NIHR | Lancashire Clinical Research Facility

STANDARD OPERATING PROCEDURE

Diagnosis and Management of Cytokine Release Syndrome Immune Effector Cell Associated Neurotoxicity Syndrome, and Haemophagocytic Lymphohistiocytosis: A Guide for Lancashire Clinical Research Facility

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1. SUMMARY

This guideline covers the clinical presentation of complications associated with immune effector cell (IEC) therapies:

1) Cytokine release syndrome (CRS)

2) Immune effector cell associated neurotoxicity syndrome (ICANS)

3.) Haemophagocytic Lymphohistiocytosis (HLH)

We describe the early investigations and protocol based management for patients suffering from these conditions. Immune effector cell therapy is extremely exciting and a step change in our treatment technology against malignancy. The number of patients receiving these therapies both in clinical trials and as standard therapy is expected to increase substantially.

BACKGROUND

CRS is a potentially life-threatening systemic inflammatory response caused by widespread immune cell activation releasing inflammatory cytokines. This can be triggered by many factors, the most common being immune-based therapies and in particular T-cell therapies. 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 symptoms of CRS can range from mild constitutional symptoms to life-threatening multi-organ failure. CRS generally occurs within the first week after therapy although it can occur later. Neurotoxicity (ICANS) is the second most common acute toxicity, again with a range of severity from language disturbance, impaired handwriting, confusion and agitation to cerebral oedema and death. HLH is a rare, but very severe complication related to CRS.

Less common toxicities include tumour lysis syndrome, prolonged cytopenia's and B-cell aplasia. These toxicities are not covered in this guidance.

PURPOSE/OBJECTIVE

This standard operating procedure has been written to provide guidance to all clinical personnel providing care for trial patients at the Lancashire Clinical Research Facility (LCRF) on how to recognize, assess, and manage patients suffering from CRS, ICANS, and HLH.

SCOPE

It is important that all clinical staff involved in the care of trial patients understand what CRS is, how to recognize it, what assessments/investigations to carry out, and most importantly how to promptly and effectively manage this emergency condition.

PROCEDURE

1. WHO?

1.1 It is the responsibility of all clinical staff caring for trial patients to screen & highlight at-risk patients that may go on to develop CRS/ICANS/HLH.

At risk are patient groups are those who are actively receiving or who have recently received

- Therapeutic monoclonal antibody infusion
- Alemtuzumab, Rituximab
- Immunotherapies for cancer especially chimeric antigen receptor therapy (CAR) T-cell therapies or other T cell therapies

It is the responsibility of all clinical staff caring for trial patients to familiarize themselves with all documents outlining the assessment and management of suspected CRS. These include this document as well as the trial/treatment specific protocol.

1.2 It is the responsibility of the Principal Investigator (PI) to ensure that staff working on trials that include a risk of CRS/ICANS/HLH have received appropriate training and support in identifying and managing CRS prior to commencement of the trial or staff members involvement.

2. WHEN?

2.1 This SOP must be followed for assessment and management of patients at risk of CRS who have developed:

a) Temperature >38°C
b) Flu-like symptoms including myalgia, arthralgia, malaise
c) Nausea and vomiting
d) Hypotension –Systolic Blood Pressure of <90mmHg or <80% of patient's baseline
e) Hypoxia – Oxygen Saturation of <94%
f) Neurological events

In the absence of sepsis or tumour lysis syndrome

3. CYTOKINE RELEASE SYNDROME (CRS)

CRS can present with a diverse spectrum of clinical features ranging from a mild flu-like illness to multi-organ failure. It can mimic severe sepsis or tumour lysis syndrome. Other potentially life-threatening complications include cardiac dysfunction, ARDS, neurological toxicity, renal failure, hepatic failure and disseminated intravascular coagulation. Haemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS) can occur with high fevers, high ferritin and raised triglycerides.

3.1 Diagnosis & Management

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

1. **Recognise** – History, examination, investigations
2. **Grade** – CRS severity must be graded to guide management
3. **Supportive Management** – as described below
4. **Targeted management** – tocilizumab +/- corticosteroids
5. **Contact and Escalate Early** – CCU, oncology and haematology teams

3.2 All patients who exhibit symptoms (see section 2.1) with a likely diagnosis of CRS should be graded in order to direct management.

a) CRS 1
- Temperature ≥38°C

b) CRS 2
- Temperature ≥38°C
- Hypotension (not requiring vasopressors)
- Hypoxia – SpO2 <94% on air but managed with low flow nasal cannulae to maintain SpO2 >94%

c) CRS 3
-Temperature ≥38°C
-Hypotension requiring vasopressors to support MAP >65mmHg
-Hypoxia requiring high flow nasal cannulae or Venturi mask to support SpO2 >94%

d) **CRS 4**
-Temperature ≥38°C
-Hypotension requiring multiple vasopressors
-Hypoxia requiring positive pressure/intubation and ventilation

3.3 ASTCT consensus grading for CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a 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, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

From: ASBMT Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells, Biology of Blood and Marrow Transplantation (2018), doi: https://doi.org/10.1016/j.bbmt.2018.12.758

3.4 CRS Management based on grade

CRS Grade	Management
CRS Grade 1	Regular vital signs as per NEWS2 protocol Manage as per Neutropenic Sepsis, including: - Paracetamol - IV fluids - Broad spectrum Antibiotics - Supplementary oxygen if required - Urine output measurements Blood tests including: FBC, U&E, LFT, CRP, Blood Cultures, Lactate, Coagulation, Ferritin, Cytokine profile (IL-6) Appropriate further investigations (e.g., CXR), EEG Consider tocilizumab 8mg/kg (max 800mg) for persistent and refractory fever [to be reviewed following COVID-19 pandemic, as not usually funded for Grade 1 CRS]
CRS Grade 2	**Manage as per Grade 1, plus:** Consider escalation to CCU Tocilizumab if not already given Consider IV Dexamethasone 10mg BD –QDS if Tocilizumab refractory
CRS Grade 3	**Manage as per Grade 2, plus:** Escalate to CCU Vasopressors Dexamethasone if not already given Cardiac monitoring +/- ECHO Cardiogram
CRS Grade 4	**Manage as per Grade 3, plus:** May require ventilation Methylprednisolone 1mg/kg IV daily if not responding to dexamethasone May require further agents (e.g. siltuximab, anakinra, anti-TNF)

Adapted from: Garcia Borrega J, Gödel P, Rüger MA, Onur ÖA, Shimabukuro-Vornhagen A, Kochanek M, Böll B. In the Eye of the Storm: Immune-mediated Toxicities Associated With CAR-T Cell Therapy. Hemasphere. 2019 Mar 29;3(2):e191 , Mason A, Gabriel S. Diagnosis and Medical Management of Acute CAR-T Cell Toxicities in Adults. https://www.sps.nhs.uk/wp-content/uploads/2020/12/Diagnosis-and-medical-management-of-acute-CAR-T-cell-toxicities-in-Adults-V1.pdf#:~:text=diagnosis%20and%20medical%20management (accessed 18/03/22), Newcastle-upon-Tyne Hospital NHS Foundation Trust. Management of CRS, Neurotoxicity and Car-T Cell Related Encephalopathy Syndrome (CRES) Post Chimeric Antigen Recepton (CAR) T-Cell Therapy, Department of Haematological Medicine, King's College Hospital NHS Trust. Diagnosis and management of toxicities of immune effector cellular therapies, including cytokine release syndrome and central nervous system complications in adults 2020.

3.3.1 General supportive management of CRS

- All patients should be commenced on antibiotics as per the trust management of febrile neutropenia guideline.
- If sepsis is suspected patients should have a sepsis 6 bundle completed (blood culture, urine output measurement, serum lactate, IV fluids, antibiotics, supplementary oxygen) as required.
- IV paracetamol can be given for patient comfort. For Adult (body weight up to 50 kg) 15 mg/kg paracetamol every 4–6 hours, dose to be administered over 15 minutes; maximum 60 mg/kg per day. For Adult (body weight 50 kg and above) 1 g paracetamol every 4–6 hours, dose to be administered over 15 minutes; maximum 4 g per day.
- Hourly monitoring of vital signs and an accurate fluid balance chart must be completed. In the context of CRS/ICANS/HLH our recommendation is that patients are discussed with the critical care team and considered for admission to Critical Care Unit (CCU) when the NEWS2 score is ≥2.
- The blood glucose should be monitored.
- Check magnesium and phosphate – if less than lower limit of normal then give IV replacement.
- CRS investigations: Specific additional tests to consider:
    - Ferritin, triglycerides, and AST – to facilitate the potential diagnosis of haemophagocytic lymphohistiocytosis and/or macrophage activation syndrome.
    - Troponin +/- transthoracic echocardiogram – to diagnose associated cardiac toxicity with CRS
    - Uric acid (& U+Es, calcium, phosphate, ABG) if tumour lysis syndrome is suspected.
    - Cytokine profile

- Steroids (and, in particular, IV hydrocortisone) should not be given to patients who have received CAR-T therapy unless specifically advised by the responsible Oncology/Haematology Consultant. They must only be given when the CRS is refractory to other supportive measures or if allowed per specific protocol.

3.3.2 Supportive management of CRS ≥ Grade 2

Note any patient who has received immune effector cell therapy and is identified with CRS ≥ Grade 2 is at increased risk of deterioration. Capillary leak and fluid overload are significant concerns.

Our recommendation is that patients are discussed with the parent clinical team, critical care team and considered for admission to CCU/HDU when the NEWS score is ≥2 if CRS is suspected.

Initial management should be focused on stabilising the patient and supporting organ function.

Cardiovascular:

1. Fluid resuscitation should be with bolus of 250mls of crystalloid (such as Plasma-Lyte® or Sodium Chloride 0.9%). This fluid should be infused via an infusion pump over 15mins. The target systolic BP should be >90mmHg or >80% of the patient's baseline SBP. The bolus can be repeated immediately if there is <10mmHg response in the patients SBP. If greater than 1L of fluid is given without improvement consideration should be made to admit the patient to CCU urgently.
2. Vasopressors should be started if >30ml/kg (or 2L in total) of fluid is required to support the patients SBP. All patients receiving CAR-T therapy will have dual lumen PICC line and to facilitate safe transfer/admission to critical care, it is reasonable to support the patient's blood pressure with intermittent boluses of metaraminol. The target mean arterial pressure, obtained from invasive blood pressure monitoring, is >65mmHg. Once admitted to CCU/HDU any patient requiring ongoing vasopressor support should have a central venous catheter and arterial line inserted.
3. If patients require >2L of crystalloid fluid, troponin and a screening echocardiogram should be performed to evaluate cardiac toxicity.

Haematology:

1. All Oncology patients should have a special transfusion status form completed and submitted to the transfusion laboratory. This should be checked to confirm that there are no specific indications for irradiated blood products.
2. The transfusion trigger is a target Hb >70g/l.
3. The platelet count should be maintained >$20x10^9$/l
4. GCSF is not routinely recommended.
5. Disseminated intravascular coagulation can occur. The INR, APTTr and fibrinogen should be measured daily.

Renal:

1. There is a risk of tumour lysis syndrome.
2. Renal replacement therapy as per the standard indications.

3.3.3 CRS not responding to supportive therapy.

On occasion despite optimal supportive therapy the patient's clinical condition will continue to deteriorate. This will manifest as increasing degrees of organ failure with a progressive escalation of organ supportive therapy. Tocilizumab is anti-IL-6R monoclonal antibody approved for the treatment of CAR-T cell induced CRS in adults and paediatric patients 2 years of age and older. It has also been used to successfully manage CRS caused by other immunotherapies. The use of tocilizumab will need to be discussed on a case by case basis and the decision to give should be made by the Oncology and ITU consultants.

As tocilizumab causes immunosuppression, patients should be monitored for the development of infection, particularly if neutropenia is present. In practice this will be the majority of patients who will have been extensively treated with chemotherapy. Caution should be used in the presence of thrombocytopenia or neutropenia. In addition to FBC, LFTs should be monitored as there is a risk of hepatic dysfunction. If ALT and AST are persistently 1-3x upper limit of normal (ULN), tocilizumab should be reduced to 4mg/kg. If there is a >3x ULN in ALT or AST levels, tocilizumab should be discontinued until this improves to less than 3x ULN.

Tocilizumab Medication Details
Tocilizumab 8mg/kg (max 800mg). Dose can be repeated every 8 hours. Maximum of 4 doses. The use of tocilizumab to treat CRS is not funded by NHSE. For the purposes of clinical trials, funding should be agreed with study sponsors prior to patient enrolment.

3.3.4 Logistics and Supply

The use of tocilizumab in non CAR-T cell induced CRS is restricted. It is the decision of the PI whether access to tocilizumab is required for any given clinical trial. This decision must be made during study setup. If tocilizumab is required, this will be obtained through general pharmacy stock, and retrospectively paid for by the trial sponsor. This arrangement, and the cost of the product, must be captured in the study contract following negotiation with the sponsor. The cost will be the British National Formulary current price. Procurement of general stock tocilizumab is through LTH Pharmacy Procurement.

If sufficient supply of tocilizumab (e.g., 4 available doses) is not available from general pharmacy stock, it is at the discretion of the PI whether to proceed with IMP dosing.

3.3.5 In the event that the interventions listed above are unsuccessful

The following approaches can be considered: T cell-depleting antibody therapies such as, methylprednisolone, alemtuzumab, IL-1R-based inhibitors (anakinra) or cyclophosphamide. These must be discussed with the treating oncologist/haematologist and ICU. In these circumstances, the use of these medicines may need additional approval/individual funding approval, on a case by case basis.

3 IMMUNE EFFECTOR CELL ASSOCIATED NEUROTOXICITY SYNDROME (ICANS)

ICANS (previously termed CAR T-cell related encephalopathy syndrome or CRES) may manifest as delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and cerebral oedema. In rare circumstances it can progress to severe neurological injury and death. These neurological symptoms may occur during CRS but commonly occur afterwards. The pathophysiology is unknown. Classically the earliest signs & symptoms of ICANS are tremor, dysgraphia, mild difficulty with expressive speech, impaired attention, apraxia and lethargy. Expressive dysphasia is a very specific symptom. The progression to severe neurotoxicity may take hours to days.

4.1 Differential diagnosis of ICANS

The differential diagnosis of ICANS includes ischaemic or haemorrhagic stroke, central nervous system infection and metastatic spread of the underlying malignancy.

4.2 Investigations:

It is important to grade the severity of ICANS, as below. This includes assessment of the Immune effector cell mediated encephalopathy (ICE) score. A CT scan of the brain is essential provided the patient's condition is stable enough to facilitate transfer. There is a high probability of thrombocytopenia and deranged coagulation; MRI scan may be helpful in demonstrating cerebral oedema and to exclude other pathologies if lumbar puncture is not safe. Fundoscopy may also aid in assessment (see below).

4.3 Management of ICANS

Management of ICANS is based on the grading system (see below). Similar to the management of CRS, patients with mild ICANS should be closely monitored to receive supportive measures. If a patient develops more severe symptoms (grade ≥2), transfer to the intensive care unit is required. A multidisciplinary approach with intensivist, oncologist, and neurologist input is paramount. An early EEG should be performed to look for subclinical seizures.

Tocilizumab should be given in acute phase ICANS when it is existent with CRS. However, it is not that effective in the delayed phase (Day 5+ from infusion), where steroids are preferred.

Prophylactic antibiotics or other antimicrobials should be given as clinically appropriate. Rigorous control of blood pressure and electrolytes (particularly calcium and magnesium) should be maintained.

4.4 Papilloedema

Patients with suspected ICANS should have fundoscopy in order to identify the presence of papilloedema/raised intracranial pressure. This should be performed by competent staff.

4.5 ICE Score calculation (Immune effector cell mediated encephalopathy)

• **Orientation**: Orientation to year, month, city, hospital: 4 points • **Naming:** Ability to name 3 objects (e.g., point to clock, pen, button): 3 points • **Following Commands:** Ability to follow simple commands (e.g., "Show me 3 fingers" or "Close your eyes and stick out your tongue"): 1 point • **Writing:** Ability to write a standard sentence: 1 point • **Attention:** Ability to count backwards from 100 by 10: 1 point
Total Score: **10:** No impairment **7-9:** Grade 1 ICANS **3-6:** Grade 2 ICANS **1-2:** Grade 3 ICANS **0:** (Unrousable): Grade 4 ICANS

From: ASBMT Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells, Biology of Blood and Marrow Transplantation (2018), doi: https://doi.org/10.1016/j.bbmt.2018.12.758

4.6 ASTCT consensus grading for ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and 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 nonconvulsive 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
Elevated ICP/ cerebral edema§	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

From: ASBMT Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells, Biology of Blood and Marrow Transplantation (2018), doi: https://doi.org/10.1016/j.bbmt.2018.12.758

4.7 ICANS management based on grade

ICANS Grade	Management
ICANS Grade 1	Close monitoring/Neurological examination Twice daily ICE scoring IV hydration, consider change medication to IV Neurology & Haematology referral Fundoscopy for papilloedema. Manage raised intracranial pressure (as per Neurology review) Consider dexamethasone 10mg IV Avoid sedating medications unless agitated. Consider lorazepam/haloperidol for agitation Consider MRI Brain +/- EEG Consider tocilizumab if concurrent CRS (see CRS management guidance)
ICANS Grade 2	**Manage as Grade 1, plus:** Dexamethasone IV 10mg can be given up to QDS if not already given Alternatively consider methylprednisolone 1mg/kg IV BD Tocilizumab if concurrent CRS (see CRS management guidance) Consider CCU escalation Consider antiepileptic medication if necessary for seizures
ICANS Grade 3	**Manage as Grade 2, plus:** Escalate to CCU Dexamethasone IV 10mg QDS/methylprednisolone Antiepileptic medications if not already given Consider alternate agents if refractory (anakinra, siltuximab, anti-TNF, cyclophosphamide)` Consider repeating neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grave 3 or above neurotoxicity
ICANS Grade 4	**Manage as Grade 3, plus:** Alternative agents as above Specific neurointensive treatment

Adapted from: Garcia Borrega J, Gödel P, Rüger MA, Onur ÖA, Shimabukuro-Vornhagen A, Kochanek M, Böll B. In the Eye of the Storm: Immune-mediated Toxicities Associated With CAR-T Cell Therapy. Hemasphere. 2019 Mar 29;3(2):e191 , Mason A, Gabriel S. Diagnosis and Medical Management of Acute CAR-T Cell Toxicities in Adults. https://www.sps.nhs.uk/wp-content/uploads/2020/12/Diagnosis-and-medical-management-of-acute-CAR-T-cell-toxicities-in-Adults-V1.pdf#:~:text=diagnosis%20and%20medical%20management (accessed 18/03/22), Newcastle-upon-Tyne Hospital NHS Foundation Trust. Management of CRS, Neurotoxicity and Car-T Cell Related Encephalopathy Syndrome (CRES) Post Chimeric Antigen Recepton (CAR) T-Cell Therapy, Department of Haematological Medicine, King's College Hospital NHS Trust. Diagnosis and management of toxicities of immune effector cellular therapies, including cytokine release syndrome and central nervous system complications in adults 2020.

4.8 Steroid Tapering

Once sustained clinical improvement is observed steroids can be tapered; for example, methylprednisolone IV 1g/day for 3 days, followed by rapid taper at 250mg every 12 hours for 2 days, 125mg every 12 hours for 2 days, and 60mg every 12 hours for 2 days. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg prednisolone) at the start of tapering or earlier.

5. CAR-RELATED HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

5.1 Initial management

Haemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome induced by activated macrophages and cytotoxic T cells. Secondary (acquired) HLH is triggered by infections or malignancies but may also be induced by autoinflammatory/autoimmune disorders. In rare cases severe CRS can evolve into HLH.

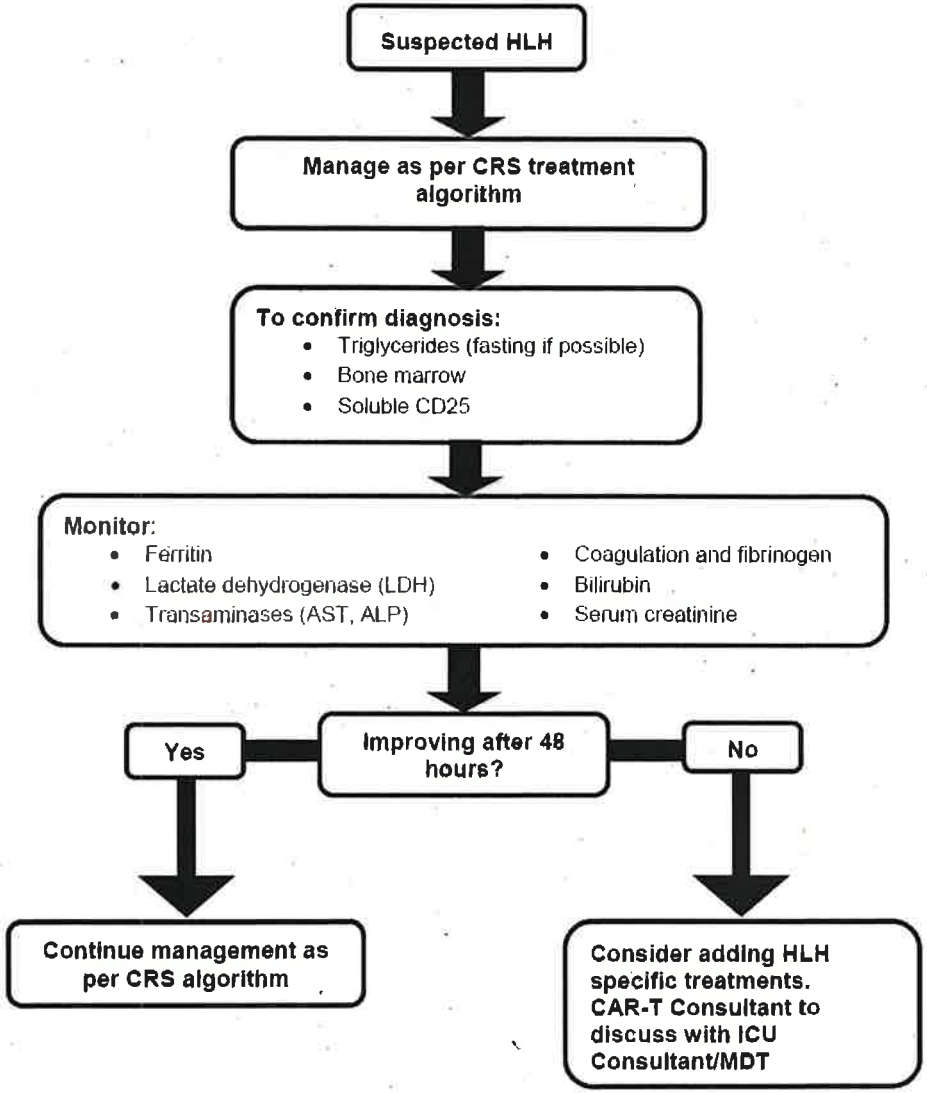
Diagnosis may be difficult as traditional markers are non-specific. Proposed diagnostic criteria are:

- Peak serum ferritin level of >10,000 ng/ml during the CRS phase

AND, subsequently, any two of the following;

- Grade ≥3 increase in serum bilirubin, aspartate aminotransferase, or alanine aminotransferase levels
- Grade ≥3 oliguria or increase in serum creatinine levels
- Grade ≥3 pulmonary oedema
- Presence of haemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and/or CD68 immunohistochemistry

The diagnosis and treatment of CAR-related HLH is not established, and therefore specialist consultant and MDT input is needed to decide on patient management.



From: Mason A, Gabriel S. Diagnosis and Medical Management of Acute CAR-T Cell Toxicities in Adults. https://www.sps.nhs.uk/wp-content/uploads/2020/12/Diagnosis-and-medical-management-of-acute-CAR-T-cell-toxicities-in-Adults-V1.pdf#:~:text=diagnosis%20and%20medical%20management (accessed 18/03/22).

5.2 Refractory HLH

Fulminant and refractory HLH to steroids and tocilizumab is observed in ~1% of all patients treated with CAR-T cell therapy. If the patient has no improvement within 48 hours after commencement of steroids and tocilizumab, additional therapy with etoposide 75-100 mg/m^2 should be considered. This agent can be used in patients with liver and kidney dysfunction. Indeed, rapid initiation of etoposide therapy, in spite of organ dysfunction, is imperative for patients with high probability of a HLH diagnosis, owing to the high risk of death. Etoposide can be repeated after 4-7 days, as indicated clinically or serologically, to achieve adequate disease control. Intrathecal cytarabine, with or without hydrocortisone, should also be considered for patients with HLH-associated neurotoxicity. Although etoposide and cytarabine are often used in the treatment of familial and malignancy-associated HLH, at present, direct evidence to support their use in patients with CAR-T-cell-associated HLH is lacking.

6. RELATED INFORMATION

Clinical Response Team (CRT) and Intensive Care

Patients should be discussed with CCU promptly as there is a potential for rapid deterioration necessitating organ support, even if the patient only exhibits grade 1 symptoms. Patients with grade 2 symptoms and above should be transferred to CCU for monitoring and organ support.

Oncology/Haematology teams

For all patients with suspected CRS, even if not known to have cancer, there should be a discussion with the oncology/haematology Specialist Registrar (SpR). The oncology and haematology SpR can be contacted via switchboard and if necessary, this discussion can be escalated to the oncology/haemato-oncology consultants on-call (also available via switchboard), e.g. in cases where the SpR cannot be reached.

Tocilizumab should be administered with approval from the oncology/haemato-oncology consultant (preferably with input from ITU consultant); therefore, early discussion is required to avoid delayed treatment.

Pharmacy Team

For any suspected cases, please contact the appropriate pharmacist to ensure timely supply of medication. It is the responsibility of the ward pharmacist to contact the oncology pharmacy team. The oncology pharmacist will liaise with the relevant medical teams and escalate to the lead oncology pharmacist if required.

For any suspected cases out of working hours, the treating team will need to contact the on-call pharmacist who will liaise with the senior pharmacy team where necessary.

Clinical Trials Team

For patients involved in a clinical trial the PI should be contacted. The NIHR LCRF team should also be contacted via telephone: 01772 522031 or email: LancashireCRF@LTHTR.nhs.uk.

Contracts

In the context of clinical trials, trial sponsors will be asked to fund a minimum of 4-8 doses of tociluzimab plus anakinra 2mg/kg daily for 5 days per trial in the upfront stage of trial setup. Trial contracts will need to take into account the possibility of critical care costs.

7 FURTHER READING/REFERENCES

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CONSULTATION WITH STAFF AND PATIENTS

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LCRF Operational Group	Review & Approval
Research Pharmacy Team	Review
Dr David Cameron	Review & Approval

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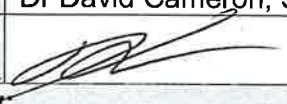
Signature		**Date**	30-OCT-2023
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Signature		**Date**	30-OCT-2023
Authorised for release by:			
Name and Position	Jacqueline Bramley, LCRF Lead		
Signature		**Date**	30-OCT-2023
Authorised for release by:			
Name and Position	Rebecca Wilby, Quality Assurance Lead / Research Access Project Manager		
Signature		**Date**	30-OCT-2023

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