line therapy is recommended	100	1	The recommendations are largely based on expert opinion; one small randomised trial found no statistically significant differences between rapid steroid and slower steroid taper[47]
Topical steroids are sufficient for grade 1 skin acute GVHD; in cases of more advanced disease, steroids can be used in addition to systemic treatment.	100	2C	This recommendation is based on standard practice and expert opinion
Non-absorbable oral steroids, such as budesonide (9 mg per day) or oral beclomethasone (1·3–2·0 mg four times a day), can be given in addition to systemic corticosteroids as treatment of gastrointestinal acute GVHD	100	1	Two small randomised trials in patients with systemic steroids for gastrointestinal acute GVHD tested beclomethasone 8 mg/day *vs* placebo and found favourable treatment responses and reduced mortality[48,49]
A second-line treatment for acute GVHD is recommended if corticosteroid resistance or dependence occurs	100	2C	This recommendation is based on standard practice and expert opinion
There is no standard second-line treatment for acute GVHD. Current practice is to prescribe one of the following drugs: alemtuzumab, α1-antitripsin, basiliximab, cellular therapies (eg, mesenchymal cells and regulatory T-cells) daclizumab, extracorporeal photopheresis, faecal microbiota transplantation, JAK inhibitors (eg, ruxulotinib which is FDA approved), mycophenolate mofetil, methotrexate, pentostatin, rATG, sirolimus, or vedolizumab; for second-line treatment of acute GVHD, centres should follow their institutional guidelines, and patients should be treated in clinical trials when possible	100	2A	Not enough data exist from well designed studies available to be able to compare the efficacy of different second-line options

GVHD=graft-versus-host disease. ATG=anti-T-cell globulin. FDA=US Food and Drug Administration. rATG=rabbit anti-thymocyte globulin.

Table 3: **Recommendations for the treatment of acute GVHD treatment**

(ruxulitinib is approved for use by the US Food and Drug Administration [FDA]), mycophenolate mofetil, methotrexate, pentostatin, rabbit anti-thymocyte globulin, sirolimus, and vedolizumab. For second-line treatment of acute GVHD, centres should follow their institutional guidelines. Patients should be treated in clinical trials when possible.

Two small randomised trials recruited patients with acute GVHD with gastrointestinal involvement who were receiving systemic steroids; favourable treatment responses and reduced mortality was reported in patients receiving 8 mg beclomethasone per day compared with placebo.[48,49] In the absence of respective clinical data, the panellists consider budesonide, which is more easily available in Europe, as equally effective as beclomethasone. As a result, we recommend the use of non-absorbable oral steroids, such as budesonide (9 mg per day) or oral beclomethasone (1·3–2·0 mg four times a day), in addition to systemic corticosteroids for acute GVHD with gastrointestinal involvement.

Treatment of chronic GVHD

The first-line treatment for newly diagnosed chronic GVHD is steroids. Randomised trials that evaluated the addition of other agents (azathioprine, ciclosporin, thalidomide, mycophenolate mofetil, or hydroxychloroquine) to a prednisone regimen did not show a clinically significant benefit in patients with standard

	Percentage approval (%)	Evidence and consensus category	Comments
The decision to start treatment for chronic GVHD is based on symptom type, severity (moderate or severe according to NIH classifications), and dynamics of progression in the context of other relevant variables, such as disease risk, chimerism, and minimal residual disease results	100	2C	This recommendation is based on standard practice and expert opinion
The first-line treatment of newly diagnosed chronic GVHD is steroids	100	2A	Randomised trials evaluated the addition of other agents (azathioprine, thalidomide, mycophenolate mofetil, hydroxychloroquine, and ciclosporin) to prednisone regimen, but a clinically meaningful benefit for patients with standard risk (according to NIH classification) chronic GVHD was reported[50–52]
In severe chronic GVHD the primary addition of another immunosuppressant to reduce steroid use is a valuable option	95	2C	This recommendation is based on expert opinion
The first-choice corticosteroid is prednisone taken orally at a dose of 1 mg/kg	100	2C	This recommendation is based on standard practice and expert opinion
If a patient is already receiving corticosteroid treatment (eg, following treatment of acute GVHD), the dose of corticosteroid can be increased (if it is <1 mg/kg) and an alternative strategy is usually applied, such as the administration of calcineurin inhibitor or extracorporeal photopheresis	95	2C	This recommendation is based on standard practice and expert opinion
If the patient is already receiving full-dose corticosteroid and ciclosporin at the time of chronic GVHD onset, no standard treatment is available: continuation of corticosteroid and ciclosporin with optimal supportive measures is a valid option, but changing the immunosuppressive therapy is often done; these patients should be treated in clinical trials, if possible	100	2C	This recommendation is based on expert opinion
As an initial treatment of bronchiolitis obliterans syndrome the fluticasone montelukast regimen is recommended in combination with systemic steroids; however, prolonged use of azithromycin after resolution of bronchiolitis obliterans syndrome is not recommended because of the possibility of increased risk of relapse	100	2A	There is encouraging data from non-randomised studies supporting the therapeutic use of FAM regimen (inhaled fluticasone 440 µg twice a day, azithromycin 250 mg three times a week, and montelukast 10 mg once a day);[53–55] by contrast, when used as prophylaxis in patients undergoing allogeneic stem-cell transplantation, azithromycin (250 mg three times a week) was associated with increased relapse[56]
The time needed to preliminarily assess the efficacy of first-line treatment of chronic GVHD is at least 1 month	100	2C	This recommendation is based on expert opinion
There is no standard second-line treatment for chronic GVHD: centres should follow their institutional guidelines and enrol patients in trials whenever possible; the most common components of second-line treatment for chronic GVHD, used in addition to corticosteroids, are calcineurin inhibitors, extracorporeal photopheresis, ibrutinib (which is FDA approved), JAK inhibitors, mycophenolate mofetil, rituximab, mTOR inhibitors, pentostatin, proteasome inhibitors, and TKI	95	2B	No data are available that allow a comparison of the efficacy of different second-line options to be done

GVHD=graft-versus-host disease. NIH=US National Institutes of Health. FAM=fluticasone, azithromycin, montelukast. FDA= US Food and Drug Administration. TKI=tyrosine kinase inhibitors.

Table 4: **Recommendations for the treatment of chronic GVHD**

risk chronic GVHD (according to NIH classification).[50–52] Despite these results in standard risk chronic GVHD, the panellists agreed that the primary addition of another immunosuppressant to reduce steroid use is a valuable option in patients with severe chronic GVHD (table 4).

Similarly to acute GVHD, there are no data available allowing the comparison of the efficacy of different second-line treatment options for chronic GVHD, and no indirect comparisons are possible. Therefore, no standard second-line treatment for chronic GVHD exists; centres should follow their institutional guidelines and enrol patients in trials as often as possible possible. The most widely used components of second-line treatment for chronic GVHD, in addition to corticosteroids, are calcineurin inhibitors, extracorporeal photopheresis, ibrutinib (which is approved by the FDA), JAK inhibitors, mycophenolate mofetil, rituximab, mammalian target of rapamycin (mTOR) inhibitors, pentostatin, proteasome inhibitors, and tyrosine kinase inhibitors.

This Review contains a recommendation to use a combination of fluticasone, azithromycin, and montelukast, the so-called FAM regimen, as initial treatment of bronchiolitis obliterans syndrome in combination with systemic steroid. A meta-analysis and retrospective trials support the use of the FAM regimen (inhaled fluticasone 440 µg twice daily, azithromycin 250 mg three times weekly, and montelukast 10 mg daily).[53–55]

Discussion

On the basis of new publications and changes in clinical practice over the past 5 years, the 2019 recommendations contain several changes when compared with the 2014 recommendations. However, for some of the updated

recommendations conflicting publications exist. One example is that the 2019 recommendations support a broader use of ATG, which is based on a number of publications—including well done randomised studies that show reduced chronic GVHD prevalence in matched-unrelated donor transplantation[7–9] and in matched-related allogeneic stem-cell transplantation.[9,24–26] The evidence supporting ATG use is stronger when peripheral blood stem-cells are used as the graft source, whereas the data for transplants using bone marrow as graft source are less solid. Soiffer and colleagues[57] reported an increased proportion of patients with relapse in those treated with ATG or alemtuzumab during dose-reduced conditioning compared with those who were not treated with ATG.[57] We conclude that the clinical effect of ATG is probably dependent on the patient's risk of relapse, the medication dose and schedule, and the choice of ATG type. Furthermore, the 2019 recommendations advise the use of the FAM regimen in combination with systemic steroids for the initial treatment of bronchiolitis obliterans syndrome.[53–55] Bergeron and colleagues[56] reported increased relapse prevalence when azithromycin (250 mg three times a week) was used as prophylaxis of bronchiolitis obliterans syndrome, compared with placebo. The additional immunosuppressive medication—used as prophylaxis— appeared to increased relapse (compared with placebo) prevalence in high-risk patients. These findings teach us to be cautious when prescribing the FAM regimen in the prophylactic setting, and the panel believes that these data should not lead to the omission of FAM in patients with clinically overt bronchiolitis obliterans syndrome. This view is reflected by considerable changes in the practical use of the FAM regimen, with many EBMT centres already using the regimen in a bronchiolitis obliterans syndrome prophylaxis.

In the setting of steroid-refractory acute and chronic GVHD, the panel has added novel agents to the available treatment options, such as JAK inhibitors (eg, ruxolitinib which is approved by the FDA),[58,59] vedolizumab,[60,61] and ibrutinib (which is approved by the FDA),[62,63] which have shown efficacy in this setting. However, none of the newer options has been compared with existing second-line treatment options. Several large clinical trials are assigning patients with steroid-refractory acute GVHD and chronic GVHD to receive ruxolitinib, vedolizumab, or itacitinib: the results of these ongoing studies are awaited to prioritise second-line options. The inclusion of patients with steroid-refractory acute and chronic GVHD in clinical trials is the preferred treatment option whenever possible.

We have not updated recommendations for GVHD management in cord blood transplantation here. This decision was made on the basis of the considerable decline in the use of cord blood transplantation in Europe. None of the experts in the panel had considerable experience with cord blood transplantation in the past 5 years. However, we have summarised the available literature (appendix pp 5–8). Despite a worldwide tendency to use post-transplant cyclophosphamide in the setting of matched-related donor and matched-unrelated donor allogeneic stem-cell transplantation, we have not provided formal recommendations on this procedure. Short-term safety of post-transplant cyclophosphamide (with a usual regimen of 50 mg/kg 3 and 4 days post-transplant) was proven in the bone marrow and peripheral blood stem-cell setting, provided that double immunosuppression is maintained in the peripheral blood stem-cells (appendix pp 5–8).[64–66] However, no long-term outcome data is available and the task force considered the available evidence too preliminary to include a recommendation for or against the use of post-transplant cyclophosphamide in this situation. Randomised studies assessing the long-term outcome are needed before drawing definite conclusions on this regimen in matched-related donor and matched-unrelated donor allogeneic stem-cell transplantation.

Regarding haploidentical transplantation, there are generally no differences between the diagnosis and treatment of acute and chronic GVHD following haploidentical grafts compared with HLA-matched transplantation. However, specific considerations apply to prophylaxis of GVHD following a haploidentical graft (appendix pp 5–8). Two distinct approaches exist for human leukocyte antigen haplotype mismatched transplants (haploidentical): T-deplete and T-replete. T-deplete approaches use ex-vivo CD34-selected or ex-vivo T-cell depleted grafts allowing adjunction of immune cells.[67,68] T-deplete approaches often use ATG in the conditioning, but no further immunosuppression for preventing GVHD.

By contrast, T-replete approaches using non-manipulated bone marrow or peripheral blood grafts require effective in-vivo GVHD prophylaxis. There are two major protocols: one is based on ATG (the Beijing protocol), the other is based on post-transplantation cyclophosphamide (the Baltimore protocol). The Beijing protocol uses high-dose rabbit ATG (Thymoglobulin 10 mg/kg), mycophenolate, ciclosporin, and methotrexate, with non-manipulated bone marrow and peripheral blood cells.[69] A modification of this protocol included granulocyte colony-stimulating factor primed bone marrow and basiliximab as an anti-CD25 antibody, which caused in-vivo allo-depletion.[70] The Baltimore protocol uses high-dose post-transplantation cyclophosphamide on the third and fourth day after the transplant and ciclosporin plus mycophenolate mofetil on the fifth day to modulate T-cell activity. The original stem-cell source was non-manipulated bone marrow, with excellent control of acute and chronic GVHD.[71] Many investigators are now using non-manipulated peripheral blood grafts instead of bone marrow, with comparable survival outcomes, although these blood grafts are associated with an increased risk of grade 3–4 acute GVHD.[72] Substitution of the calcineurin inhibitor with sirolimus in the post-transplantation cyclophosphamide setting is also

Search strategy and selection criteria

Data for these 2019 updated recommendations were identified by searches of embase, PubMed, and Cochrane Library, and references from relevant articles using the search terms "GVHD" and "Graft-versus-Host Disease". Only articles published in English between Jan 1, 2009, and Feb 28, 2019, were included.

promising, but this technique is still considered experimental.[73]

The management of paediatric GVHD is similar to the management of the disease in adults, but some specific differences exist (tables 1–4). The available literature and further comments are given in the appendix (pp 5–8). Regarding acute GVHD prophylaxis and treatment we refer to the results of a survey done on behalf of the EBMT Paediatric Diseases Working Party on paediatric GVHD prophylaxis and first-line treatment of acute GVHD (A Lawitschka, Medical University Vienna, Vienna, Austria, personal communication) that revealed some important differences between paediatric and adult practices. High consensus was achieved regarding GVHD prophylaxis after myeloablative conditioning in matched-related donor: single agent ciclosporin or use of ciclosporin in combination with methotrexate (table 1). Additional ATG and T-cell depletion for matched-unrelated donor (and mismatched donor) allogeneic stem-cell transplantation were used by most specialists (table 1). Furthermore, the higher risk of relapse in malignant diseases affected GVHD prophylaxis, with earlier withdrawal of ciclosporin. About 70% of centres stopped ciclosporin before or at 100 days after transplant in paediatric patients with malignant diseases. In patients who receive allogeneic stem-cell transplantation for non-malignant indications, a distinctly longer duration of ciclosporin was used (table 2). Of note, the indication for paediatric allogeneic stem-cell transplantation is more heterogeneous with up to 40–50% of patients receiving transplants for non-malignant diseases. In this regard, patients cannot benefit from the graft-versus-leukaemia effect and therefore merit a more aggressive approach to GVHD prevention.

Conclusions

Key updates to the 2014 recommendations[1] include a broader use of ATG; grade 2 acute GVHD with isolated skin or upper gastrointestinal tract manifestations should be treated with lower steroid doses; the FAM regimen should be used to treat bronchiolitis obliterans syndrome; and the addition of drugs to the available treatment options for steroid-refractory acute and chronic GVHD.

We were able to reach a high level of consensus (≥95%) for each of the included recommendations. This was because of the good evidence base for a subset of recommendations (11 of 28) and the consistency of the shared clinical practices for most recommendations. The high consensus is a valid basis for clinical implementation of the recommendations given. However, as shown in a survey after the release of the previous guidelines, there are difficulties to expect regarding the standardised clinical implementation and the adherence to these recommendations in daily practice.[2] An audit will follow the dissemination of the recommendations, to check adherence and verify the barriers to their adoption.

Contributors

All authors contributed substantially to the manuscript. OP, MMa, TR, NK, and GWB designed the statements. AL wrote the section regarding paediatric disease. All remaining authors were panel members and approved or disapproved the statements across different rounds of discussions. OP drafted the Review and all authors critically revised and approved the manuscript. All authors agree that they are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

Declaration of interests

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