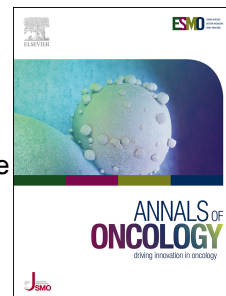


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Management of Adults and Children receiving CAR T-cell therapy: 2021 Best Practice Recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)



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Management of Adults and Children receiving CAR T-cell therapy: 2021 Best Practice Recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)

AUTHORS AND AFFILIATIONS:

P. J. Hayden^{1*}, C. Roddie^{2,3*}, P. Bader⁴, G. W. Basak⁵, H. Bonig⁶, C. Bonini⁷, C. Chabannon⁸, F. Ciceri⁹, S. Corbacioglu¹⁰, R. Ellard¹¹, F. Sanchez-Guijo¹², U. Jäger¹³, M. Hildebrandt¹⁴, M. Hudecek¹⁵, M. J. Kersten¹⁶, U. Köhl¹⁷, J. Kuball¹⁸, S. Mielke¹⁹, M. Mohty²⁰, J. Murray²¹, A. Nagler²², J. Rees^{3, 23}, C. Rioufol²⁴, R. Saccardi²⁵, J. A. Snowden²⁶, J. Styczynski²⁷, M. Subklewe²⁸, C. Thieblemont²⁹, M. Topp¹⁵, Á. U. Ispizua³⁰, D. Chen^{3,32}, R. Vrhovac³¹, J. G. Gribben³², N. Kröger³³, H. Einsele¹⁵ and I. Yakoub-Agha³⁴

* Participated equally to this work and should be considered as first author.

¹Dept. of Haematology, Trinity College Dublin, St. James's Hospital, Dublin 8, Ireland

²UCL Cancer Institute, London, UK

³University College Hospital, University College of London Hospitals NHS Foundation Trust, NW1 2BU, UK

⁴Clinic for children and adolescents, University Children's Hospital, Frankfurt, Germany

⁵Medical University of Warsaw, Department of Hematology, Transplantation and Internal Medicine, Warsaw, Poland

⁶Institute for Transfusion Medicine and Immunohematology of Goethe University and German Red Cross Blood Service, 60528 Frankfurt, Germany

⁷Ospedale San Raffaele and Università Vita-Salute San Raffaele, Milano, Italy

⁸Institut Paoli-Calmettes & Module Biothérapies, Centre d'Investigations Cliniques de Marseille, Inserm CBT-1409 – AMU – AP-HM – IPC

⁹Università Vita-Salute San Raffaele, IRCCS Ospedale San Raffaele, via Olgettina 60, Milan, 20132, Italy

¹⁰Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, University Franz-Josef-Strauss-Allee 11, University Hospital of Regensburg, Regensburg, Germany

¹¹Cellular Therapy Clinical Nurse Specialist, Royal Marsden Hospital, UK

¹²IBSAL-Hospital Universitario de Salamanca, CIC, Universidad de Salamanca, 37007 Salamanca, Spain

¹³Department of Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna

¹⁴Department of Transfusion Medicine, Cell Therapeutics and Haemostaseology, LMU University Hospital Grosshadern, Munich, Germany

¹⁵Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Josef-Schneider-Str. 2, 97080, Würzburg, Germany

¹⁶Department of Hematology, Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam and LYMMCARE, The Netherlands

¹⁷Fraunhofer Institute for Cell Therapy and Immunology (IZI) and Institute of Clinical Immunology, University of Leipzig, Leipzig as well as Institute of Cellular Therapeutics, Hannover Medical School, Hannover, Germany

¹⁸Department of Hematology and Centre for Translational Immunology, University Medical Center Utrecht, Utrecht, The Netherlands

¹⁹Karolinska Institutet and University Hospital, Department of Laboratory Medicine/Department of Cell Therapy and Allogeneic Stem Cell Transplantation (CAST), Stockholm, Sweden

²⁰Hôpital Saint-Antoine, APHP, Sorbonne Université, INSERM UMRs 938, Paris, France

²¹Christie Hospital NHS Trust, Manchester, United Kingdom

²²The Chaim Sheba Medical Center, Tel-Hashomer, Affiliated with the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

²³UCL Institute of Neurology, University College of London Hospitals NHS Foundation Trust, NW1 2BU, UK

²⁴Hospices Civils de Lyon, UCBL1, EMR 3738 CICLY, Lyon, France

²⁵ Cell Therapy and Transfusion Medicine Department, Careggi University Hospital, Florence, Italy

²⁶Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

²⁷Department of Pediatric Hematology and Oncology, Collegium Medicum, Collegium Medicum, Nicolaus Copernicus University Torun, Bydgoszcz, Poland

²⁸German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

²⁹ AP-HP, Saint-Louis Hospital, Hemato-oncology, University of Paris, Paris, France

³⁰ Department of Hematology, ICMHO, Hospital Clínic de Barcelona, Villarroel 170, 08036 Barcelona, Spain

³¹Department of Haematology, University Hospital Centre Zagreb, Zagreb, Croatia

³² Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, London, UK

³³Department of Stem Cell Transplantation, University Medical Center Hamburg, Germany

³⁴CHU de Lille, Univ Lille, INSERM U1286, Infinite, 59000 Lille, France

RUNNING HEAD:

EBMT/EHA Management of patients undergoing CAR T-cell therapy

CORRESPONDING AUTHOR:

Dr Claire Roddie, UCL Cancer Institute, 72 Huntley Street, London, WC1E 6DD, UK. Phone: +44 (0)20 7679 6500. (e-mail address: c.roddie@ucl.ac.uk).

ABSTRACT:

Background: Several commercial and academic autologous chimeric antigen receptor T-cell products targeting CD19 have been approved in Europe for relapsed/refractory B-cell acute lymphoblastic leukemia, high-grade B-cell lymphoma, and mantle cell lymphoma. Products for other diseases such as multiple myeloma and follicular lymphoma are likely to be approved by the European Medicines Agency in the near future.

Design: EBMT-JACIE and the European Haematology association (EHA) proposed to draft best practice recommendations based on the current literature, to support healthcare professionals in delivering consistent, high-quality care in this rapidly moving field

Results: Thirty-six CAR-T experts (medical; nursing; pharmacy/laboratory) assembled to draft recommendations to cover all aspects of CAR-T patient care and supply chain management, from patient selection to long-term follow-up, post-authorisation safety surveillance and regulatory issues.

Conclusions: We provide practical, clinically relevant recommendations on the use of these high-cost, logistically complex therapies for hematologists/oncologists, nurses and other stakeholders including pharmacists and health sector administrators involved in the delivery of CAR-T in the clinic.

KEYWORDS:

CAR T-cells (CAR-T), B-cell acute lymphoblastic leukemia (B-ALL), adult relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL), Multiple myeloma (MM), Mantle cell lymphoma (MCL), follicular lymphoma (FL), cytokine release syndrome (CRS), Macrophage activation syndrome (MAS), immune effector cell-associated neurotoxicity syndrome (ICANS), JACIE, long-term follow-up (LTFU).

INTRODUCTION:

CD19 chimeric antigen receptor T-cell (CAR-T) therapeutics are widely used for relapsed/refractory (r/r) B-cell malignancies including acute lymphoblastic leukemia (B-ALL), large B-cell lymphoma (LBCL) and mantle cell lymphoma (MCL)¹⁻³. CAR-T are also under evaluation in multiple myeloma, acute myeloid leukemia and solid tumors^{4,5}.

Three CAR-T products are licensed: Tisagenlecleucel (Kymriah®, Novartis) for r/r paediatric B-ALL and adult LBCL; Axicabtagene ciloleucel (Yescarta®, Gilead), for r/r adult LBCL and Tecartus (brexucabtagene autoleucel), for r/r adult MCL. In the US, lisocabtagene maraleucel (Liso-Cel, BMS) is approved for r/r LBCL and idecabtagene vicleucel [ide-cel, Abecma]⁶ and JNJ-4528⁷ have been approved for r/r multiple myeloma⁴. In Spain, regulators have approved academic CD19 CAR-T (ARI-0001) for r/r B-ALL⁸.

CAR-T confers a risk of potentially life-threatening immunological toxicities and comprehensive training of personnel involved in CAR-T delivery, including intensive care unit (ICU) and neurology specialists, is key⁹.

Post-marketing pharmacovigilance over 15 years post-infusion is mandated by EMA to ensure ongoing evaluation of efficacy and safety of licensed CAR-T in the real-world setting via the EBMT registry. CIBMTR (Center for International Blood and Marrow Transplant Research) fulfils a similar role. Further, the PASS (post-authorization safety studies) initiative makes an assessment of the value of CAR-T in relation to standard-of-care treatments.

METHODOLOGY

In 2021, EBMT and EHA proposed an expanded revision of the 2019 EBMT-JACIE CAR-T guidelines^{10,11}. Thirty-six CAR-T experts (medical; nursing; pharmacy/laboratory) assembled to draft recommendations based on the current literature, to reflect current best practice in this rapidly moving field and to support healthcare professionals in delivering consistent, high-quality care. Given the absence of randomized trial evidence, a decision was made not to grade these recommendations. They therefore represent the consensus view of the authors.

The recommendations principally apply to licensed CAR-T therapies. For CAR-T clinical trials, healthcare teams should follow relevant trial protocols.

PATIENT ELIGIBILITY

Patient eligibility should be assessed by a CAR-T centre multi-disciplinary team including cellular therapy and haematology/oncology disease specialists. Medical history, performance status and CAR-T product should be considered with respect to tolerability (Table 1).

Eligibility Criteria	EBMT/EHA recommendations	Comments
Age limit	No age limit	Decision should be based on physical condition rather than age, although ability to collect sufficient cells by apheresis can be a limiting factor in infants and small children. Real-world CAR-T data suggests that 5.9% of treated patients with B-ALL were <3 years old and 53.5% of treated patients with NHL were >65 years old and that CR rates was comparable in both groups to the rest of the population.
Performance Status	ECOG <2, Karnofsky > 60% or Lansky >60%	Although patients with ECOG>1 were treated outside clinical trials, it was associated with significantly decreased OS and PFS.

Life expectancy	More than 6-8 weeks	Requires careful consideration in terms of risk-benefit ratio.
High tumour burden	Risk-benefit assessment required	High tumor burden in B-ALL and LBCL is a risk factor for treatment failure and greater toxicity and careful consideration of the individual risk-benefit ratio is required.
History of malignancy	Absence of active malignancy requiring treatment other than non-melanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast).	Requires careful consideration of the risk-benefit ratio.
Prior allo-HCT	Not a contraindication	Not a contraindication when off immunosuppression but in ALL may increase risk of CAR-T associated toxicity
Prior treatments directed towards antigenic target of CAR-T e.g. bispecific antibodies/ prior CAR-T	Not a contraindication, but antigen negative escape should be excluded at relapse post-targeted therapy and prior to CAR-T especially in B-cell ALL	Reduced CD19 expression may not decrease the efficacy of anti-CD19 CAR-T in B-ALL; however, prior treatment with blinatumomab may impair efficacy A second infusion of anti-CD19 CAR T-cells may be feasible and can induce remission in a subset of patients.
Immunosuppressive treatment	Relative contraindication	Any systemic immunosuppressive treatment may impair the efficacy of CAR-T. Intermittent topical, inhaled, or intranasal corticosteroids are permitted.
Bacterial or fungal infections	Active infection is a contraindication	Infection should be treated and well controlled such that the patient should be stable prior to leukapheresis. In most cases, active infection requires only a temporary deferral.
Viral infection	Viremia is a contra-indication. Treatment should be delayed in cases of positive COVID-19 PCR. ¹²	Active viral infection should prompt deferral of initiation of CAR-T therapy until the infection is controlled. Some latent infections, e.g. HIV, are a contraindication to manufacturing for several (but not all) commercial and trial CAR-T products. When proceeding to CAR-T in cases of latent HBV, HCV or HIV infections, prophylactic anti-viral treatment is required. Asymptomatic patients testing positive for COVID-19 by qPCR may proceed to CAR-T manufacture, but this is done at risk and at the physician's discretion. Before proceeding, feasibility should be checked with the CAR-T manufacturer well in advance of leukapheresis.
History of central nervous system (CNS) involvement	Relative contraindication	Requires careful consideration of the risk-benefit ratio. LBCL: for ZUMA-1 and Juliet, CNS involvement was an exclusion criterion, but in Transcend-world, controlled SCNSL was permitted on study. MCL: on ZUMA-2, CNS involvement was an exclusion. B-ALL: on ELIANA, active CNS involvement was an exclusion. Real world evidence (RWE) on CAR-T for CNS involvement in DLBCL is emerging: suggesting that it is well tolerated and has potential efficacy. MM: CNS involvement was an exclusion in KarMMa study

Table 1. Patient eligibility criteria for CAR-T

SCREENING LABORATORY TESTS AND IMAGING

To ensure patient eligibility and fitness, the screening tests in Table 2 should be considered. This list is not exhaustive, and, in the trial setting, trial protocols should be followed.

Screening tests	EBMT/EHA recommendations	Comments
Disease confirmation	Diagnosis should be confirmed using appropriate tests	e.g. histology for NHL; immunophenotyping for ALL
Haematology	Evidence of adequate bone marrow reserve	Bone marrow reserve is difficult to evaluate in high burden t/r ALL and MM.
Bilirubin	<34µmol/L in trials; higher limit acceptable (<43µmol/L) with Gilbert's syndrome	No trial data regarding patients outside of these parameters.

AST/ALT	<4x ULN a contra-indication in some trials	Attempt to identify cause of liver derangement e.g. infection, drug toxicity including antifungals, VoD, GvHD.
Creatinine clearance	> 30 ml/min	Physicians should consider appropriate dose reductions in cyclophosphamide and fludarabine when creatinine clearance is below 60ml/min and potentially an increased interval between LD and CAR-T return to permit clearance of Fludarabine metabolites.
Hepatitis B	As per national guidelines	Serology/molecular testing
Hepatitis C	As per national guidelines	Serology/molecular testing
HIV	Leukapheresis for Kymriah™ manufacturing will not be accepted from patients with a positive test for active HBV, HCV, or HIV (SPC). This is not the case for Yescarta™	Kymriah™ employs lentiviral vectors for CAR gene transfer whereas Yescarta™ uses retroviral vectors. There is a theoretical concern regarding lentiviral recombination events.
COVID-19	Nasopharyngeal PCR before leukapheresis should be negative	Asymptomatic patients testing positive for COVID-19 by qPCR may proceed to CAR-T manufacture, but this is done at risk and at the physician's discretion. Before proceeding, feasibility should be checked with the CAR-T manufacturer well in advance of leukapheresis.
COVID-19 vaccination	Recommended	Though data is limited, patients should be vaccinated against COVID-19, where possible, prior to admission for CAR-T.
Cardiac function	TTE to assess cardiac function and exclude significant pericardial effusions and structural abnormalities – LVEF <40% (via 4DEF or Simpson's Biplane method) is a relative contraindication. ECG to exclude significant arrhythmias. Cardiac biomarkers (troponin and NT-proBNP) at baseline CMR to assess extent disease in PMBCL with cardiac involvement.	Consider cardio-oncology review for further assessment of treatment suitability and scope for cardiac optimisation
CNS imaging	MRI not required except in those with a history of CNS disease or current neurological symptoms	
Lumbar puncture	Lumbar puncture not required except in those with a history of CNS disease or current neurological symptoms	
Fertility	Females of childbearing potential must have a negative serum or urine pregnancy test	Test must be repeated and confirmed negative within 8 days of the CAR-T cell infusion

Table 2. Screening tests prior to CAR-T therapy. Key. NHL: Non-Hodgkin Lymphoma; ALL: acute lymphoblastic leukemia; ULN: upper limit of normal; TTE: transthoracic echocardiogram; LVEF: left ventricular ejection fraction; ECG: electrocardiogram; CMR: cardiac magnetic resonance; PMBCL: primary mediastinal B cell lymphoma; MRI: Magnetic resonance imaging; CNS: central nervous system; VoD: veno-occlusive disease; GvHD: graft versus host disease.

WORK-UP FOR LEUKAPHERESIS

Leukapheresis procurement in the European Union must comply with the Tissue and Cell Directives (2004/23/EC; 2006/17/EC; 2006/86/EC). Shipment across borders requires current viral serology and compliance with regulations in both the countries of origin and destination^{13,14}.

A pre-leukapheresis checklist and suggested washout periods for pre-leukapheresis therapeutics are listed in Tables 3 and 4.

Prior to Apheresis	EBMT/EHA recommendations	Comments
Performance status	ECOG <2, Karnowski > 60%	At discretion of leukapheresis practitioner
Interval following exposure to chemotherapy	Allow sufficient time for recovery from cytotoxic chemotherapy/immunosuppression/ steroids (see Table 4 for washout periods)	Adequate marrow recovery from prior chemotherapy required
Interval following exposure to steroids	A minimum of 3 days prior to leukapheresis. Optimally, 7 days to minimise impact on leukapheresis	Physiological replacement doses of hydrocortisone permitted, Topical and inhalational steroids also permitted
Blood oxygen saturation	≥ 92% on room air	
Hepatitis B, Hepatitis C, HIV, Syphilis, and HTLV	To be done within 30 days of leukapheresis. Results must be available at the time of collection and shipment. Mandatory in some countries	In some countries, only serological testing is required; nucleic acid testing (NAT) is not necessary if all serological testing is negative
COVID-19 PCR	Not a contraindication in asymptomatic patients. Contraindication in symptomatic patients	Apheresis physician and manufacturing facility should be informed if positive PCR
COVID-19 vaccination	Recommended	Though data is limited, patients should be vaccinated against COVID-19, where possible, prior to admission for CAR-T.
Standard electrolytes and renal function	Required	Leukapheresis can be complicated by electrolyte imbalance and fluid shifts during the procedure
Haemoglobin	Hemoglobin >80 g/L recommended Hematocrit >0.24 recommended	To help establish a good interface during leukapheresis
Absolute Lymphocyte count (ALC)	≥ 0.2x10 ⁹ /L recommended	Low counts indicate insufficient haematological recovery and may predict for production failure. Higher count required in small children. Of note, 0.2x10 ⁹ /L CD3 ⁺ count is the minimum recommended threshold
Platelet count	> 30x10 ⁹ /L recommended	Transfuse as required, particularly for insertion of central line prior to leukapheresis.
Full Blood Count (FBC)	To be repeated at the end of apheresis procedure	Apheresis can remove more than 30% of circulating platelets

Table 3. Checklist prior to leukapheresis

Type of therapy	EBMT/EHA recommendations	Comments
Allo-HCT	Patients should be off immunosuppression and GvHD-free	A minimum of one month is recommended with the requirement to be GvHD-free and off immunosuppression
DLI	At least 4 weeks	6-8 weeks may be safer to rule out any GvHD
High-dose chemotherapy	3-4 weeks	Recovery from cytopenias is required
Intrathecal therapy	One week	
Short-acting cytotoxic/anti-proliferative drugs	3 days	Recovery from cytopenias is required
Systemic corticosteroids	Minimum of 3 days but ideally 7 days	ALC ≥ 0.2x10 ⁹ /L is recommended

Table 4. Washout period before leukapheresis [adapted from Kansagra et al, *BBMT 2019*¹⁵] Key. Allo-SCT: allogeneic stem cell transplantation; GvHD: graft versus host disease; DLI: donor lymphocyte infusion; ALC Absolute Lymphocyte Count.

PERFORMING LEUKAPHERESIS

To be a CAR-T delivery site, accreditation with FACT-JACIE is recommended. Pharmaceutical providers and health service commissioners may have additional requirements.

CAR-T product prescription/order and non-mobilised leukapheresis^{16,17} scheduling/shipping, is co-ordinated with the CAR-T manufacturing facility (often via proprietary web-based platforms),

Most manufacturers stipulate storage of fresh leukapheresis at 2-8 °C prior to shipping. Novartis additionally accept locally cryopreserved starting material (within 30 months).

Accredited, validated leukapheresis testing methods should be compatible with manufacturer's requirements and authorizations. An absolute lymphocyte count (ALC) threshold of $0.2 \times 10^9/L$ ^{17,18} is generally recommended^{19,20}, but emerging evidence supports CAR-T leukapheresis in paediatric and adult patients with low ALC^{21,22}.

Infectious disease markers must be tested on peripheral blood (PB) within 30 days of leukapheresis (with results available on the day of shipment). Microbial contamination is rare and the presence of leukemic blasts is acceptable to manufacturers.

Based on the observation that T-cells suffer qualitative damage from chemotherapy, feasibility of pre-emptive leukapheresis in high-risk patients is currently being explored, but with significant regulatory, infrastructural, and cost implications.

BRIDGING THERAPY

'Bridging' therapy, administered in the 4-6 weeks between leukapheresis and CAR-T admission, aims to reduce disease burden and in doing so, improve intention-to-treat and reduce CAR-T immunotoxicity²³⁻²⁵.

Patient-specific bridging recommendations should be made by a multi-disciplinary team following review of response to prior therapy, overall tumour burden, and anatomical sites of disease. Bridging can be omitted if the CAR-T 'vein-to-vein' time is short and the disease burden is low. Otherwise, bridging is broadly split into: (a) high-dose chemotherapy; (b) low-dose chemotherapy; (c) radiotherapy; and (d) novel agents/approaches. Radiation therapy can be an effective bridge, but the impact on circulating lymphocytes should be considered if radiation is commenced prior to leukapheresis. Further studies are warranted to optimise bridging approaches²⁶.

Bridging can be delivered at the CAR-T centre or at the referring center, provided there is clear communication regarding the selected bridging strategy, management of complications, and scheduling of bridging in relation to CAR-T admission, fastidiously observing recommended washout periods (Table 5).

Type of therapy	EBMT/EHA recommendations	Comments
High-dose chemotherapy	3-4 weeks	To avoid additional toxicity and prolonged cytopenias
Intrathecal therapy	1 week	To avoid additional toxicity
Short-acting cytotoxic/anti-proliferative drugs	3 days	To avoid additional toxicity
Radiotherapy	1 weeks (2 weeks for lung)	To avoid additional toxicity
TKI	3 days	To avoid additional toxicity

Table 5. Washout period between the bridging therapy and the onset of LD conditioning [Expert opinion]. Key: TKI: tyrosine-kinase inhibitor.

HOSPITALIZATION

Outpatient CAR-T administration can be done safely, provided clear policies, appropriate infrastructure, well-trained staff, and capacity for 24/7 hospitalization in the event of complications is in place¹⁴. As such facilities are not available in most European centers, we recommend that patients remain hospitalized for at least 14 days following infusion (Table 6).

Period	EBMT/EHA recommendations	Comments
Day 0 to Day +14 post-infusion	Ideally 14 days hospitalization. Consider 10 days in patients with no post-infusion complications.	Outpatient follow-up is possible in centres that can provide 24/7 contact with immediate availability of specialist inpatient care. For this arrangement, patients should be located within 30-60 minutes of the CAR-T centre
From hospital discharge to Day +28 post-infusion	Patients should be located within 60 minutes of the center and the continuous presence of a caregiver who is educated to recognize the signs and symptoms of CRS and ICANS is required	Delayed CRS and ICANS can emerge following discharge from hospital

Table 6. Recommendations on hospitalisation in the first 28 days after CAR-T infusion.

LYMPHODEPLETING CONDITIONING (LD)

LD acts to enhance CAR-T proliferation by modulating cytokine and immune pathways. Fludarabine and cyclophosphamide (FC) is widely used²⁷. Fludarabine dosing is consistent between products and indications (25-30 mg/m²/day x3 days) whilst cyclophosphamide schedules differ²⁸. Bendamustine (+/- fludarabine) has been tested in CD30CAR-T for Hodgkin Lymphoma as an alternative to FC²⁹.

LD is administered following CAR-T product release, the week prior to CAR-T infusion with a minimum of two rest days. Where CAR-T infusion is delayed by ≥ 4 weeks, repeat LD is recommended, with consideration given to patient fitness, blood counts and prior fludarabine exposure¹⁰.

Potential complications from LD include pancytopenia, immunosuppression, infection, neurotoxicity, haemorrhagic cystitis, pericarditis and secondary malignancy. Renal or hepatic impairment should prompt appropriate dose modification. Considerations prior to LD are outlined in Table 7.

Criterion	EBMT/EHA recommendations	Comments
CAR T-cell product	LD should be administered following receipt of CAR-T product on site	Exceptional situations may necessitate the administration of LD following confirmation of successful CAR-T manufacture, but prior to receipt.
Clinical conditions	Active infections should be ruled out before starting LD	Patient should be medically fit to proceed to LD
Blood oxygen saturation	≥ 92% on air	
WBC	Administer LD to all patients irrespective of WBC or ALC	The SPC for Kymriah™ state that patients with low WBC (<1x10 ⁹ /L) 1 week prior to CAR-T infusion may not require LD. Some investigators use LD with caution when unexplained neutropenia pre-dates CAR-T admission. However, LD is important to CAR-T activity and proceeding with CAR-T without LD is not generally recommended.
C-reactive protein, ferritin, lactate dehydrogenase, metabolic profiling, fibrinogen level	Required to rule out ongoing infection.	Baseline assessments of risk for CRS and NT
Bilirubin	<34µmol/L; higher limit acceptable (>43µmol/L) with Gilbert's syndrome Trial criteria	No trial data regarding patients outside of these parameters
AST/ALT	≤ 4xULN or trial-specific criteria should be met	Attempt to identify cause of liver derangement e.g. infection, drug toxicity including antifungals, VoD, GvHD, disease
Creatinine clearance	> 30 ml/min	Physicians should consider appropriate dose reductions in cyclophosphamide and fludarabine when creatinine clearance is below 60ml/min and potentially an increased interval between LD and CAR-T return to permit clearance of Fludarabine metabolites.
Cardiac function	Repeat cardiac investigations only if clinically indicated e.g. clinical signs and symptoms of heart failure, cardiotoxic bridging chemotherapy.	Repeat TTE, ECG and cardiac biomarkers (troponin and NT-proBNP); Cardio-oncology assessment is required
Assessment of disease burden	Baseline assessment	PET-CT/ other imaging; bone marrow; LP as indicated

Table 7. Checklist before starting LD conditioning. Key. LD: lymphodepletion; WBC: white blood cell count; ALC: absolute lymphocyte count; ULN: upper limit of normal; VoD: veno-occlusive disease; GvHD: graft versus host disease; TTE: trans-thoracic echography; ECG: electrocardiogram

PRODUCT RECEIPT

Oversight and responsibility for this process varies nationally. Country-specific guidance is beyond the scope of this document. Centers should have regulatory approval for storage of genetically modified organisms (GMOs).

Transport tracking on the manufacturer's website enables the date and time of product shipment to be known in advance. At receipt, checks should include: (1) inspection of the dry shipper seal for breaches; (2) review of the temperature log throughout transportation; (3) inspection of product integrity; (4) CAR-T identity label checks, prior to completion of receipt forms. In the event of non-conformance, cells are quarantined, and the hospital delegate and manufacturer should be immediately informed. Back-up bags are sometimes available as a replacement for defective products.

Out-of-specification (OOS) CAR-T may still be used (exceptions include microbial/noxious contamination), provided the release certificate lists the OOS details, written agreement is provided from the manufacturer (with acceptance of responsibility by both manufacturer and physician), and the patient has given written consent³⁰⁻³².

THAWING AND INFUSION

Prior to thawing and infusion, patients are medically assessed to ensure they are fit to proceed (Table 8); identity and consent is confirmed; the prescription reviewed, and vital signs and IV access (central venous catheter or a newly inserted and pre-tested peripheral cannula) checked at the bedside. Pre-medication with paracetamol and antihistamine (NOT corticosteroids) is recommended. No concurrent medication should be administered during CAR-T infusion.

Product thawing is performed in a pharmacy clean room, cell therapy unit or patient bedside, double wrapped in a watertight plastic bag, using thawing devices according to manufacturer's instructions and local regulations (automated thawing device, $37\pm 2^{\circ}\text{C}$ water bath, or dry-thaw method). CAR-T is stable at room temperature for 30-90 minutes after thawing³³.

CAR-T should be administered rapidly after thawing during working hours by competent medical or nursing personnel^{13,14}. Vital signs should be assessed and recorded before, during and following infusion. Using aseptic non-touch technique (ANTT), cells in vials are drawn up into a syringe to be administered as a slow bolus. CAR-T infusion bags are infused through a non-filtered giving set. Fluid infusion sets with sub-micrometre bacterial filters and blood transfusion sets with leukocyte depletion filters should NOT be used for CAR-T infusion.

Infusion reactions are rare but should be treated symptomatically. Corticosteroids should be avoided unless the patient becomes critically unwell.

Following infusion, the vial/bag and giving set should be disposed of as a GMO biohazard in compliance with institutional policies and country-specific regulations.

Complications	EBMT/EHA recommendations	Comments
Active infection	Contraindication	CAR T-cell infusion should be delayed until the infection is controlled
Clinical evidence of fluid overload or congestive cardiac failure	Contraindication	Specific individualized risk-benefit; cardio oncology assessment is required
Cardiac arrhythmia not controlled with medical management	Contraindication	Specific individualized risk-benefit; cardio oncology assessment is required
Hypotension requiring vasopressor support	Contraindication: work-up is required to identify cause	CAR T-cell infusion should be delayed until the hypotension is controlled
New-onset or worsening of another non-hematologic organ dysfunction \geq Grade 3	Work-up is needed to identify the cause	Specific individualized risk-benefit assessment required
Significant worsening of clinical condition since start of LD	Work-up is needed to identify the cause	Specific individualized risk-benefit assessment required
Neurological evaluation including ICE score (adult) or CAPD score (children)	To be routinely performed	Serving as a baseline

Table 8. Potential complications to be ruled out before product thawing and CAR-T infusion. Key. LD: lymphodepletion

SHORT-TERM COMPLICATIONS: ADMISSION TO DAY +28

Tumour lysis syndrome: TLS can occur following LD/CAR-T, and should be prevented and managed with standard local protocols.

Infection: Active infection should be controlled prior to initiation of LD. Following LD, all patients will be neutropenic. A fever should prompt empiric antimicrobial therapy (based on institutional protocols) and investigation with blood and urine cultures; chest x-ray and/or high-resolution CT chest, when indicated; respiratory viral screening including COVID-19 and other tests such as influenza A PCR testing; cytomegalovirus (CMV) and Epstein-Barr virus (EBV) nucleic acid testing (NAT); and lumbar puncture and brain MRI in selected cases. The specific risk profile of the patient (duration of neutropenia, prior allo-HCT, previous infections, and local antibiotic resistance profiles) should guide diagnostic work-up and selection of antimicrobial agents.

Cytokine release syndrome (CRS): CRS affects 30-100% of all patients, with \geq grade 3 CRS reported in 10-30%³⁴. Incidence depends on the CAR-T product, disease characteristics and CRS grading system used. Typical onset is between 1-14 days post-CAR-T infusion and duration is commonly between 1-10 days. Rare delayed cases are reported⁹.

CRS is characterised by fever $\geq 38^{\circ}\text{C}$, hemodynamic instability and hypoxemia. Severity is graded according to the ASTCT consensus criteria (Figure 1)³⁵ and the differential diagnosis includes neutropenic sepsis. Empiric, broad-spectrum IV antibiotics should be commenced.

CAR-T activation leads to effector cytokine release (IFN- γ , TNF- α , IL-2) which can trigger pro-inflammatory cytokine release (IL-1, IL-6, IFN- γ , IL-10 and MCP1), with increased CRP and hyperferritinemia²⁴. Risk factors for high-grade CRS include tumor burden, concurrent infection, CAR-T dose and product, and LD conditioning intensity³⁶.

CRS management combines symptomatic measures (antipyretics, fluids) with tocilizumab (IL6 receptor antagonist) +/-corticosteroids¹⁰. When two doses of tocilizumab (8mg/kg) fail to control CRS, dexamethasone should be administered. Tocilizumab should be used earlier in older, co-morbid patients. Early/prophylactic tocilizumab has been studied in CRS but there is insufficient data to date to support a formal recommendation of this approach.

Clinicians should be vigilant for occult sepsis emerging post-tocilizumab. Gastrointestinal perforation has also been reported³⁷. Corticosteroids should be subject to rapid taper once CRS is controlled.

If CRS does not respond to tocilizumab/corticosteroids, alternative therapeutic options include siltuximab and anakinra, but limited clinical data is available³⁸. There should additionally be a high index of suspicion for underlying/concurrent infection or macrophage activation syndrome (MAS). A suggested CRS management algorithm is shown in Figure 1.

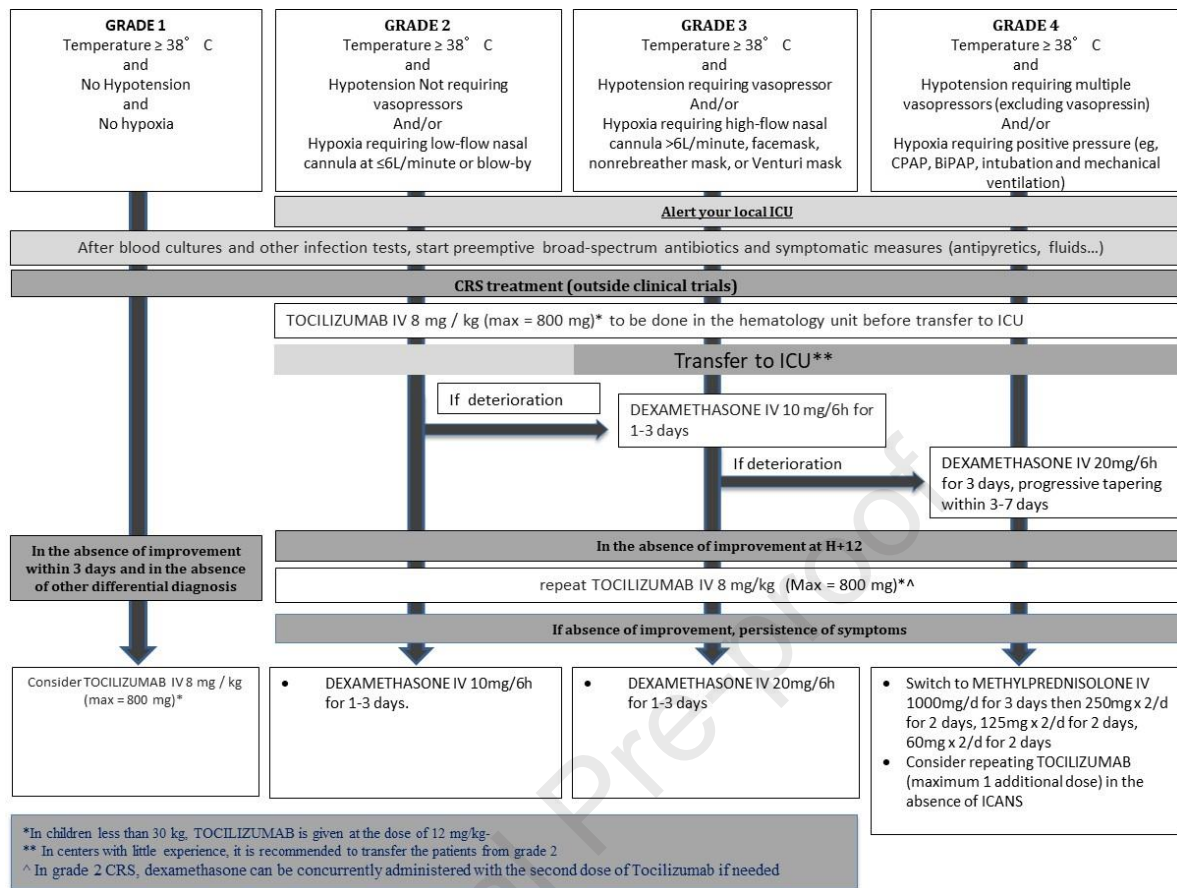


Figure 1: Algorithm outlining the grading and management of CRS

Macrophage Activation Syndrome (MAS): Persistent fever despite tocilizumab with organomegaly, cytopenias (+/- hemophagocytosis in the bone marrow), hyperferritinemia ($>10,000$ ng/mL), liver dysfunction, coagulopathy (hypofibrinogenemia requiring cryoprecipitate/fibrinogen concentrate) and hypertriglyceridemia, favors a CRS/MAS overlap syndrome rather than CRS³⁹.

Patients should be monitored with twice daily blood tests (WBC, liver function, ferritin, CRP) and treated with anakinra, a recombinant humanised IL-1 receptor antagonist, in combination with corticosteroids⁴⁰ (Figure 2). In refractory CRS/MAS, chemotherapy can be used, albeit there is a lack of data and a high risk of ablating CAR-T. Where there is neurological involvement, intrathecal chemotherapy can be considered^{41,42}.

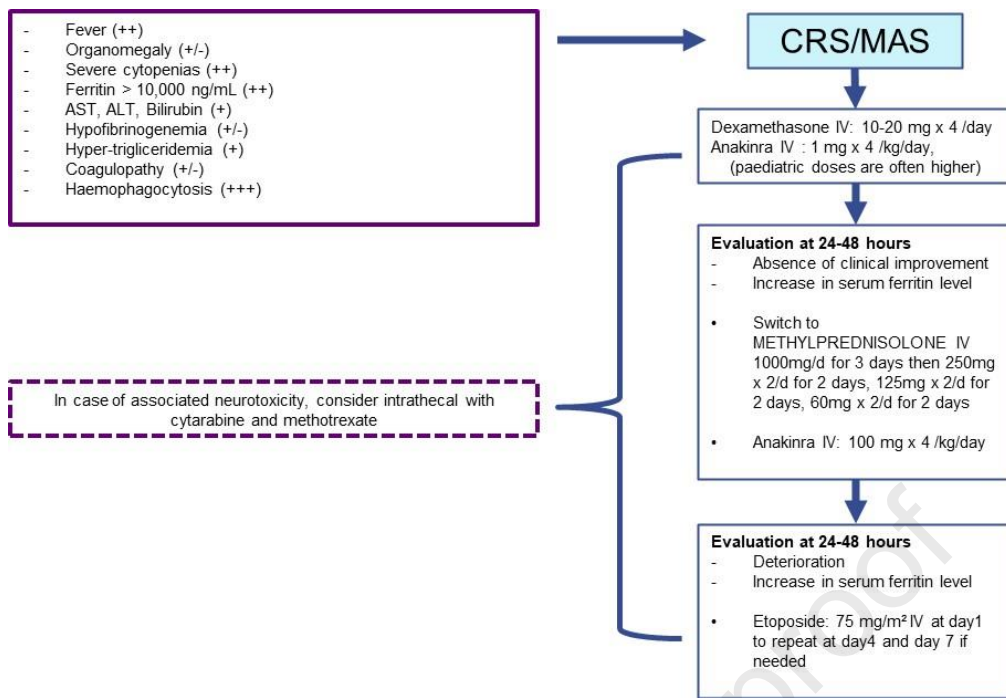


Figure 2: Management of CRS/MAS (expert opinion based on literature review) ³⁸⁻⁴²

Immune effector cell-associated neurotoxicity syndrome (ICANS): ICANS affects 20-60% of CD19CAR-T patients (grade ≥ 3 , 12-30%). Onset is typically three to five days after CAR-T but can occur concurrently with/shortly after CRS, and 10% of patients develop ‘delayed ICANS’ more than three weeks after infusion^{43,44}. Classical ICANS is also reported, to a lesser extent, with CD22- and BCMA-targeting CAR-T⁴. On the CARTITUDE study of LCAR-B38M, a series of movement/neurocognitive disorders/nerve palsies/peripheral motor neuropathies have been observed (12% of cases), not temporally associated with CRS, that are of later onset (median day 27), and take longer to resolve (median 75 days)⁴⁵. These will require ongoing evaluation in clinical trials. ICANS is rarely reported in solid tumor CAR-T studies.

The pathophysiology of ICANS is likely to be due to a combination of inflammatory cytokines increasing vascular permeability; endothelial activation leading to blood-brain barrier breakdown; increased CSF cytokines and in some cases leading to cerebral edema⁴⁰. Pharmacokinetics indicate that greater, earlier CAR-T expansion in vivo correlates with higher ICANS risk⁴⁶. Risk factors for \geq grade 3 ICANS include CD28-CAR-T products, higher CAR-T doses, high disease burden, pre-existing neurological conditions, low platelet count, and early, severe CRS⁴⁷. High fever ($\geq 38.9^{\circ}\text{C}$) and hemodynamic instability within 36 hours of CAR-T infusion predicts for severe ICANS with high sensitivity⁴⁸.

Symptoms include tremor, confusion, agitation, and seizures. Dysphasia, hesitant speech and deterioration in handwriting is prominent and can progress to expressive and receptive aphasia⁴⁸. Routine anti-convulsant prophylaxis is not recommended except in high-risk cases. Fatal cerebral edema has been described⁴⁸. Late psychiatric presentations have also been reported⁴⁹.

ICANS is a clinical diagnosis, but MRI brain and CSF examination can exclude alternative diagnoses¹⁰. Electroencephalogram (EEG) can be normal but can also demonstrate slowing and non-convulsive status epilepticus. Diagnostic work-up should include CT head, clotting screen/fibrinogen and EEG, MRI, and lumbar puncture (LP) in severe ICANS, or steroid-refractory cases.

Duration and frequency of ICANS monitoring should be conducted as per product label/trial protocol. The ten-point Immune Effector Cell Encephalopathy (ICE) score in adults (Table 9) and the CAPD assessment in children (Table 10) is usually performed twice daily. ICANS grading integrates the ICE/CAPD scores into an overall assessment of neurological function (Figure 3).

Management is supportive for grade 1 ICANS. Corticosteroid therapy with a rapid taper is indicated for grade ≥ 2 ICANS and ICU transfer should be considered (Figure 3). Evidence suggests that steroids do not impact CAR-T efficacy, although longer courses can be associated with shorter PFS⁵⁰. Seizures are treated with levetiracetam and status epilepticus with benzodiazepines. There is no clear therapeutic role for tocilizumab in ICANS and it has been suggested that it may contribute to ICANS through increase circulating IL-6⁴⁶. In the specific setting of grade 1 CRS with concurrent \geq grade 2 ICANS, it is appropriate that steroids (and not tocilizumab) be administered, but this does not apply in higher grade CRS. Alternative agents include siltuximab and anakinra, but clinical data on their utility in ICANS is limited. A management algorithm for ICANS is shown in **Figure 3**.

Test	Points
Orientation: orientation to year, month, city, hospital	4
Naming: ability to name three objects (e.g., table, television, pillow)	3
Following commands: ability to follow simple commands (e.g., “smile” or “open your mouth”)	1
Writing: ability to write a standard sentence (e.g., “Happy to have my family around”)	1
Attention: ability to count backwards from 100 by 10	1

Table 9. ICE score for neurological toxicity assessment. Adapted from Lee et al⁴⁸

Test	always	often	sometimes	rarely	never
Eye contact with caregiver	0	1	2	3	4
Purposeful actions	0	1	2	3	4
Aware of their surroundings	0	1	2	3	4
Being restless	4	3	2	1	0
Being inconsolable	4	3	2	1	0
Being underactive	4	3	2	1	0
Slow response to interactions	4	3	2	1	0
Communicating needs and wants	5	4	3	2	0

Table 10. CAPD for encephalopathy assessment in children < 12 years, Adapted from Traube et al^{51,52}.

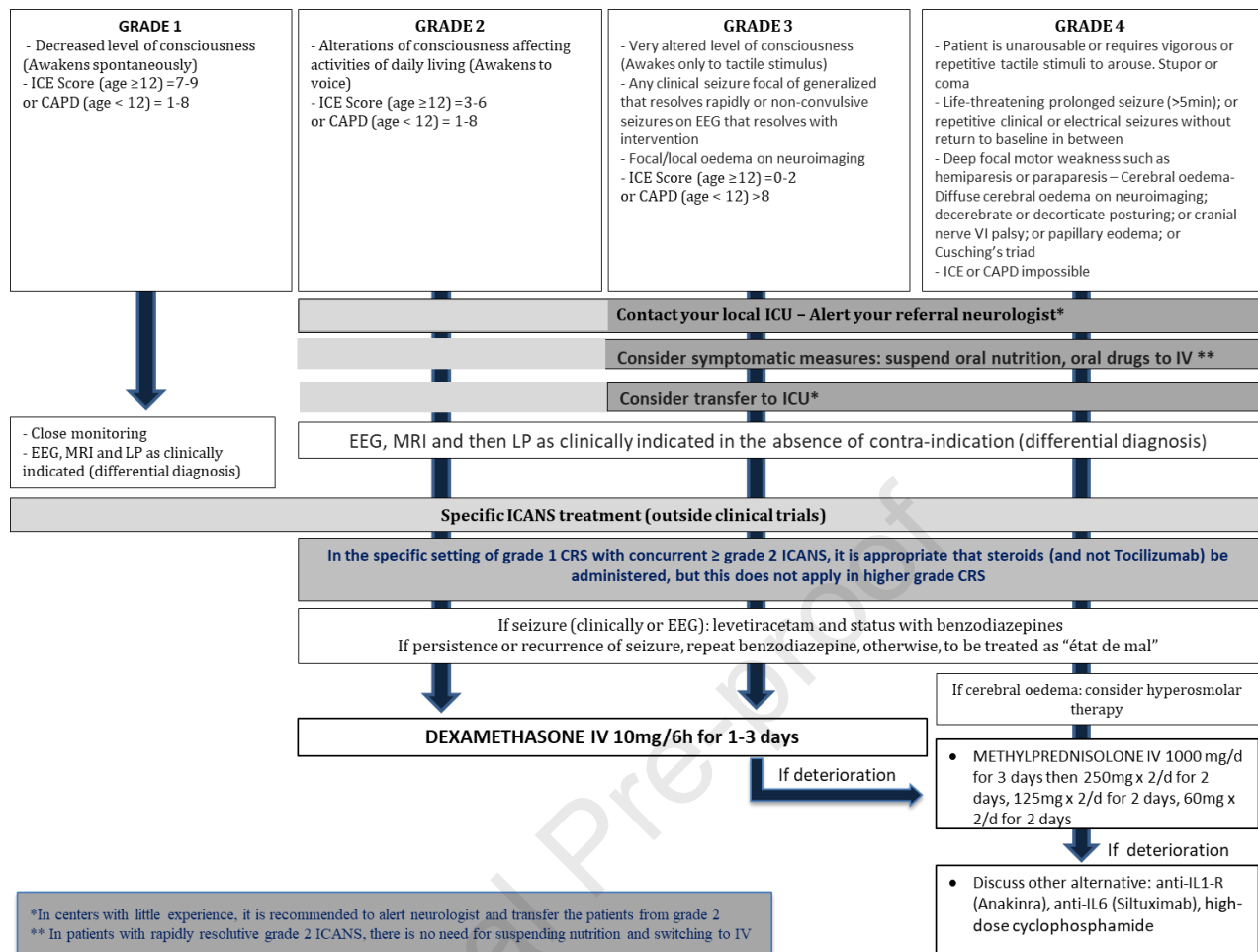


Figure 3: Grading and management of ICANS

Cardiovascular Toxicity: 10-20% of CAR-T patients experience cardiovascular complications⁵³. Hypotension requiring vasopressor support was the main cardiac complication observed in pediatric CAR-T studies, but arrhythmias, myocardial impairment, left ventricular systolic dysfunction (LVSD), decompensated cardiac failure, and cardiovascular death are reported⁵⁴.

Risk factors for CAR-T-cardiotoxicity include \geq grade 2 CRS⁵⁵, more often in high disease burden and patients with pre-existing cardiac dysfunction following prior exposure to cardiotoxins including anthracyclines, radiation, and tyrosine kinase inhibitors.

Thorough pre-CAR-T cardiovascular assessment with appropriate surveillance and risk reduction strategies may reduce CAR-T-cardiovascular complications. Elevated baseline serum cardiac biomarkers (troponin, N-terminal-pro-brain-natriuretic-peptide (NT-proBNP), may signal a greater risk of CAR-T-cardiotoxicity. Electrocardiograph (ECG) will exclude underlying arrhythmias and QT interval (as a surrogate for cardiac repolarisation abnormalities) and transthoracic echocardiography (TTE) defines baseline left ventricular ejection fraction (LVEF) and diastolic function to identify pre-existing LVSD (using 4D volumetric, 2D Simpson's Biplane, and global longitudinal strain assessment tools). Cardiac magnetic resonance (CMR) can be considered in the setting of poor image quality, including patients with pericardial/myocardial involvement on PET to assess lymphomatous infiltration.

On admission, baseline ‘dry weight’ and daily weights should be recorded, where weight increase as a surrogate for fluid overload should prompt repeat cardiac assessment with serum biomarkers, ECG, TTE and cardiologist review.

Tocilizumab is also associated with rapid improvement in cardiovascular complications⁵⁶. One retrospective analysis showed a 1.7-fold increased risk of CAR-T-cardiotoxicity with each 12-hour delay in tocilizumab administration from CRS onset⁵⁵. Current experience suggests that CAR-T-cardiotoxicity is an early, largely reversible phenomenon, with rare LVSD beyond 6 months and no late cardiovascular effects at one year⁴⁹.

Laboratory testing: CRP, fibrinogen, liver function tests and ferritin are checked daily. Cytokine testing is not routinely performed in most centers. Atypical lymphocytes that resemble leukemic blasts are not uncommon at peak CAR-T expansion. Repeat microbiological testing and imaging to exclude infection is recommended in febrile patients.

MEDIUM TERM COMPLICATIONS: DAY +28 TO DAY +100

Delayed TLS/CRS/ICANS: Although rare, delayed events can occur and should be managed according to standard protocols (Figures 1, 2 and 3). Table 11 outlines recommended testing during this period to monitor for complications.

Tests	EBMT/EHA recommendations		Comments
	Purpose	Frequency	
FBC, Biochemistry panel, AST, ALT, bilirubin, LDH, Fibrinogen, CRP	Standard follow-up	At every visit and as clinically indicated	
CMV, EBV, Adenovirus, COVID-19	Viral reactivation/ infection (post-allo-HCT)	As clinically indicated	
Quantitative Immunoglobulins or Serum protein electrophoresis	Immune reconstitution	1-3 monthly	Consider IV (or SC) immunoglobulin replacement
Peripheral blood Immunophenotyping – CD3/4/8/16+56/19+	Immune recovery	Once monthly for first three months, three monthly thereafter in first year	Guide to anti-infective prophylaxis and vaccination schedule
CAR T monitoring	CAR T persistence	Peripheral blood flow cytometry or transgene by molecular methods as clinically indicated	This is not feasible in most centers. For B-ALL, B-cell aplasia may be used as a surrogate for persistence

Table 11. Patient monitoring during medium-term follow-up. Abbreviations. FBC: full blood count; CMV: cytomegalovirus; EBV; Epstein-Barr virus; IV: intravenous; SC: subcutaneous. * Additional tests and imaging can be performed as clinically indicated.

Infections and antimicrobial prophylaxis: Opportunistic infections are common and prophylaxis is warranted until immune reconstitution (Table 12)⁴³. Risks include prior autologous/allo-HCT, bridging therapy, and steroids/tocilizumab for CRS/ICANS. Prolonged neutropenia, CD4 T-cell lymphopenia and B-cell aplasia/hypogammaglobulinemia (affecting up to 46% of patients at Day +90) also contribute. Neutropenia beyond day +30 and beyond

day +90 affects 30% and 10-20% of patients, respectively. Prolonged CD4 T-cell lymphopenia resolves to $>200/\mu\text{L}$ by 1 and 2 years in 65% and 86% of patients, respectively⁵⁷.

Most early infections (first 30 days) are bacterial, or respiratory viral infections. Invasive fungal infections are rare. Risk factors include B-ALL with prior allo-HCT; prior fungal infection and prior long-term/high-dose steroid exposure⁵⁸.

Beyond Day +30, viral infections predominate. HSV and VZV reactivation is uncommon in patients on valaciclovir prophylaxis. CMV, EBV, adenovirus, HHV6, BK-virus and JC-virus reactivation are rare and routine monitoring is not advised, except in high-risk patients (allo-HCT; high-dose/long-term corticosteroids)⁵⁹. COVID-19 is a formidable challenge in CAR-T patients and consortium guidance on how to maintain CAR-T delivery through the pandemic is available.

Evidence suggests that CAR-T manufacturing is feasible in HBV, HCV and HIV infection and treatment is safe provided the virus is undetectable before apheresis and prior to starting LD. In hepatitis B infection (especially if HBsAg+ and HBV-DNA+), long-term entecavir/tenofovir/equivalent prophylaxis is recommended.

	EBMT/EHA recommendation	Comments
Neutropenia	G-CSF to shorten duration of neutropenia from day +14 or after resolution of CRS or ICANS. Can consider starting earlier, e.g., day 5*, if patient is at high risk of infection, e.g., ALL, post-allo-HCT, high-dose steroids. For persistent neutropenia ($<0.5 \times 10^9/\text{L}$) following Day +28, consider G-CSF.	Avoid if patient has CRS or ICANS
Antibacterial prophylaxis	Not routinely recommended**	Can be considered in case of prolonged neutropenia and should be based on local guidelines e.g., with levofloxacin or ciprofloxacin.
Anti-viral	Valaciclovir 500 mg bid or aciclovir 800mg bid	Start from LD conditioning until one-year post-CAR T-cell infusion AND until CD4^+ count $>0.2 \times 10^9/\text{L}$
Anti-pneumocystis	Co-trimoxazole 480 mg once daily or 960 mg three times each week. To start from LD conditioning until one-year post-CAR-T cell infusion AND until CD4^+ count $>0.2 \times 10^9/\text{L}$. Where there is prolonged myelosuppression, postpone start after $\text{ANC} > 0.5 \times 10^9/\text{L}$.	Can be started later depending on centre guidelines. In case of co-trimoxazole allergy (or cytopenias precluding use of co-trimoxazole), pentamidine inhalation (300 mg once every month), dapsone 100 mg daily or atovaquone 1500 mg once daily can be considered.
Systemic anti-fungal prophylaxis	Not recommended routinely; consider posaconazole (300mg/d) or fluconazole (200 mg/d) or micafungin (50 mg i.v./d) in patients with severe ($\text{ANC} < 0.5 \times 10^9/\text{L}$) or prolonged (> 14 days) neutropenia and/or in patients on long-term or high dose (> 72 h) corticosteroids or in patients post-allo-HCT.	In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids, posaconazole prophylaxis should be considered.
IV Immunoglobulin	Routine in children. Consider in adults with serious/recurrent infections with encapsulated organisms and hypogammaglobulinemia ($< 4\text{g/L}$).	Clinical evidence does not support routine use in adults following allo-HCT.

Table 12. Infection prophylaxis post-CAR-T. Abbreviations. G-CSF: granulocyte colony stimulating factor; CRS: cytokine release syndrome; LD: lymphodepleting conditioning; NCCN: The National Comprehensive Cancer Network, allo-HCT: allogeneic hematopoietic cell transplantation.

* A negative impact of G-CSF applied earlier after CAR-T has not been clearly demonstrated; a recent report starting G-CSF on day 5 after CAR-T infusion showed no increase in CRS or ICANS, indicating that earlier application may be safe and may reduce duration of neutropenia. Further data to support this observation is required.⁶⁰

** In patients with neutropenic fever, empiric treatment with broad-spectrum antibiotics is strongly recommended.

B-cell aplasia & hypogammaglobulinemia: Following CAR-T, B-cell aplasia is associated with sino-pulmonary infections and should be measured regularly¹⁰. 83% of paediatric B-ALL patients on the ELIANA study had ongoing B-cell aplasia at 6 months. In ZUMA-1 responders, 25% had ongoing B-cell aplasia at 12months.

Due to immunological immaturity, immunoglobulin replacement is routine in pediatric CAR-T. In adults, long-lived plasma cells following CD19 CAR-T may confer an immune-protective effect, but a common approach is immunoglobulin replacement for hypogammaglobulinemia (<4g/L) with serious or recurrent/chronic infections. Data on efficacy of immunoglobulin replacement in CAR-T is limited and current recommendations are mainly extrapolated from primary immunodeficiencies (e.g., Bruton's agammaglobulinemia). One study showed that increased serum IgG led to significantly less sinopulmonary infection post-CAR-T⁶¹.

Immunoglobulin replacement aims to maintain serum levels above 4 g/L in adults and within age-adapted normal ranges for children, titrated to the incidence of breakthrough infection.

Intravenous immunoglobulins (IVIGs) (0.4g/kg) and subcutaneous (SCIGs) (0.1–0.15g/kg) are administered 3-6 weekly, and weekly, respectively. After reaching steady state, levels should be measured three monthly.

Cessation of immunoglobulin replacement should be guided by recovery of functional B-cells. This also provides a surrogate for functional CAR-T persistence and may be useful in clinical decision making, particularly in B-ALL.

Vaccinations: General guidance is outlined in Table 13, applicable to adults and children. Incomplete immune reconstitution or ongoing immunosuppression confers a high likelihood of lower vaccine responses (including COVID-19), but consensus view is that vaccination may reduce infection rates and improve clinical outcome. Recommendations and adherence to national schedules require individualized assessment based on infection history and laboratory assessments of cellular/humoral immunity, where available. Specific antibody responses to vaccination should be assessed where possible. A recent analysis in adults following CD19- and BCMA-CAR-T indicated that despite hypogammaglobulinemia, CD19-CAR-T patients developed seroprotection comparable to the general population (with the exception of specific pathogens e.g., pneumococcus), but that in BCMA-CAR-T patients, fewer pathogen-specific antibodies were detected⁶². This highlights the need for vaccine and immunoglobulin replacement studies in this at-risk population. Further analysis of T-cell vaccine responses is also warranted in this group.

Agent	EBMT/EHA recommendations		Comments
	Pre-CAR-T	Post-CAR-T	
Influenza Vaccine	Preferably vaccinate 2 weeks prior to LD. In B-cell aplasia low likelihood of serological response	> 3 months after CAR-T patients should be vaccinated irrespective of immunological reconstitution	Where there is incomplete immune reconstitution* or ongoing immunosuppression, there is a high likelihood of lower vaccine responses. Consensus view is that vaccination may still be beneficial to reduce rates of infection and improve clinical course. Consider boost upon B-cell recovery.
SARS-Cov-19	Preferably vaccinate prior to CAR-T therapy. In B-cell aplasia low likelihood of serological response	> 3 months after CAR T-cell infusion.	No reports on vaccine response after CAR-T exist. However, SARS-Cov-19 vaccine-induced protection relies heavily on T-cell mediated immunity, therefore B-cell aplasia does not seem to be a contraindication; No T cell threshold has been defined. Post vaccination response monitoring is desirable. Consider boost upon B-cell recovery.

Killed / Inactivated vaccines		> 6 months after CAR-T and > 2 months after immunoglobulin replacement	Contraindications include concurrent immunosuppressive or cytotoxic therapy.
Live and non-live adjuvant vaccines		1 year after CAR-T and fully immune reconstituted *	Contraindications include < 2 years post allo-HCT, < 8 months after completion of immunoglobulin replacement.

Table 13. Eligibility Criteria for Vaccination in patients receiving CD19-targeted CAR T-cell therapy [adapted from Hill and Seo.⁶³ * Absolute CD4 T cells > 0.2x10⁹/L, CD19 or CD20 positive B-cells > 0.2x10⁹/L, no concomitant immunosuppressive or cytotoxic therapy

Graft-versus-Host Disease (GvHD): CAR-T post-allo-HCT is generally considered safe without increased risk of high-grade GvHD. However, a recent publication describes histologically confirmed GvHD in 4 pediatric patients post-KymriahTM.⁶⁴ GvHD post-CAR-T should be diagnosed and managed using standard protocols, balancing the benefits of systemic immunosuppression against the adverse impact on CAR-T viability.

Delayed cytopenias: Haematological toxicity has a cumulative one-year-incidence of 58%, post-CD19-CAR-T, is often prolonged and can follow a biphasic temporal course, with initial neutrophil recovery followed by a ‘second dip’⁶⁵.

Duration and severity vary between products and indications, but there is a high incidence of persistent grade ≥ 3 neutropenia (30-38%), thrombocytopenia (21-29%), and anemia (5-17%) after Day +28⁶⁶⁻⁶⁹. Risk factors include baseline cytopenias, pre-treatment bone marrow disease burden, an inflammatory state, prior allo-HCT within one year, and severe CRS/ICANS^{65,70}. Protracted cytopenias are less pronounced in BCMA- and solid tumor targeting CAR-T.^{6,68}

The pathophysiology remains poorly understood and there may be product-intrinsic and/or disease-specific factors. Investigations should consider hematinic deficiency, myelosuppressive medications (co-trimoxazole), and viral infections (HHV6, Parvovirus B19). Bone marrow biopsy may be useful beyond day 28 to exclude recurrent disease, hemophagocytosis and rarely, myelodysplasia.

G-CSF can be used for severe neutropenia ($< 0.5 \times 10^9/L$) from day +14 onwards, following resolution of CRS/ICANS. Recent data on earlier prophylactic G-CSF found no effect on immunotoxicity, CAR-T expansion, or prognosis.⁶⁰

G-CSF-refractory neutropenia (ANC $< 100/\mu l$) lasting ≥ 30 days affects 5-10% of patients, with a risk of fungal infection⁷¹. Autologous stem cell rescue is an option, where cells are available⁷² and donor-derived, unconditioned CD34+-selected ‘top-up’ can be considered in post-allo-HCT patients⁷³. Anti-inflammatory therapies (dexamethasone) and EPO/TPO-agonists may have a role. Allo-HCT is the last resort in patients with refractory cytopenias.

LONG-TERM FOLLOW-UP (LTFU): FROM DAY +100

LTFU should be conducted by a multi-disciplinary team (CAR-T physicians; disease-specific specialists; LTFU nursing staff; data managers; clinical trial staff) to capture disease status and late effects¹⁴.

Prolonged cytopenias, hypogammaglobulinemia and infections are common. Neurological complications and pulmonary toxicity confer an increased mortality risk. Secondary malignancy is rare: a single report of relapse following transduction of a leukemic B-cell during the manufacturing process is described⁷⁴ and a case of myelodysplastic syndrome was reported

in the ZUMA-1 trial. A recent publication described CAR-T-derived malignancies following genome-edited CD19-CAR-T due to insertional mutagenesis⁷⁵. This area requires ongoing surveillance.

CAR-T centres should liaise with referral centres, providing protocols and policies for LTFU, to sustain shared care arrangements.

A recommended LTFU schedule of attendance and testing schedule are outlined in Tables 13 and 14.

Period	EBMT/EHA recommendations	
	Visit frequency	Outcomes to be monitored:
Day +100 to one year	Monthly	<ul style="list-style-type: none"> • Disease – remission, minimal residual disease (MRD) status, relapse, death • Subsequent treatments including allo-HCT and other IEC therapy/ATMP • Immunological status – immune cell markers, immunoglobulins, CAR T persistence
One year to two years	Six-monthly	<ul style="list-style-type: none"> • New cancers/ secondary myeloid diseases • Autoimmunity and new autoimmune diseases • Endocrine, reproductive and bone health including growth and development
Two to fifteen years	Annually	<ul style="list-style-type: none"> • Neurological status (recovery from ICANS) • Psychological status and quality of life • Cardiovascular disease, including risk factors such as metabolic syndrome • Respiratory function • Gastrointestinal and liver health • Vaccination guidance (see Section 3.4) • Patients who proceed to subsequent allo-HCT, cytotoxic therapy and/or immune effector cell therapy should be followed as per Majhail et al 2012¹³¹

Table 13. Recommended minimum frequency of attendance at CAR-T centre for patients in remission for Late Effect monitoring.

Test	Purpose	EBMT/EHA recommendations	Comments
		Frequency	
Full Blood Count, Biochemistry panel	Standard follow-up	At every visit	
Viral infection (PB PCR, NPA)	Viral reactivation/infection	As clinically indicated	
Quantitative Immunoglobulins +/- serum protein electrophoresis	Immune reconstitution	At every visit	
Peripheral blood Immunophenotyping – CD3/4/8/16+56/19*	Immune reconstitution	Every second visit	No longer required following normalization
CAR-T monitoring where commercial kits are available for routine monitoring of anti-CD19 CAR-T*	CAR-T persistence	Every visit	No longer required when absent for two consecutive tests
Endocrine function and other standard late effects testing appropriate to age	Standard follow-up	Yearly or as clinically indicated	

Table 14. Recommended tests to be performed at LTFU clinic. Key: PB: peripheral blood; NPA: nasopharyngeal aspiration. *Equivalent test methods for other immune effector cells as they become available.

POST-AUTHORISATION SAFETY SURVEILLANCE/ REGISTRY

CAR-T qualify as ‘Genetically Modified Organisms’ or GMOs and competent authorities (US Food and Drug Administration (FDA); EMA) mandate LTFU for 15 years.

Post-Authorization Safety Studies (PASS) collect data on adverse events via pre-existing or dedicated registries. The EBMT Registry has created a Cellular Therapy Form (CTF) to register and monitor European CAR-T recipients.

Working with the North American CIBMTR Cellular Immunotherapy Data Resource (CIDR), EBMT is uniquely positioned to provide a global overview of this new therapy class. Further, EBMT and EHA established the GoCART consortium to harmonize standards, guidelines and regulatory requirements relating to ATMP delivery across the EU (<https://www.ebmt.org/ebmt/gocart-coalition>).

JACIE AND REGULATORY ISSUES

FACT-JACIE standards guide accreditation of HCT program activity across the US and the EU with the aim of improving outcomes. Version 6.1 included a section on Immune Effector Cells (IEC). The currently active 7th and 8th editions of the standards subsequently integrated IEC standards covering CAR-T therapy throughout the clinical, collection and processing sections. Documentation is available at <http://www.jacie.org>.

EBMT and JACIE recommend that CAR-T is best delivered from within an accredited HCT program. JACIE facilitate inspections and ensure that programs comply with data submission to the EBMT Registry, with a view to benchmarking purposes.

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Patrick J. Hayden - Janssen, Takeda, Amgen, Celgene, Alnylam

Claire Roddie – Novartis, Gilead, BMS

Peter Bader - Neovii, Riemsler, Medac, Novartis, Gilead, Celgene BMS, Miltenyi, Jazz, Riemsler, Amgen, Servier

Grzegorz W. Basak – Kite/Gilead, Novartis, Celgene/BMS and FamicordTx

Halvard Bonig - Novartis and Celgene

Chiara Bonini - Intellia Therapeutics, TxCell, Novartis, GSK, Molmed, Kite/Gilead, Miltenyi, Kiadis, QuellTx, Janssen, Allogene

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Jan Styczynski – MSD, Gilead, Pfizer, Kite, Novartis, TEVA

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CONTRIBUTION

PH, CR and IYA-designed the research and wrote the methodology chapter and the first draft of the manuscript. Each co-author participated in writing his/her own chapter according to their field of expertise. They all participated in the discussion during the 3 teleconferences and the final 2-day meeting. They discussed and approved all recommendations. The final manuscript has been approved by all co-authors.

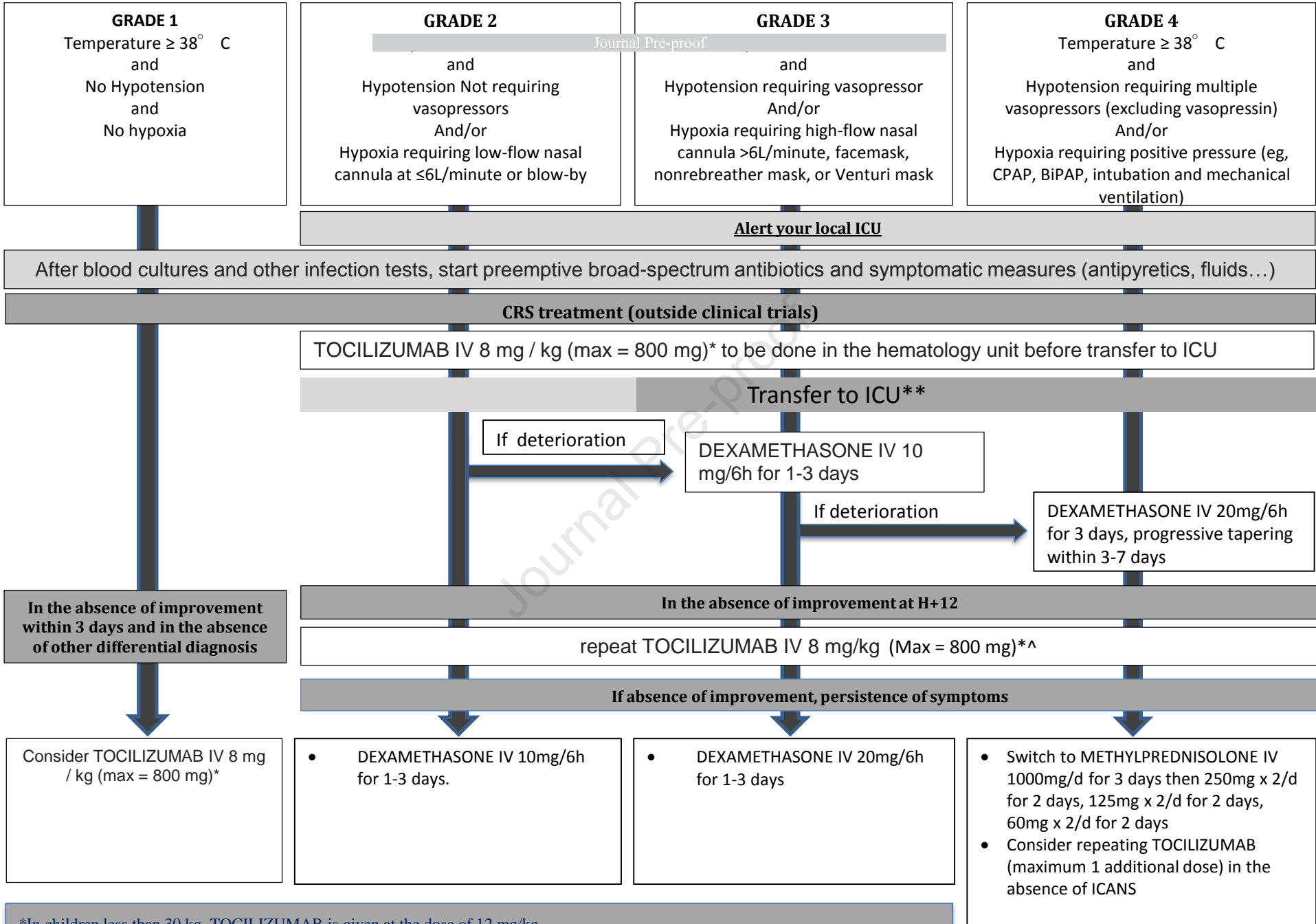
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*In children less than 30 kg, TOCILIZUMAB is given at the dose of 12 mg/kg-

** In centers with little experience, it is recommended to transfer the patients from grade 2

^ In grade 2 CRS, dexamethasone can be concurrently administered with the second dose of Tocilizumab if needed

- Fever (++)
- Organomegaly (+/-)
- Severe cytopenias (++)
- Ferritin > 10,000 ng/mL (++)
- AST, ALT, Bilirubin (+)
- Hypofibrinogenemia (+/-)
- Hyper-triglyceridemia (+)
- Coagulopathy (+/-)
- Haemophagocytosis (+++)

CRS/MAS

Dexamethasone IV: 10-20 mg x 4 /day
Anakinra IV : 1 mg x 4 /kg/day,
(paediatric doses are often higher)

Evaluation at 24-48 hours

- Absence of clinical improvement
- Increase in serum ferritin level
- Switch to METHYLPREDNISOLONE IV 1000mg/d for 3 days then 250mg x 2/d for 2 days, 125mg x 2/d for 2 days, 60mg x 2/d for 2 days
- Anakinra IV: 100 mg x 4 /day

Evaluation at 24-48 hours

- Deterioration
- Increase in serum ferritin level
- Consider Etoposide: 75 mg/m² IV at day1 to repeat at day4 and day 7 if needed

In case of associated neurotoxicity, consider intrathecal with cytarabine and methotrexate

or CAPD (age < 12) = 1-8

- ICE Score (age ≥12) =3-6
or CAPD (age < 12) = 1-8

Journal Pre-proof
- Focal/local oedema on neuroimaging
- ICE Score (age ≥12) =0-2
or CAPD (age < 12) >8

- Life-threatening prolonged seizure (>5min);
or repetitive clinical or electrical seizures without return to baseline in between
- Deep focal motor weakness such as hemiparesis or paraparesis – Cerebral oedema- Diffuse cerebral oedema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papillary oedema; or Cushing's triad
- ICE or CAPD impossible



- Close monitoring
- EEG, MRI and LP as clinically indicated (differential diagnosis)

Contact your local ICU – Alert your referral neurologist*

Consider symptomatic measures: suspend oral nutrition, oral drugs to IV **

Consider transfer to ICU*

EEG, MRI and then LP as clinically indicated in the absence of contra-indication (differential diagnosis)

Specific ICANS treatment (outside clinical trials)

In the specific setting of grade 1 CRS with concurrent ≥ grade 2 ICANS, it is appropriate that steroids (and not Tocilizumab) be administered, but this does not apply in higher grade CRS

If seizure (clinically or EEG): levetiracetam and status with benzodiazepines
If persistence or recurrence of seizure, repeat benzodiazepine, otherwise, to be treated as “état de mal”

DEXAMETHASONE IV 10mg/6h for 1-3 days

If cerebral oedema: consider hyperosmolar therapy

• METHYLPREDNISOLONE IV 1000 mg/d for 3 days then 250mg x 2/d for 2 days, 125mg x 2/d for 2 days, 60mg x 2/d for 2 days

If deterioration
• Discuss other alternative: anti-IL1-R (Anakinra), anti-IL6 (Siltuximab), high-dose cyclophosphamide

*In centers with little experience, it is recommended to alert neurologist and transfer the patients from grade 2
** In patients with rapidly resolvable grade 2 ICANS, there is no need for suspending nutrition and switching to IV