

MANAGEMENT OF POST-TRANSPLANT EBV-ASSOCIATED COMPLICATIONS: ECIL-11 UPDATE

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PREVIOUS ECIL RECOMMENDATIONS ON EBV

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GUIDELINES

Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia

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REVIEW ARTICLE

Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines

Jan Styczynski,¹ Walter van der Velden,² Christopher P. Fox,³ Dan Engelhard,⁴ Rafael de la Camara,⁵ Catherine Cordonnier,⁶ and Per Ljungman⁷ on behalf of the Sixth European Conference on Infections in Leukemia, a joint venture of the Infectious Diseases Working Party of the European Society of Blood and Marrow Transplantation (EBMT-IDWP), the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG), the International Immunocompromised Host Society (ICHS) and the European Leukemia Net (ELN)

Haematologica 2016
Volume 101(7):803-811

2026 Update is based mainly on publications from period: September 2015 – September 2026

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DEFINITIONS: DIAGNOSIS (1)

- **Primary EBV infection**
 - EBV detected by nucleic acid or serologically documented in a previously EBV-seronegative patient
- **EBV reactivation**
 - detection of EBV (EBV DNA, EBV RNA, antigens) in a patient with evidence of previous EBV infection (usually in the form of positive EBV antibodies)



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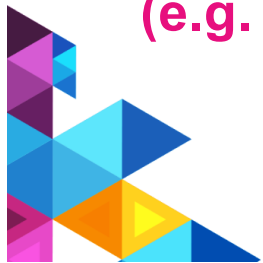


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DEFINITIONS: DIAGNOSIS (2)

- **Proven EBV-associated PTLD**
 - Histopathological evidence of a lymphoproliferative disorder consistent with PTLD, with detection of EBV nucleic acids or EBV-encoded proteins in a tissue specimen, together with symptoms and/or signs from the affected organ
- **Probable EBV-associated PTLD**
 - Clinical and radiological (PET-CT preferred) evidence of PTLD accompanied by significant increase of EBV DNA-emia (at least 1 log10 increase per week), but without histopathological confirmation.
- These definitions do not apply to other EBV-associated end-organ disease (e.g. EBV encephalitis)



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Definitions of Refractory EBV DNA-emia and Disease in Transplant Recipients

Definition	Description
Refractory EBV-DNA-emia	(1) EBV-DNA-emia that increases or persists (≤ 1 log ₁₀ decrease in EBV DNA levels) after at least 2 weeks of appropriate therapy; (2) Failure to achieve complete EBV DNA clearance after 4 weeks of therapy (*)
Refractory EBV disease (PTLD)	(1) Lack of significant response or disease progression, confirmed by imaging, after at least 2-4 weeks of therapy; (2) Evidence of residual disease (by imaging or biopsy; histopathological confirmation preferred) after 4-8 weeks of therapy
Relapse (recurrent) EBV-DNA-emia/disease	Evidence of recurrent EBV-DNA-emia/disease diagnosed after complete resolution/remission of a prior episode.

(*) **PERSISTENT VIRAL LOAD:** EBV viral load at the same level or higher than the peak viral load within 1 week but <1 log₁₀ increase in EBV DNA titers done in the same laboratory and with the same assay. Persistent EBV DNA titers <1000 IU/mL, and in particular detected but not quantifiable, should not be considered refractory EBV-DNA-emia.



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INCIDENCE OF EBV-DNA-emia after HCT

45

Studies reporting EBV DNAemia /
reactivation
2015–Apr 2026

~10,700

Total patients included in EBV DNAemia
studies

3.7–100%

Reported EBV reactivation range

~43%

Median reported EBV DNAemia incidence

- Marked heterogeneity across studies
- Highest incidence in high-risk allo-HCT (>50%)
- PTCy-based platforms without additional T-cell depletion: lower incidence
- In vivo T cell depletion increases the risk, particularly with ATG

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INCIDENCE OF EBV-PTLD AFTER HCT

36

Studies reporting
EBV-PTLD data

~76,400

Patients included in
EBV-PTLD analyses

0–5%

EBV-PTLD incidence in most
contemporary cohorts

~3.2%

Median reported
EBV-PTLD incidence

- EBV-PTLD remains uncommon: generally <5%,
- Large registries report approximately 1% incidence
- Most cases occur early (2-4 months) after HCT

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LETERMIVIR IMPACT IN EBV-ASSOCIATED COMPLICATIONS AFTER HCT

10

Studies identified on letermovir and EBV outcomes (all but one of the studies are from China)

~3,700

Patients included in LET-exposed/control cohorts

Inconsistency

Variable effect on EBV DNAemia across available studies

No proven causal link

Between letermovir and EBV-PTLD

- Evidence remains limited and heterogeneous
- Most cases occur early (2-4 months) after HCT
- Increased EBV signal mainly in high-risk HCT settings
- Current evidence does not support letermovir as an independent risk factor

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FACTORS ASSOCIATED WITH EBV-PTLD RISK AFTER ALLO-HCT

TIMING / CONTEXT	FACTORS ASSOCIATED WITH INCREASED RISK	LOWER-RISK / POTENTIALLY PROTECTIVE FACTORS	UNCLEAR / INSUFFICIENT EVIDENCE
Pre-transplant / transplant-related	• T-cell depletion, either <i>in vivo</i> or <i>ex vivo</i> • ATG/Alemtuzumab exposure, especially higher cumulative dose • EBV donor/recipient serostatus mismatch, especially D+/R- • Cord blood transplantation • Unrelated or HLA-mismatched donor, including haploidentical HCT • Reduced-intensity / non-myeloablative conditioning, especially with CBT or serotherapy • Older age, particularly >50 years • Second HCT	• PTCy-based platforms without additional ATG or ex vivo T-cell depletion • Rituximab exposure within 6 months before HCT • Matched family donor HCT without additional risk factors	• Patient ethnicity • EBV genetic strains
Post-transplant	• Severe acute or chronic GvHD requiring intensive immunosuppression • High or rapidly rising EBV-DNAemia • Delayed CD4+ and/or CD8+ T-cell reconstitution • CMV reactivation	• CD4+ T-cell count >50/μL at day 30 • Sirolimus use for GvHD prophylaxis	• LMV prophylaxis

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DIAGNOSIS OF EBV-DNA-emia: TECHNIQUES

- Prospective monitoring of EBV-DNA by quantitative PCR **in blood** is recommended after high-risk (Allu) **and standard risk (Bllu)** allo-HCT (except MFD patients not receiving T-cell depletion)
- **Monitoring of EBV-DNA load for a given patient should be performed using the same specimen type (plasma or whole blood) and QNAT platform (Alltu)**

- High risk (MFD with at least one risk factor, MUD/MMUD, alternative donors including CBT).
- Standard risk: MFD-HCT, PTCy-HCT
- Low risk (auto-HCT)

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SURVEILLANCE FOR EBV-DNA-EMIA

- Individualised monitoring plans informed by risk factors for EBV-PTLD are recommended
- Start to monitor no later than 4 weeks after HCT (Allu)
- Frequency:
 - screening (in EBV-DNA negative pts) testing is recommended **at least** once a week (Bllu)
 - in patients with rising EBV-DNA more frequent sampling **is recommended (Allu)**
- End of screening: at least up to 4 months after HCT in high risk patients; longer screening/monitoring is recommended in patients considered to have poor T-cell reconstitution **(at day +100, i.e. CD3<500/ μ l, CD4<200/ μ l, CD8<150/ μ l)** or in those who experienced an early EBV reactivation **or received alemtuzumab or ATG during conditioning (Bllu).**



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Uhlin M, Wikell H, Sundin M, et al. Risk factors for EBV-related post-transplant lymphoproliferative disease after allogeneic HSCT. Haematologica. 2014;99(2):346–352; Styczynski et al. Prevention of EBV-related lymphoproliferative disorders after HSCT: guidelines from the Infectious Diseases Working Party of EBMT. Haematologica. 2016;101(7):803–811; Tichadou T, et al. EBV serostatus and risk of PTLD after HSCT in children. Blood. 2023;142:443–445.

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DIAGNOSIS OF EBV-PTLD

- A histopathological diagnosis is strongly recommended and required for a diagnosis of proven PTLD (Allu). If a biopsy cannot be performed, a diagnosis of probable PTLD can be made based on strong clinical and radiological evidence together with a high or rapidly increasing EBV-DNA viral load.
- EBV-DNA-emia alone does not support a diagnosis of PTLD.
- Publications should always give information on how EBV-PTLD was diagnosed.
- Confirmation of EBV in tissue biopsy requires detection of viral antigens and/or in situ hybridization for the EBER transcripts.



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EBV CELL-MEDIATED IMMUNITY: SUMMARY OF FINDINGS

- 4 cohort observational studies, 208 patients, no RCTs
- Variability of study designs, assays and cutoffs
- Preliminary data suggest some value of a positive EBV CMI test for predicting:
 - High EBV viral loads
 - Necessity of anti-CD20 MoAbs* usebut quality and strength of evidence is very low
- EBV Elispot is the established monitoring standard in EBV-specific T-cell therapy trials and correlates with DNAemia clearance

() anti-CD20 MoAbs – almost exclusively: RITUXIMAB*

- EBV-CMI: Meij et al., 2003; Clave et al., 2004; D'Aveni et al., 2011; Chiereghin et al., 2019
- Immune monitoring after EBV T-cell therapy: Burns et al., 2019; Comoli et al., 2007; Schweitzer et al., OFID, 2026; Icheva et al., 2013; Leen et al., Blood, 2013

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EBV CELL-MEDIATED IMMUNITY: ECIL-11 RECOMMENDATION

- In allo-HCT recipients with EBV-DNA-emia, monitoring of EBV-specific CMI by ELISpot may hold some predictive value in identifying patients likely to self-clear viremia and defer anti-CD20 MoAbs use.
- However, due to insufficient evidence limited to small observational cohorts, no recommendation can be made regarding the routine use of EBV-specific CMI monitoring to guide anti-CD20 MoAbs use in this setting.



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TWO STRATEGIES FOR PREVENTION OF EBV-PTLD

- Prevention of EBV-PTLD can be achieved by using anti-CD20 antibodies either as **PROPHYLAXIS** and/or as **PREEMPTIVE THERAPY** (All hu).
- These strategies have not been compared in a randomized controlled trial, but both have been shown to reduce the risk of PTLD, especially in higher-risk patients.
- Each center can use either strategy depending on patients risk factors and centers preferences.



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PROPHYLAXIS IN ALLO-HCT RECIPIENTS

7+2a

Studies reporting anti-EBV prophylaxis
+2 abstracts
2012–Apr 2026

~1000

Total patients included in prophylaxis
studies

significant

Reduction of EBV reactivation range

significant

Reduction of PTLT rates , analyzed in 3(=1a)
studies

6 retrospective, 3 prospective (non-randomized) studies

All studies: historical group

Significant decrease EBV-DNA-emia in all studies

Significant decrease EBV-PTLD analyzed in 3 studies and 1 abstract

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RECOMMENDATIONS FOR EBV PROPHYLAXIS AFTER ALLO-HCT

- In selected patients at high risk for EBV-PTLD:
 - B-cell depletion with prophylactic anti-CD20 MoAbs should be considered (BIIh).
 - Prophylactic use of EBV-specific T-cells can be considered, if available (CIIu).
- Prophylaxis strategy does not apply to negative D/R EBV-IgG.
- There are no data to support any impact of antiviral drugs on the development of EBV-PTLD. Antiviral drugs are not recommended for EBV prophylaxis (DIIu).
- IVIG are not recommended for EBV prophylaxis (DIII).



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ANTI-CD20 MOABs IN PROPHYLAXIS: TIMING

- Performed depending on studies either before or after allo-HCT
- No data comparing before (varies between **D-35 to D-1**, mainly during conditioning) vs after (usually **D+5**) infusion. Pre-allo-HCT or D+5 single dose of anti-CD20 MoAbs was associated with a significant reduction in the risk of EBV reactivation and PTLD.
- Same success rates for both schedules

ECIL-11 RECOMMENDATION:

If used as a strategy of EBV prophylaxis, anti-CD20 MoAbs can be administered either before or after allo-HCT according to center policy (BIHh). The administration before HCT is expected to have probably less negative impact on post-HCT B-cell recovery.

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ANTI-CD20 MOABs IN PROPHYLAXIS: DOSAGE

- For non-lymphoma patients, most studies used one single dose of 375 mg/m² (150 mg/m² pediatrics)
- One study 500 mg; one study 200 mg. No comparative data

ECIL-11 RECOMMENDATION:

- If used as a strategy of EBV prophylaxis, administer anti-CD20 MoAbs at 200-375 mg/m² single dose (150-375 mg/m² pediatrics) (BIlh)
- Prospective studies should investigate optimal dosing strategies.



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PROPHYLAXIS OF EBV: CYTOTOXIC T-LYMPHOCYTES

- Several prospective non-controlled studies show feasibility
- Very different manufacturing protocols (mainly multi-CTLs)
- Treatment failure (EBV reactivation requiring treatment): 10-21.7%
- Emergent acute GVHD: 8-50%

ECIL-11 RECOMMENDATION:

- Prophylactic use of EBV-specific T-cells can be considered, if available, in high risk patients (CIIu).



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*Rubinstein et al., 2022; Gottfried et al. 2021; Muranski et al., 2018(ASH abstract);
Dadwal et al., 2024; Ma et al., 2015; Naik et al., 2016; Roex et al., 2020*

PREEMPTIVE THERAPY FOR EBV-DNA-emia

- Anti-CD20 MoAbs, 375 mg/m², once weekly (Allu) 2-4 doses
- Anti-CD20 MoAbs at low-dose 100-200 mg/m², once weekly (no grading) [in selected patients, e.g, with low viremia]. The efficacy of a lower dose should be explored by a dedicated study.
- Reduction of immunosuppressive therapy, if possible (Allu)
- EBV-specific T-cells can be considered, if available (Cllu)
- Antiviral drugs are not recommended (DlIh)



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Doses provided for RITUXIMAB

References: 12 papers

THERAPY IN PTLD: FIRST LINE

- Anti-CD20 MoAbs, 375 mg/m², once weekly (Allu)
- Reduction of immunosuppressive therapy, if possible (Allu)
- Donor or third-party EBV-specific T-cells therapy if available (Cllu)

Full assesment of response to therapy after 4 weeks is recommended.



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Doses provided for RITUXIMAB

THERAPY OF REFRACTORY AND RELAPSED PTLD

- **EBV-specific T-cells therapy (Allu):**
 - EBV-specific T-cells therapy may be provided as an authorized product (tabelecleucel, where approved) or from other established EBV-specific T-cells sources, including academic and institutional programs
- **Immunochemotherapy, CAR-T and other targeted therapies are potential options for therapy of EBV-PTLD after failure of anti-CD20 MoAbs and/or EBV-specific T-cells therapy (Clluh)**
- **Unselected DLI (CIII)**
- **Antiviral agents are not recommended for PTLD therapy (DIIh)**
- **IVIG is not recommended for PTLD (DIII)**

Withers et al., (2017), Blood Advances; Kallay et al., (2018), Journal of Immunotherapy; Kazi et al., (2019), Haematologica; Hong et al., (2020), International Journal of Hematology; Prockop et al., (2020), Journal of Clinical Investigation; Bonifacius et al., (2023), Journal of Clinical Investigation; Pfeiffer et al., (2023), Clinical Cancer Research; Mahadeo et al., (2024), Lancet Oncology; Nikiforow et al., (2025), Blood (ASH); Farid et al., (2026), Blood Advances; Cao et al., (2026), Advanced Science; Schweitzer et al., (2026), Open Forum Infectious Diseases

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OTHER THERAPIES FOR REFRACTORY EBV-PTLD

- Available reports on 97 patients with EBV-PTLD treated with new therapies.
- Overall 65 patients (mainly adults) with (r)EBV-PTLD were treated with CAR-T (including 55/65 after SOT). Overall response rate was 49/65=75.4%.
- 22 adults were treated with brentuximab vedotin. Response rate was 17/22=77.3%.
- Other case reports included successful treatment: 2/3 with daratumumab, 2/2 with blinatumomab, and single cases with nivolumab, ofatumumab, zanubrutinib, acalabrutinib, and epcoritamab (CD3CD20 bispecific antibody).



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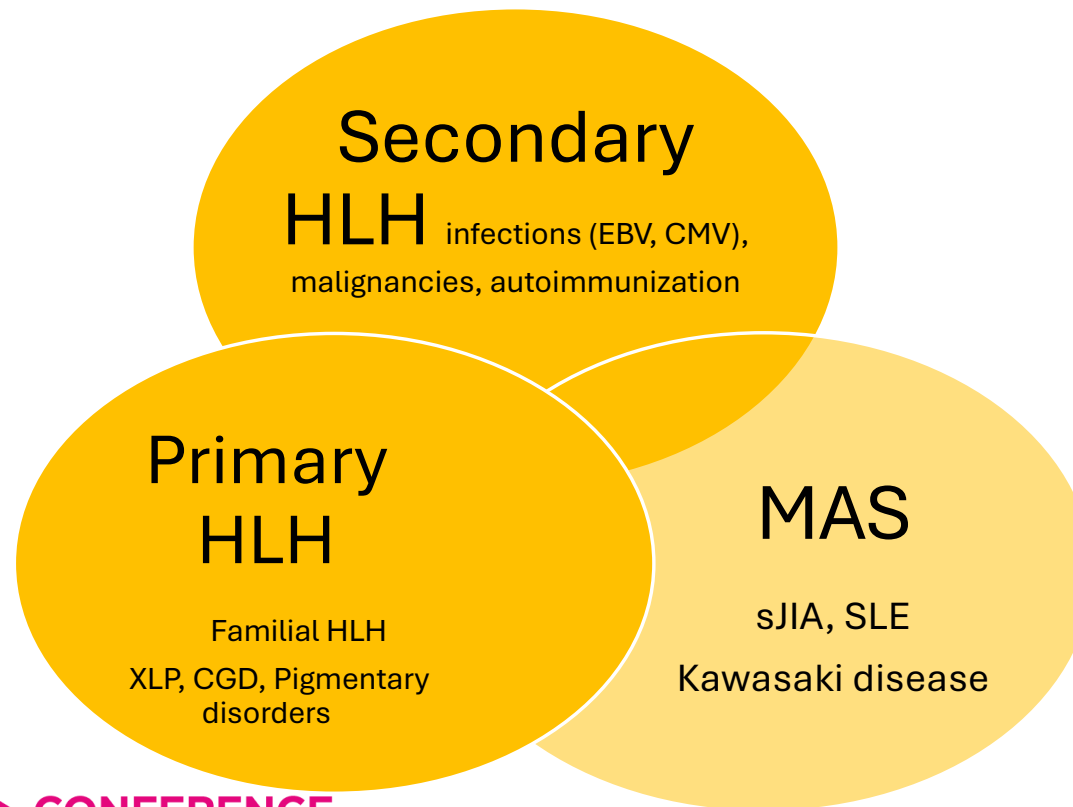
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References: 28 papers

EBV-ASSOCIATED HLH AFTER ALLO-HCT

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening inflammatory syndrome that can occur either in genetically predisposed individuals (primary HLH) or in particular conditions in immunocompromised patients (secondary HLH)



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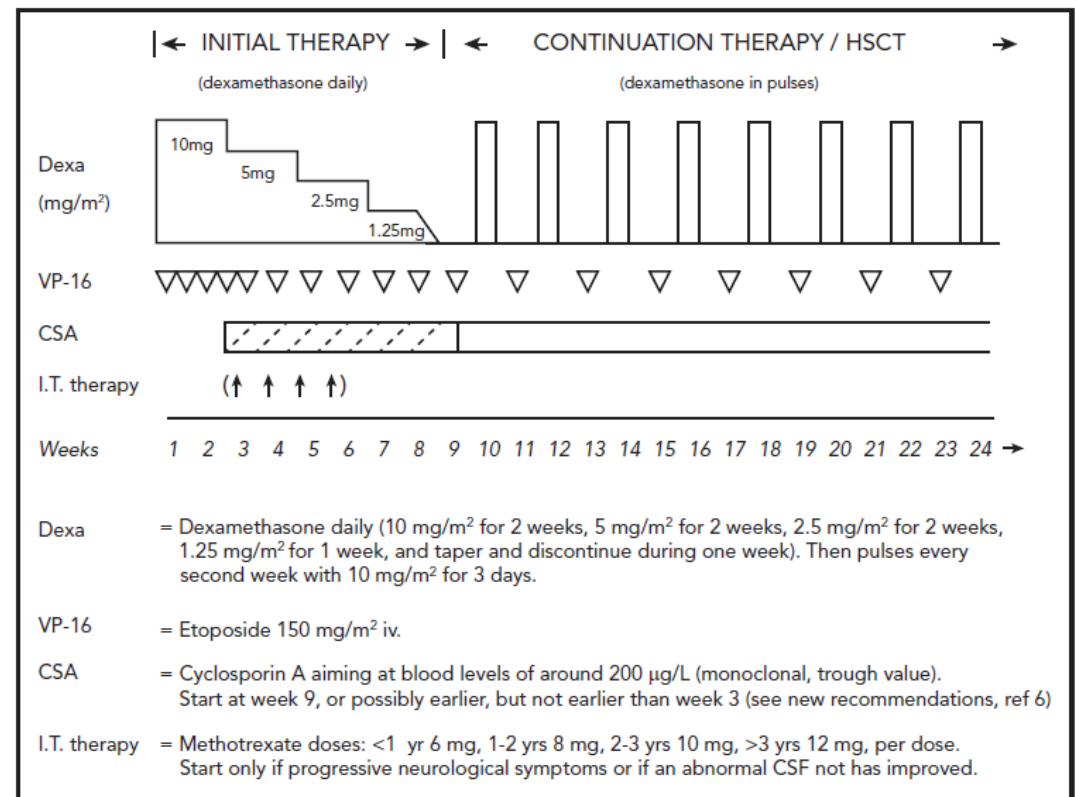
Selected HLH/MAS (HPS) diagnostic criteria, including post-HCT approaches

	HLH-2004	HScore	MAS-2016 / PRINTO	Takagi / HCT-HPS	Abdelkefi / post-HCT HPS
Target population	Primary / pediatric HLH	Adult sHLH	sJIA-MAS	Post-HCT HPS, mainly CBT	Post-HCT HPS
Fever	+	<38.4°C = 0; 38.4–39.4°C = 33; >39.4°C = 49	+	High-grade fever	>7 days
Hepatomegaly	–	Hepatomegaly or splenomegaly = 23; both = 38	–	Hepatosplenomegaly	–
Splenomegaly	+	Hepatomegaly or splenomegaly = 23; both = 38	–	Hepatosplenomegaly	–
Immunosuppression	–	No = 0; yes = 18	–	–	–
Engraftment failure / secondary graft failure	–	–	–	Major criterion	–
Cytopenia	≥2 lineages	1 lineage = 0; 2 = 24; 3 = 34	Platelets only	–	≥2 lineages
Hemoglobin	<90 g/L	Part of cytopenia score	–	–	<90 g/L
Platelets	<100 × 10 ⁹ /L	Part of cytopenia score	≤181 × 10 ⁹ /L	–	<100 × 10 ⁹ /L
Neutrophils	<1.0 × 10 ⁹ /L	Part of cytopenia score	–	–	<1.0 × 10 ⁹ /L
Ferritin	≥500 ng/mL	<2000 = 0; 2000–6000 = 35; >6000 = 50	>684 ng/mL	Elevated	>1000 ng/mL
Triglycerides	≥3.0 mmol/L	<1.5 = 0; 1.5–4 = 44; >4 = 64	>156 mg/dL / >1.76 mmol/L	–	–
Fibrinogen	≤1.5 g/L	>2.5 = 0; ≤2.5 = 30	≤360 mg/dL / ≤3.6 g/L	–	–
AST	–	<30 IU/L = 0; ≥30 = 19	>48 U/L	–	–
LDH	–	–	–	Elevated	–
Hemophagocytosis	+	absent = 0; present = 35	–	Major criterion	>3% mature macrophages in BM
NK-cell activity	Low/absent	–	–	–	–
sCD25 / soluble IL-2R	≥2400 U/mL	–	–	–	–
Fulfilment of criteria	Molecular diagnosis or ≥5/8 criteria	Total score; ≥169 supports HLH	Ferritin >684 + ≥2 lab criteria	2 major or 1 major + all 4 minor	All criteria required

TREATMENT PRINCIPLES OF HLH

Principle: management should combine EBV-directed therapy and anti-inflammatory therapy, adapted to clinical severity.

Treatment target	Possible interventions	Clinical considerations
Reduce EBV burden	Anti-CD20 MoAbs; EBV-specific T-Cells therapy; reduction of immunosuppression when feasible	most effective when EBV is B-cell driven; consider EBV PCR in lymphocyte subsets if PCR persists despite B-cell depletion
Control hyperinflammation	corticosteroids; etoposide; ruxolitinib; IVIG; anakinra / emapalumab / alemtuzumab in selected contexts	treatment intensity should reflect severity, organ dysfunction and risk of toxicity
Treat associated conditions	antimicrobial therapy; PTLT-directed therapy; GVHD/TMA management	mimickers and triggers must be addressed simultaneously
Monitor response	fever, ferritin, CBC, fibrinogen, D-dimers, liver tests, LDH, sCD25 if available, EBV PCR	persistent EBV PCR alone should not automatically trigger escalation if the patient is clinically improving



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La Rosée, Blood 2019; Shakoory, Ann Rheum Dis 2023; Pagano, Leukemia 2025; Maertens, J Antimicrob Chemother 2016; McCann, Lancet Rheumatol 2026.

ECIL-11 recommendations: treatment for EBV-HLH after allo-HCT

EBV-HLH after allo-HCT requires combined EBV-directed and anti-inflammatory treatment. Escalation should be individualized according to clinical severity, organ dysfunction, EBV compartment involvement, response to rituximab/steroids and toxicity risk.

Therapeutic goal	Intervention	Proposed grade	Rationale / when to consider	Key limitations / comments
Reduction of EBV burden	Anti-CD20 MoAbs	A II ut	First-line EBV-directed therapy, especially in B-cell EBV disease or EBV-PTLD; should be started early when EBV-driven HLH is suspected.	Limited effect if EBV is mainly within T/NK cells; monitor B-cell depletion and EBV kinetics.
Suppression of pathologic inflammation	Corticosteroids	A II ut	Core anti-inflammatory treatment; rapid suppression of HLH/MAS-related hyperinflammation.	Dose and duration should be adapted to severity, infection risk and concomitant GVHD.
	Etoposide-based chemotherapy	A II ut	Should be discussed in severe, rapidly progressive or refractory EBV-HLH, particularly with organ dysfunction.	Caution after allo-HSCT because of myelotoxicity, infectious risk and organ toxicity.
	Ruxolitinib	C II ut	May be considered as adjunctive or rescue therapy to target cytokine-driven inflammation through JAK/STAT inhibition.	Limited post-allo-HCT EBV-HLH data; monitor cytopenias and infections.
	IVIG	C II ut	May be used as supportive immunomodulatory therapy in selected patients.	Evidence is weak and the specific benefit in EBV-HLH after allo-HSCT is uncertain.
Interleukin-1 α (IL-1 α) and 1 β (IL-1 β) inhibitor	Anakinra	C II ut	Potential role in selected HLH/MAS contexts.	Case reports among allo-HCT recipients with EBV-HLH
EBV-directed cellular / rescue therapy	EBV-specific T-cells therapy	C II ut	Consider in refractory or persistent EBV-driven disease, especially when available rapidly.	Access, timing and patient condition may limit feasibility.
Experimental / insufficient evidence after allo-HSCT	Anti-PD1 therapy	No grade	Biological rationale in refractory EBV-HLH outside allo-HCT.	Caution after allo-HSCT due to GVHD risk; insufficient evidence for recommendation
	Alemtuzumab, emapalumab	No grade	Potential role in selected HLH/MAS contexts.	No reports among allo-HCT recipients with EBV-HLH; insufficient evidence for recommendation.

From September 17, to 19, 2020

ANTI-INFECTIVE PROPHYLAXIS IN SECONDARY HLH

Patients with EBV-associated HLH after allo-HCT are considered to be at high risk of infection and should receive appropriate antimicrobial prophylaxis.



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PLEASE SEND YOUR COMMENTS TO:

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