

CAR.6.1. Appendix 2. Immune Effector Cell-Associated Neurotoxicity Syndrome [ICANS] assessment and management[^]

[Link to main protocol \[CAR.6.1\]](#) [^]For clinical trials – please refer to the relevant clinical trial protocol

ICANS Assessment – Immune Effector Cell Encephalopathy (ICE) score – max. 10 points

Orientation: Orientation to year, month, city, hospital	4 points
Naming: Name 3 objects (e.g., point to clock, pen, button)	3 points
Following commands: (e.g., close your eyes and stick out your tongue)	1 point
Writing: Ability to write a sentence (e.g., Today is a lovely sunny day)	1 point
Attention: Count backwards from 100 by 10	1 point

ICANS Assessment – ASTCT Consensus ICANS Grading*

ICANS	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7–9	3–6	0–2	0
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	Not applicable		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***	Not applicable			Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP (intracranial pressure)	Not applicable		Focal/local oedema on neuroimaging****	Diffuse cerebral oedema on neuro-imaging; Decerebrate or decorticate posturing; or cranial nerve VI palsy; or Papilloedema; or Cushing's triad*****

* ICANS grade is determined by the most severe event 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. ** Depressed level of consciousness should be attributable to no other cause (e.g., 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 haemorrhage with or without associated oedema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v 5.0. ***** Widened pulse pressure (increasing systolic, decreasing diastolic), bradycardia, and irregular respirations.

Symptoms of ICANS

Headache	Confusion	Lethargy	Delirium	Apraxia	Word finding difficulties
Dysgraphia	Altered gait	Tremor	Aphasia	Seizures	Changed mental status

ICANS assessment – Summary of investigations

ICE score & ICANS grading	Minimum twice daily [four times daily if ICANS is suspected]. Consider early referral to Neurology and ICU teams, especially when falling GCS (Glasgow Coma Score).
MRI/CT brain*	Neuroimaging should be urgently sought for any suspected ICANS to exclude cerebral oedema, features of raised ICP (intracranial pressure) or alternative cause (for example, disease progression, CNS infection). * Within working hours this should be an MRI head with contrast. Out of hours, or if there is delay (>4-6 hours) in obtaining MRI, this should be an urgent CT head with contrast. The main differential diagnoses in the acute onset of abnormal neurology post CAR infusion are: ICANS vs acute bleeding vs CNS infection vs raised ICP. Consider repeat imaging every 2-3 days for persistent Grade ≥ 3 ICANS.
MRI spine	Consider if the patient has focal peripheral neurological deficits
Lumbar puncture	Consider diagnostic lumbar puncture (LP) with measurement of opening pressure where possible (check platelets and coagulation screen). See LP Investigations below.
Fundoscopy exam* [*if not possible, CT brain]	Perform to assess for papilloedema. For stage 1 or 2 papilloedema with CSF (cerebrospinal fluid) opening pressure ≥ 20 mmHg, seek urgent advice from Neurology team. For stage ≥ 3 papilloedema with a CSF opening pressure ≥ 20 mmHg or cerebral oedema, seek urgent advice from Neurology and Neurosurgery.
EEG	Consider electroencephalogram (EEG). When results show status epilepticus, seek urgent advice from Neurology.

Lumbar Puncture (LP) Investigations - if arranging an LP, please ensure the following tests are obtained:

✓ Opening pressure	✓ Fungal culture
✓ MC&S	✓ CSF cryptococcal antigen testing
✓ Glucose [plus paired plasma glucose], lactate, protein	✓ Cytology, cytospin and immunophenotyping [unlikely to be processed out of hours]
✓ Biofire PCR	✓ Save serum and CSF sample to immunology
✓ Oligoclonal bands	

ICANS management – SYMPTOMATIC MEASURES – Notify attending/on-call Consultant of any ICANS development

ICANS	Grade 1	Grade 2	Grade 3	Grade 4
ITU	Consider alerting ICU	Alert ICU, consider transfer	Transfer to ICU (Intensive Care Unit)	
Supportive care	Vigilant supportive care and aspiration precautions; raise head 30°; switch oral medications to IV; suspend oral nutrition; start intravenous (IV) hydration where appropriate; consider mechanical ventilation for airway protection when in ITU. Avoid medications that can cause central nervous system depression.			
Agitation	Low doses of lorazepam (for example, 0.25–0.5mg IV 8-hourly when required) can be considered with careful monitoring			
Seizure prophylaxis*	Continue prophylactic doses of anti-epileptic if no seizures on EEG; most patients will have levetiracetam PO prescribed 500mg BD from day 0 to +28, reduced to 250mg BD [D+29 to 42] – refer to CAR.6.0 Supportive medications for CAR therapy Escalation to higher doses may be required in individual cases (discuss with Neurology) IV route should be used if concerns with PO administration/absorption, or in acutely unwell patients			
Seizure management	N/A	N/A	Status Epilepticus after CAR therapy (non-convulsive and convulsive status) Grade 3-4 ICANS ▪ Seek urgent Neurology opinion ▪ Assess airway, breathing, and circulation: check blood glucose ▪ Administer lorazepam and levetiracetam – refer to MIL Vol 3, No. 8; discuss maintenance doses after resolution of status epilepticus with Neurology Consultant ▪ Continuous electroencephalogram (EEG) monitoring should be performed for convulsive status epilepticus where possible, if seizures are refractory to treatment, in consultation with Neurology Team	

*The following patients should receive seizure prophylaxis:

- Patients who have had CNS disease or CNS irradiation in the past.
- Prior history of convulsions
- Prior history of treatment-related neurological toxicity
- Receiving CAR product with > 5% risk of Grade 3-4 ICANS e.g. Yescarta®, Tecartus®

ICANS management - **STERIODS** – Only prescribe on advice of the Consultant

ICANS	1 st line	2 nd line ¹
Grade 1	Supportive management (applies to all grades) Consider steroids in selected cases ²	Dexamethasone 10mg IV ³ OD-BD and re-assess in 6 hours or earlier if indicated
Grade 2	Dexamethasone 10mg IV ^{3,4} BD-QDS (given at regular intervals) until Grade ≤ 1, then taper dose to stop	Dexamethasone 20mg IV ^{4,5} BD-QDS (given at regular intervals) until Grade ≤ 1, then taper dose to stop
Grade 3	Dexamethasone 10mg IV ^{3,4} QDS (6-hourly) until Grade ≤ 1, then taper dose to stop	Dexamethasone 20mg IV ^{5,6,8} QDS (6-hourly) until Grade ≤ 1, then taper dose to stop
Grade 4	Methylprednisolone 1000mg IV OD for 3 days, then consider rapid tapering (if improving ⁷): 250mg IV BD for 2 days, then 125mg IV BD for 2 days, then 60mg IV BD for 2 days, then once Grade ≤ 1, continue tapering to stop over 3 days	Consider 3 rd line treatments ⁸

¹ In presence of deterioration, absence of improvement after 12 hours or persistence of symptoms.

² If ICANS develops within 72 hours after infusion, consider dexamethasone 10mg IV OD-BD for 2 doses and reassess.

³ Dexamethasone 10mg IV = 8.25mg dexamethasone base [2.5mL x 3.3mg/mL] – prescribe on inpatient prescription as dexamethasone base injection.

⁴ As alternative to dexamethasone – methylprednisolone at equivalent dose can be considered.

⁵ Dexamethasone 20mg IV = 16.5mg dexamethasone base [5.0mL x 3.3mg/mL] – prescribe on inpatient prescription as dexamethasone base injection.

⁶ Grade 3 ICANS refractory to dexamethasone – methylprednisolone can be considered at the dose as per grade 4 ICANS.

⁷ If no clinical improvement, methylprednisolone 1000mg OD should still be weaned after 3 days, albeit more slowly.

3rd line

⁸ For ICANS grade 3 or 4, refractory to tocilizumab and steroids, alternative treatments should be considered, for example, ▪ **anakinra** 200mg SC* OD, increased if necessary up to 8mg/kg/day, continued until clinical response (*IV route is unlicensed - when used in critical illness, it should be switched back to SC route as soon as patient's condition improved and is clinically stable), or ▪ **siltuximab** IVI 11mg/kg (single dose) - discuss with ACT Consultant and Pharmacist (note off-label use of both anakinra and siltuximab – clinical governance framework and local approvals for funding must be ensured).

Tocilizumab should only be considered in the presence of concurrent CRS – refer to [Appendix 1](#).