Specialist Pharmacy Service

NHS

Diagnosis and Medical Management of Acute CAR-T Cell Side Effects in Adults

Pan UK Pharmacy Working Groups for ATMPs

September 2022
Version 2

The first stop for professional medicines advice

Introduction

The Pan UK Pharmacy Working Group (PWG) for Advanced Therapy Medicinal Products (ATMPs) acts as an expert and informed body to support the activities of UK Pharmacies to facilitate ATMP usage. The group consists of pharmacists from across the UK that specialise in the governance, prescribing, administration and monitoring of ATMPs. The aims of the group are to promote good practice, identify and resolve pharmacy issues to maximise the effectiveness and development of services for hospitals to administer advanced therapies. The Pan UK PWG for ATMPs has a clinical subgroup which identified a need for consistent clinical advice regarding diagnosis and medical management of acute side effects for CAR-T cell therapy patients.

Author's Foreword

This guidance document has been produced by representatives of the Pan UK PWG for ATMPs which convened in order to provide exemplar documents for the key steps in the delivery of ATMPs.
This is a consensus guideline developed with input from the pharmacists and consultants from the first and second wave CAR-T centres across the UK. Thank you to all who have supported the development of this document.

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Scope

These consensus recommendations, prepared by the Pan UK Pharmacy Working Group for ATMPs, provide guidance on the management of acute side effects in adults receiving licensed CD-19 targeted CAR-T cell products. As new CAR-T products emerge, the principles in this guidance document can be applied to other newly licensed CAR-T cell products (e.g. BCMA targeted CARs for multiple myeloma) where clinically appropriate, but management must be in line with latest licensing and clinical guidance for these new products.
The purpose of this document is to provide guidance on the management of acute CAR-T cell side effects in adults to help inform the development of local guidelines and to standardise the management of acute CAR-T cell side effects across the UK.
This guidance is to support the use of licensed CAR-T cell products. Concepts can be applied to the management of patients participating in a CAR-T cell clinical trials but the clinical trial protocol must always be followed. It is also important to note that licensing and funding of treatments recommended in this document may not be applicable within the clinical trial setting.

Summary of Changes since Version 1

- Title changed from 'toxicity' to 'side effect'
- Scope added
- Removal of section on HLH – refer to separate HLH consensus guidelines (HLH Resources – Histio UK (hihasc.org)
- Medication details section moved from appendix to core text
- Updated steroid and alternative therapies dosing based on most recent evidence and publications

The Pan UK PWG for ATMPs would like to acknowledge and thank clinical subgroup members Alice Tam and Sumantha Gabriel for their work in the production of this document.

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Abbreviation	Expansion & Definition for this document
ASTCT	American Society of Transplant and Cellular Therapy
ATMP	Advanced Therapy Medicinal Product
IEC	Immune Effector Cell
CAR	Chimeric Antigen Receptor
DLBCL	Diffuse Large B-cell Lymphoma
B-ALL	B-cell Acute Lymphoblastic Leukaemia
CRS	Cytokine Release Syndrome
ICANS	Immune Effector Cell Associated Neurotoxicity Syndrome
HLH	Haemophagocytic Lymphohistiocytosis
ICE score	Immune Effector Cell-associated Encephalopathy score
ICP	Intracranial Pressure
CTCAE	Common Terminology Criteria for Adverse Events

1. Introduction to CAR-T Cell Therapy Side Effects

1.1 Introduction to CAR-T Cell Therapy

Chimeric Antigen Receptor T cells (CAR-T cells) are a type of Advanced Therapy Medicinal Product (ATMP), classified as ex-vivo (cell-based) gene therapy. They are a type of immunotherapy classed as Immune effector cell (IEC) therapies that are used to modulate an immune response for therapeutic intent. CAR-T cells are a novel class of systemic anti-cancer therapy in which autologous or allogeneic T cells are engineered to express a chimeric antigen receptor (CAR) targeting a membrane antigen which then enables the T cells to recognise and kill the targeted cancer cells.[1].

CAR-T cell therapy is a promising new area of cancer treatment. The first CAR-T cell products to receive NICE approval were axicabtagene ciloleucel (Yescarta®) and tisagenlecleucel (Kymriah®) which target CD19 and provide a promising treatment option for patients with diffuse large B-cell lymphoma (DLBCL) and B-cell acute lymphoblastic leukaemia (B-ALL)[2,3]. Trials are underway targeting a variety of cancers including other B-cell malignancies, myeloma, acute myeloid leukaemia and solid tumours. It is anticipated that the availability of licensed CAR-T products and new indications will increase and these guidelines can be applied to future products where clinically appropriate.

1.2 Common Acute Side Effects

CAR-T cell therapy offers promising results, but there are a range of serious side effects associated with treatment with CAR-T cells. Accurate assessment and prompt recognition and treatment of these side effects is essential as there is a high mortality risk if treatment is delayed or suboptimal. This guidance highlights the signs and symptoms of acute CAR-T cell related side effects and describes the management strategy.

The most common acute side effect is cytokine release syndrome (CRS) which can occur in up to 95% of recipients. The symptoms of CRS can range from mild constitutional symptoms to life-threatening multi-organ failure. CRS generally occurs within the first week after CAR-T therapy although it can occur later[4,5,6].
Neurotoxicity [immune effector cell associated neurotoxicity syndrome (ICANS)] is the second most common acute side effect affecting up to 80% of patients. Severity can vary from language disturbance, impaired handwriting, confusion and agitation to cerebral oedema and death[4,5,6].
This guidance focusses on the management of these two main acute side effects and **Figure 1** outlines a summary algorithm of these two main acute side effects. In the event of uncertainty over the diagnosis and/or appropriate management algorithm, the case should be escalated to the lead CAR-T consultant for further advice.

1.3 Less Common Side Effects

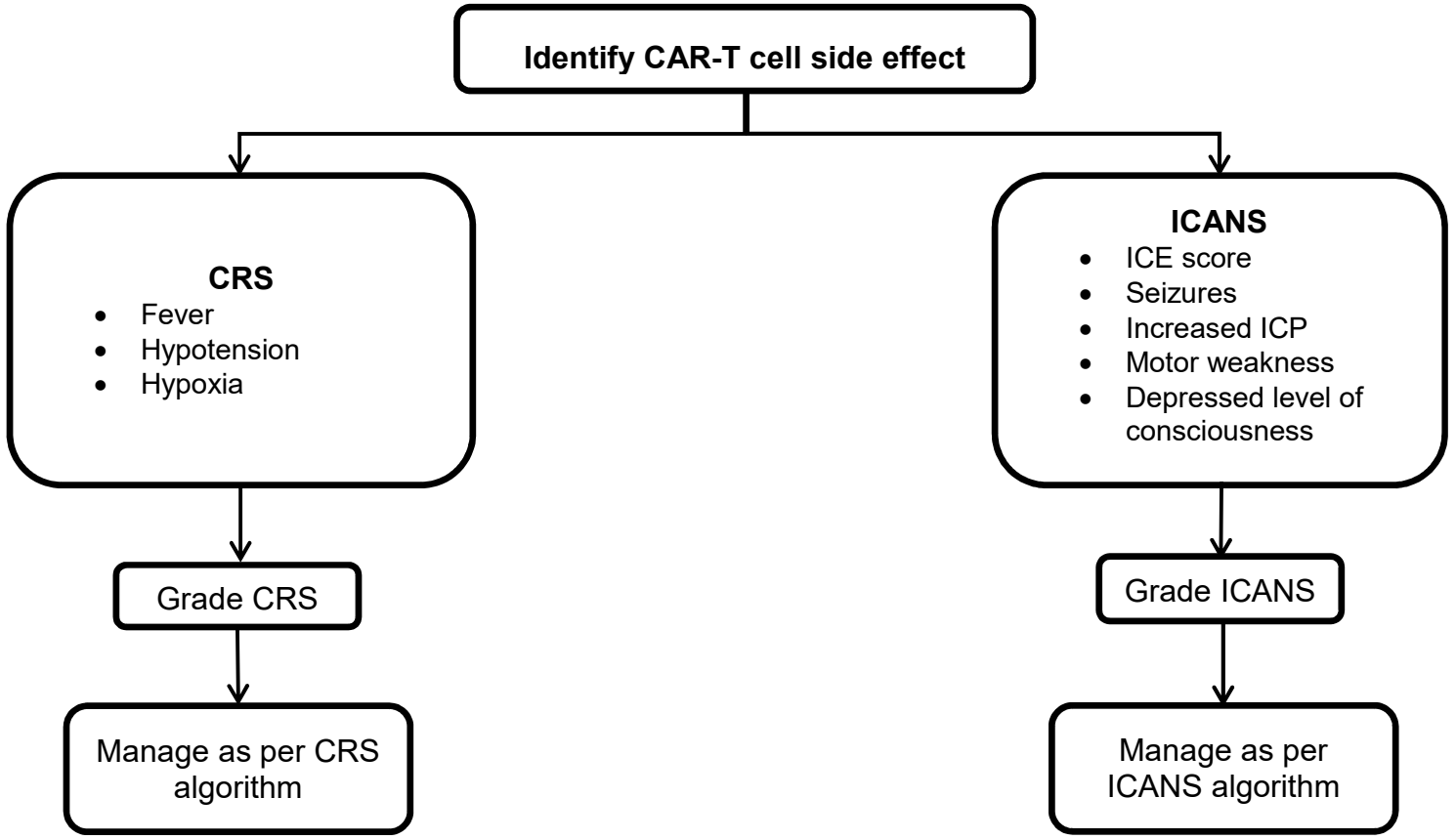
Haemophagocytic lymphohistiocytosis (HLH) is a rare, but very severe complication related to CRS. HLH should be managed in line with the *International consensus based guidelines for the treatment of people with HLH (adults and children) 2021*[7].
Tumour lysis syndrome (TLS) is another acute side effect that may occur post CAR-T cell treatment. The management of TLS is outside the scope of this guidance, and local and national guidance on the management of TLS should be followed[8].
CAR-T cell therapy can also cause longer term side effects including prolonged cytopenias and B-cell aplasia. Long term side effects are outside the scope of this guidance and the use of immunoglobulins should be managed in line with *NHS England Commissioning criteria policy for the use of therapeutic immunoglobulin in England (2021)*[9].
For recommended supportive medications alongside CAR-T cell therapy refer to the Pan UK PWG document *Supportive Medications Recommended for Adults Receiving Licensed Chimeric Antigen Receptor-T (CAR-T) Cell Therapy*.

1.4 Toxicity Grading Systems

Historically there was no consensus system for grading CAR-T related toxicities and the scales used varied between different products and clinical trial protocols. Lee et al[4], Penn Grading Scale[5] and the common terminology criteria for adverse events (CTCAE) were the most widely used scales.

These grading systems have been reviewed, and the American Society for Transplantation and Cellular Therapy (ASTCT) has established a consensus grading system for IEC toxicities[10] (**Appendix A**) which has been adopted in UK CAR-T centres. This grading system allows more objective clinical grading of toxicities. Other grading systems may still be used if specified in the clinical trial protocol.

Figure 1: Identification and assessment of CAR-T related side effects



Three-step approach to the assessment and management of acute side effects associated with CAR-T cell therapy

Step 1: The patient's clinical and biological symptoms should be monitored to determine the nature of the CAR-T cell related side effect.
Note: patients may have overlapping conditions

Step 2: The severity of CRS and/or ICANS should be graded as per ASTCT grading system (**Appendix A**)

Step 3: The side effects should be managed according to the management algorithms provided for CRS and ICANS. This includes early escalation, supportive care and targeted treatment.

2. Diagnosis and Management of Cytokine Release Syndrome (CRS)

Cytokine release syndrome (CRS) is a potentially serious but expected side effect of CAR-T cell therapy. It is an acute inflammatory process characterised by pyrexia, hypotension, hypoxia and elevated serum cytokines (predominately IL-6, IL-1, IL-2, TNFα and IFNγ) that usually occurs in the first 1-2 weeks following CAR-T infusion and typically lasts 2-7 days[4,5,6]. The severity of CRS is dependent on the tumour burden, the intensity of lymphodepletion and the proliferation rate and cytotoxicity of the CAR-T cell product.
CRS is graded as per the ASTCT Consensus Grading System[10] (**Appendix A**). Other grading scales may be used if specified by a particular clinical trial protocol.

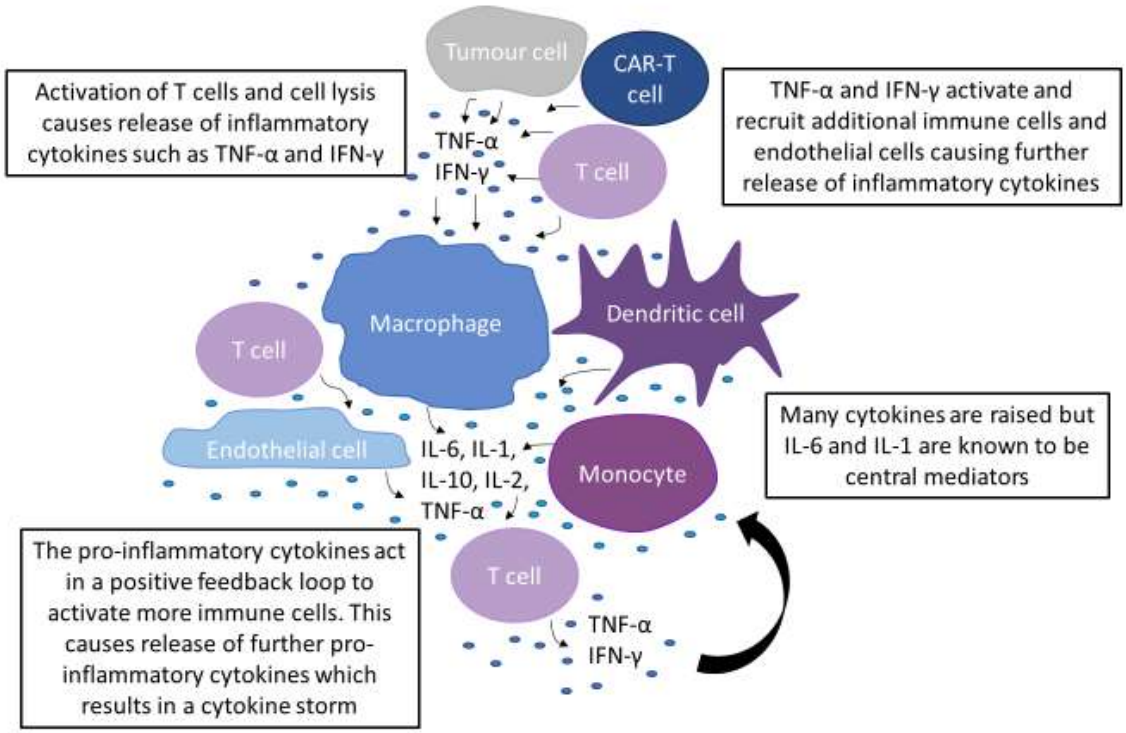
The signs and symptoms of CRS can mimic neutropenic sepsis and need to be treated with broad spectrum antimicrobials, paracetamol and intravenous fluids as per institutional guidelines to cover possible concurrent infection. Specific licensed medicines used to treat CRS are tocilizumab and corticosteroids. Alternative, unlicensed treatments include anakinra, siltuximab and other immune modulators.

All patients should be monitored closely for signs of CRS and remain as in-patients for at least 10 days post CAR-T cell infusion, as specified for current licensed CAR-T cell therapy. Delayed onset CRS has been reported so patients and carers must be informed of symptoms and when to escalate once discharged from hospital.

2.1 Pathophysiology

Figure 2 shows the current understanding of the pathophysiology of CRS. CRS clinically manifests when large numbers of lymphocytes (B cells, T cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines. The elevated inflammatory cytokines are product and patient specific, but studies have shown interferon gamma (IFN-γ), tumour necrosis factor (TNF-α), interleukin 6 (IL-6) and interleukin 1 (IL-1) are consistently raised[4,5,6,11]. IL-6 is the central mediator of toxicity in CRS and high levels of IL-6 mediate a pro-inflammatory signalling cascade.

Figure 2: Proposed pathophysiology of CRS



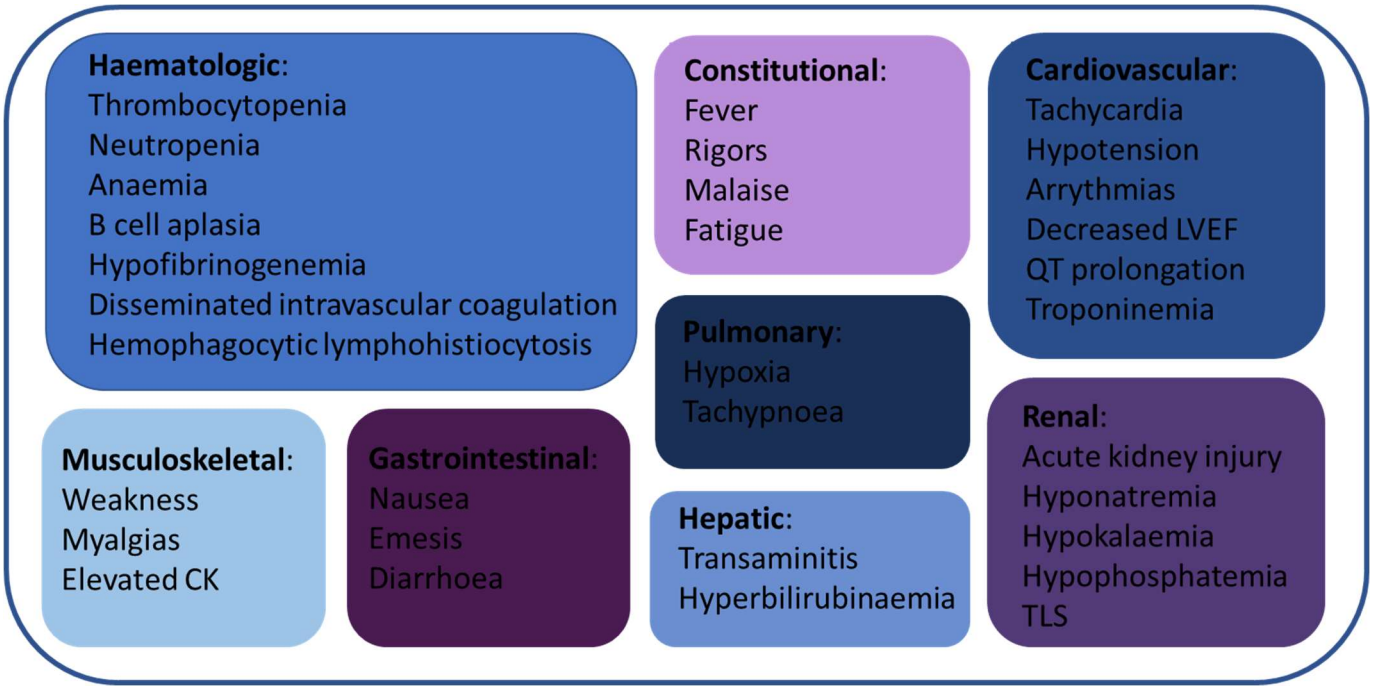
2.2 Recognition and Differential Diagnosis

CRS has a varied presentation from a mild flu-like illness to multi-organ failure[11]. The signs and symptoms of CRS can mimic tumour lysis syndrome or sepsis and therefore needs to be treated with broad spectrum antimicrobials, paracetamol and intravenous fluids as per institutional guidelines to cover possible concurrent infection.

In addition, both licensed treatments for CRS (tocilizumab and corticosteroids) can exacerbate severe active infection. This must be considered in all patients presenting with CRS symptoms. It is recommended to take appropriate cultures and initiate empirical antibiotic therapy prior to starting CRS specific treatments.

Figure 3 illustrates the possible signs and symptoms of CRS.
Potentially life-threatening complications of CRS include cardiac dysfunction, acute respiratory distress syndrome, neurological toxicity, renal failure, hepatic failure and disseminated intravascular coagulation. Haemophagocytic lymphohistiocytosis (HLH) can occur with high fevers, high ferritin, cytopenias and raised triglycerides. HLH should be managed in line with the *International consensus based guidelines for the treatment of people with HLH (adults and children) 2021*[7].

Figure 3: Cytokine release syndrome – signs and symptoms



2.3 Investigations and Management

If CRS is suspected, the following approach should be taken to ensure patients receive the correct therapy promptly:

1. **Identify** – History, examination, investigations
2. **Grade** – CRS severity should be graded to guide management (**Appendix A**)
3. **Escalate Early** – Contact ICU and CAR-T teams early to ensure prompt management
4. **Supportive Management** – Organ support, symptomatic management and monitoring
5. **Targeted management** – Tocilizumab, corticosteroids, and alternative treatments where applicable

The management of CRS is based on the grade. The treatment algorithm is shown below.
Please note that these are suggested guidelines based on evidence base and consensus opinion throughout the UK and some recommendations may differ from the current Summary of Product Characteristics (SmPC) for each of the licensed CAR-T products.

It is important to note that temperature often normalises within a few hours after tocilizumab administration whereas the other components of CRS take longer to resolve. The patient is considered to still have CRS even in the absence of fever, until all signs and symptoms leading to the diagnosis of CRS have resolved[10]. Refer to Appendix A for grading.

If CRS is suspected, immediately contact the CAR-T Team

Use of tocilizumab or corticosteroids must be authorised by the attending CAR-T

If CRS is suspected the following investigations should be performed:

- Ferritin
- FBC
- U&Es
- LFTs
- CRP
- Bone profile (if TLS in differential)
- Coagulation
- Daily ECG
- Appropriate imaging (e.g. chest X-ray)
- Blood and urine cultures
- Cytokine profile (if available)

For CRS grade 3 or 4 monitor with continuous cardiac telemetry and pulse oximetry
Consider performing an echocardiogram to assess cardiac function

Follow management table below

(If part of a clinical trial, contact the trial team and follow the specific trial protocol for management of CRS)

Grade 1 CRS
 	
Temp ≥38°C
No hypotension
No hypoxia
	• Monitor vital signs every 4 hours
	• Treat as per neutropenic sepsis guidelines:
	  - paracetamol
	  - intravenous fluids
	  - broad spectrum antibiotics
	• If persistent fevers >24hrs, consider IV tocilizumab [8mg/kg (max 800mg), every 8 hours, max 4 doses] (Note: this is an interim funding measure during COVID-19)

Grade 2 CRS Temp ≥38°C *AND* Hypotension responsive to fluids *AND/OR* Hypoxia requiring <6L/min oxygen	• Monitor vital signs hourly • Treat as per neutropenic sepsis guidelines • Administer IV tocilizumab [8mg/kg (max 800mg), every 8 hours, max 4 doses] • Consider IV dexamethasone [10mg – 20mg BD – QDS] • Inform ICU team/consider transfer • Administer oxygen and fluids as required
Grade 3 CRS Temp ≥38°C *AND* Hypotension requiring vasopressors *AND/OR* Hypoxia requiring >6L/min oxygen	• Transfer to ICU • Treat as per neutropenic sepsis guidelines • Continuous cardiac monitoring, consider ECHO • Administer vasopressors as required • Administer oxygen as required • Administer IV tocilizumab [8mg/kg (max 800mg), every 8 hours, max 4 doses] • Administer IV dexamethasone [10mg – 20mg BD – QDS] • If refractory, consider IV methylprednisolone 1g and/or alternative agents (e.g anakinra or siltuximab)
Grade 4 CRS Temp ≥38°C *AND* Hypotension requiring multiple vasopressors *AND/OR* Hypoxia requiring CPAP/BiPAP/Ventilation	• Transfer to ICU • Treat as per neutropenic sepsis guidelines • Continuous cardiac monitoring, ECHO • Administer vasopressors • Administer oxygen • Administer tocilizumab [8mg/kg (max 800mg), every 8 hours, max 4 doses] • Administer IV methylprednisolone 1g and/or alternative agents (e.g anakinra or siltuximab)

3. Diagnosis and Management of Immune Effector Cell Neurotoxicity Syndrome (ICANS)

3.1 Pathophysiology

Immune effector cell associated neurotoxicity syndrome (ICANS) is a known neurological complication in patients who have received CAR-T cell therapy. The incidence of ICANS varies depending on the CAR-T product.

The pathophysiological mechanism underlying ICANS is not as clear as for CRS and two potential explanations are postulated. Firstly, passive diffusion of cytokines into the brain, supported by the finding that high serum levels of IL-6 are associated with severe neurotoxicity in patients treated with CAR-T-cell therapy, and that ICANS usually presents a few days after CRS[6,13]. Secondly, trafficking of T cells into the CNS, as indicated by the detection of CAR T cells in cerebrospinal fluid (CSF) from patients with neurotoxicity[6,13].

3.2 Recognition and Differential Diagnosis

ICANS may manifest as delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures and rarely cerebral oedema[10]. In addition, headache is very common, although its existence does not necessarily represent neurotoxicity in every case. Alteration in handwriting is often an early sign of ICANS[10].

The onset of neurotoxicity can coincide with CRS but can also occur as late as the third or fourth week following CAR-T infusion after resolution of CRS. ICANS typically lasts 2-4 days but can occasionally persist for weeks.

Alternative causes of neurological dysfunction such as infection, opioid toxicity, haemorrhage, drugs, electrolyte imbalance, or metabolic acidosis should be considered and treated.

3.3 Investigations and Management

Please note that these are suggested guidelines based on evidence base and consensus opinion throughout the UK and some recommendations may differ from the current Summary of Product Characteristics (SmPC) for each of the licensed CAR-T products.

Encephalopathy is measured using an encephalopathy assessment tool, the immune effector cell-associated encephalopathy (ICE) score as described in **Appendix B**. This should be completed twice per day, and frequency increased if ICANS suspected.

The management of ICANS involves the use of corticosteroids. Alternative, unlicensed treatments include anakinra and siltuximab. Input from a neurologist should be sought and early transfer to ICU for monitoring is recommended. Seizures should be treated on advice of the neurology team or as per institutional seizure guidelines.

Seizure prophylaxis with levetiracetam should be considered for CAR-T products and patients with a known increased risk of ICANS. Refer to the *Pan UK PWG document Supportive Medications Recommended for Adults Receiving Licensed Chimeric Antigen Receptor-T (CAR-T) Cell Therapy* for details on prophylactic medications.

Every patient should have a baseline ICE assessment
Baseline CT or MRI brain is recommened
Undertake a twice daily ICE assessment

If ICANS is suspected, immediately contact the CAR-T team

Management should be guided by the CAR-T consultant in conjunction with a neurologist

If concurrent CRS also follow the CRS management algorithm

If ICANS is suspected a thorough neurological examination should be performed. Investigations should include:

- EEG
- MRI / CT Brain
- Frequent monitoring for cognitive function e.g. handwriting tests
- Three times daily ICE assessment
- Consider diagnostic lumbar puncture

Alternative causes of neurological dysfunction such as infection, opioid toxicity, haemorrhage, drugs, electrolyte imbalance or metabolic acidosis should be considered and treated

Supportive Care

- Avoid medications that suppress consciousness
- Assess swallow (aspiration precautions)
- Manage agitation
- Assess papilloedema
- IV hydration

Grade 1 ICANS ICE score 7-9 Awakes spontaneously	• Close monitoring • Neurological examination • Three times daily ICE score • Consider seizure prophylaxis • If persistent symptoms >48hrs discuss treatment options with attending CAR-T consultants and consider steroids • Consider tocilizumab if concurrent CRS
Grade 2 ICANS ICE score 3-6 Awakes to voice	• Regular neurological observations • Three times daily ICE score • Administer IV dexamethasone [10mg – 20mg BD – QDS] • Inform ICU team • Consider tocilizumab if concurrent CRS
Grade 3 ICANS ICE score 0-2 Awakes only to tactile stimuli Seizures that resolve rapidly Focal cerebral oedema on imaging	• Transfer to ICU/Neuro ICU • Regular neurological observations • Three times daily ICE score • Repeat neuroimaging and EEG • Administer antiepileptics for seizures • Administer IV dexamethasone [10mg – 20mg QDS] • If refractory, consider IV methylprednisolone 1g or alternative agents (e.g anakinra or siltuximab) • Administer tocilizumab if concurrent CRS
Grade 4 ICANS ICE score 0 Unrousable Prolonged (>5min) or frequent seizures Motor weakness Diffuse cerebral oedema on imaging	• Transfer to ICU/Neuro ICU • Regular neurological observations • Three times daily ICE score • Repeat neuroimaging and EEG • Administer antiepileptics for seizures • Administer IV methylprednisolone 1g and/or alternative agents (e.g anakinra or siltuximab) • Administer tocilizumab if concurrent CRS

4. Medication Details

The below treatments should be incorporated into local clinical guidelines with a robust process in place to ensure treatments are only used where clinically appropriate. Hospitals must ensure there is access to these treatments prior to infusion with CAR-T cell therapy.

4.1 Licensed Treatments

Currently tocilizumab and corticosteroids form the basis of treatment of acute CAR-T cell side effects. Tocilizumab is only licensed to treat CRS, not ICANS. Corticosteroids (IV dexamethasone and methylprednisolone) are recommended to treat both CRS and ICANS.

Medication details are provided in the summary tables below:

Tocilizumab[14]	
Dose	8mg/kg (max 800mg)
Indication	CRS
Frequency	Dose can be repeated every 8 hours Maximum of 4 doses in total
Dilution	Dilute required dose to a final volume of 100mL with sodium chloride 0.9% To mix, gently invert the infusion bag to avoid foaming
Administration	Intravenous infusion over 1 hour via central or peripheral line
Additional information	• Does not need to be adjusted for renal or hepatic impairment, but use with caution if deranged LFTs • Tocilizumab can be administered by any member of qualified nursing staff who has been assessed competent in administration of IV drugs, does NOT need to be a SACT trained nurse • Prior to CAR-T administration 4 doses of tocilizumab will be supplied on an individual patient basis and stored in the ward fridge • If transferred to ICU, ensure tocilizumab is moved to new ward's fridge • Tocilizumab to treat grade 1 CRS is not routinely funded by NHSE, however this has been approved as an interim measure during COVID-19. • A Blueteq form should be submitted retrospectively for all tocilizumab administered. • Tocilizumab is a monoclonal antibody directed against IL-6 receptor

Dexamethasone	
Dose	10mg – 20mg
Indication	CRS and ICANS
Frequency	BD – QDS
Administration	Slow IV injection over 3-5 minutes
Additional information	• Dose varies depending on patient condition – adjust as needed. Doses should escalated rapidly as clinically indicated with a low threshold for switching to methylprednisolone or alternative agents if clinical deterioration. • Does not need to be adjusted for renal or hepatic impairment • Corticosteroids should be used for the shortest time period possible to minimise impact on CAR-T efficacy. However emerging data is showing low doses for short durations do not impact CAR efficacy. • Note: Clinical trials are currently exploring the use of prophylactic corticosteroids. This is outside the scope of this guidance.

Methylprednisolone (as sodium succinate)	
Dose	500mg - 1g
Indication	Refractory CRS and ICANS
Frequency	Once a day Response to be assessed by CAR-T consultant after each dose
Dilution	Reconstitute vial with water for injection. Further dilute required dose to a final volume of 100mL with sodium chloride 0.9% or glucose 5%
Administration	Intravenous infusion over 30 minutes
Additional information	• Does not need to be adjusted for renal or hepatic impairment • Only to be given in life-threatening situations on approval of a CAR-T consultant. High dose corticosteroids should be used for the shortest time period possible to minimise impact on CAR-T efficacy.

4.2 Alternative Therapies

For refractory grade 3 or grade 4 CRS and ICANS it may be necessary to use alternative treatments which are unlicensed and unfunded. The most commonly used alternative agents are the targeted immunosuppressive medicines anakinra and siltuximab. Other investigational agents (e.g etanercept, dasatinib, ruxolitinib) may be used on an individual basis and as outlined in trial protocols[15]. Alternative treatments should only be used on approval from the CAR-T consultant and in line with hospital unlicensed medicines management policy.

The use of these agents is currently 'off label' and unfunded. Although these products are unlicensed it is important to have access to alternative treatments in case of tocilizumab or steroid failure due to the life-threatening consequences of CAR-T cell toxicities. Follow local Trust medical management and funding procedures for unlicensed medication or the clinical trial protocol as appropriate. Where possible patients should be enrolled into clinical trials for managing CAR-T toxicities.

Given the unlicensed status of these treatments, the doses and frequencies are subject to change as more data emerges. Medication details for the two main alternative treatments (anakinra and siltuximab) are provided in the summary tables below:

Anakinra	
Dose	200mg*
Indication	Refractory grade 3 and 4 CRS and ICANS
Frequency	OD until resolution of symptoms
Administration	Subcutaneous injection (can be given IV but unlicensed route)
Additional information	• *Dosing schedules vary and is subject to change based on emerging data. A starting dose of 200mg OD is currently the consensus recommendation; however 100mg BD has also been used. In refractory cases, doses have been safely increased incrementally to a maximum dose of 8mg/kg/day[16,17,18] . • Response to be assessed by CAR-T consultant after each dose • Hepatic impairment: Does not need to be adjusted • Renal impairment: if eGFR< 30mL/min or renal replacement therapy consider alternate day dosing[19] • To be stored in the fridge • Anakinra inhibits IL-1 by competitively binding IL-1R

Siltuximab	
Dose	11mg/kg
Indication	Refractory grade 3 and 4 CRS and ICANS
Frequency	Single dose
Dilution	Reconstitute each vial with water for injection. Further dilute required dose to a final volume of 250mL with glucose 5%
Administration	Intravenous infusion over 1 hour via 0.2 micron in-line filter
Additional information	• Does not need to be adjusted for renal or hepatic impairment • Does not need to be capped for extreme body weight • To be stored in the fridge • Monitor for infusion related reactions • Siltuximab is a monoclonal antibody directed against IL-6

5. Monitoring

All patients receiving CAR-T cell therapy should be monitored regularly for signs of CRS and have twice daily ICE assessments whilst an inpatient. If a patient is suspected to have CRS or ICANS they should be monitored more frequently as outlined in the treatment algorithms.

Patients should be NEWS2 assessed, however, given that patients with CRS and ICANS are at significant risk of deterioration and may require organ support, it is advised that any patients with suspected CRS or ICANS are monitored more frequently and referred earlier to ICU than the recommended NEWS2 thresholds and triggers. Regardless of NEWS2 score, the ICU team should be made aware of any patients exhibiting signs of CRS or ICANS in order to facilitate prompt transfer to ICU if needed.

Although there are currently no licensed treatments for grade 1 CRS or ICANS, patients are at risk of rapid deterioration so symptoms must be monitored closely as intervention and treatment may be required.

Patients should continue to be monitored until discharge, even after the resolution of symptoms. Upon discharge from hospital patients and their carers must be informed of the risk of delayed side effects and the management plan.

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Appendix A

ASTCT Consensus Grading Scales[10]

ASTCT Consensus Grading for CRS[7]

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/Or				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask or Venturi mask	Requiring positive pressure (e.g.: CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT ICANS Consensus Grading for Adults[10]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (patient is unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between.
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP	N/A	N/A	Focal/local oedema on neuroimaging#	Cerebral oedema Diffuse cerebral oedema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

Appendix B

Immune Effector Cell Associated Encephalopathy (ICE) Tool[10]

ASSIGN ONE POINT FOR EACH TASK PERFORMED CORRECTLY
(SCORE OF 10 = NORMAL)

ICE	Question
1	What year is it?
2	What month is it?
3	What city/town are we in?
4	What hospital are we in?
5	Follow instruction[1]
6-8	Name 3 objects (one point for each)[2]
9	Write a standard sentence* (patient can choose but use the same one each time)
10	Count backwards from 100 in 10's
Grade 0 1 2 3 4	Score 10 7-9 3-6 0-2 Patient critical/obtunded

[1] Examples for following instructions: Do NOT demonstrate to the patient.

"Touch your nose", "Lift your right/left arm", "Lift your right/left leg", "Shrug your shoulders"

[2] The nurse is to point to an object, and the patient should name the object without assistance from anyone. For example, the nurse points to a clock, television, fridge, mobile, cup, remote control and then patient should name the item.

*If a change is handwriting is noted escalate to CAR T team. This may need review by neurology

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