

Immune Effector Cell (IEC) CRS and ICANS Grading and Management Algorithm

Cytokine Release Syndrome (CRS)

Definition: CRS is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction and is caused by a large, rapid release of cytokines into the blood from immune cells.

Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ damage. CRS manifests as an initial fever and a constellation of nonspecific clinical findings. A temporal relationship to the triggering immune therapy is important for establishing the diagnosis of CRS.

CRS GRADING

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever [†]	Temperature greater than or equal to 38C	Temperature greater than or equal to 38C	Temperature greater than or equal to 38C	Temperature greater than or equal to 38C
WITH				
Hypotension	None	Not requiring vasopressors	Requiring 1 vasopressor (+/- vasopressin)	Requiring 2 or more vasopressors excluding vasopressin
AND/OR [§]				
Hypoxia	None	Requiring low-flow nasal cannula [‡]	Requiring high-flow nasal cannula [‡] , facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg. CPAP, BiPAP, intubation and mechanical ventilation)

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

[†] Fever is defined as temperature $\geq 38C$ not attributable to any other cause. In patients who have CRS then received antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS 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 examples, a patient with temperature of 39.5C, 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 $\leq 6L/minute$. Low-flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at $\geq 6L/minute$.

CRS MANAGEMENT*

GRADING ASSESSMENT	TREATMENT
<p>Grade 1 CRS Management on the floor Fever In-person evaluation by medical professional *also assess neurologic status*</p>	<p>Supportive care</p> <ul style="list-style-type: none"> • Investigate for infection and start broad spectrum antibiotics (meropenem or piperacillin tazobactam) • Antipyretic (acetaminophen) for fever • IV hydration <p>Investigations</p> <ul style="list-style-type: none"> • Blood and urine cultures, chest x-ray • Vitals every 1 hour for at least 12 hours or until resolution of symptoms • Complete additional ICE assessment <p>If no improvement in 3 days (72 hours) provider to consider tocilizumab (see grade 2)</p>
<p>Grade 2 CRS Management on the floor Hypotension: responds to fluids Hypoxia: responds to low-flow oxygen</p> <p>In-person evaluation by medical professional *also assess neurologic status*</p>	<p>Supportive care</p> <ul style="list-style-type: none"> • IV fluid boluses for hypotension (up to 2L) <ul style="list-style-type: none"> ○ If no response to first 1L of fluid, involve CCOT • low-flow oxygen • Investigate for infection and start broad spectrum antibiotics if not already started • Antipyretic (acetaminophen) for fever <p>Anticytokine therapy</p> <ul style="list-style-type: none"> • Tocilizumab 8 mg/kg IV every 8 hours (maximum dose 800 mg) for a maximum of 4 doses <p>Steroids – if no improvement within 1-2 doses of tocilizumab consider or if concurrent ICANS consider after 1 dose of tocilizumab</p> <ul style="list-style-type: none"> • Dexamethasone 10 mg IV every 12 hours. Reassess ongoing need after 2 doses. <p>Investigations</p> <ul style="list-style-type: none"> • STAT bloodwork including CBC, lytes, liver function, INR/PTT, fibrinogen, ferritin • Vitals every 30 minutes until back to baseline pressure and oxygen requirements • Complete additional ICE assessment

* If concurrent ICANS/neurotoxicity see CRS + ICANS management chart for medication therapy

GRADING ASSESSMENT	TREATMENT
<p>Grade 3 CRS Management in ICU Hypotension: requires 1 vasopressor (+/- vasopressin) Hypoxia: requires high-flow oxygen</p> <p>In-person evaluation by medical professional *also assess neurologic status*</p>	<p>Supportive care</p> <ul style="list-style-type: none"> • IV fluid boluses for hypotension • Oxygen • Investigate for infection and start broad spectrum antibiotics • Antipyretics (acetaminophen) for fever • Vasopressor support <p>Anticytokine therapy</p> <ul style="list-style-type: none"> • Tocilizumab 8 mg/kg IV every 8 hours (maximum dose 800 mg) for a maximum of 4 doses <p>Steroids</p> <ul style="list-style-type: none"> • Dexamethasone 10 mg IV every 6 hours <p>Investigations</p> <ul style="list-style-type: none"> • ECHO or POCUS to assess cardiac function
<p>Grade 4 CRS Management in ICU Hypotension: requiring 2 or more vasopressors (excluding vasopressin) Hypoxia with respiratory support requiring positive pressure</p>	<p>Supportive care</p> <ul style="list-style-type: none"> • IV fluid boluses for hypotension • Mechanical ventilation • Investigate for infection and start broad spectrum antibiotics • Antipyretics (acetaminophen) for fever • Vasopressor support <p>Anticytokine therapy</p> <ul style="list-style-type: none"> • Tocilizumab 8 mg/kg IV every 8 hours (maximum dose 800 mg) for a maximum of 4 doses • If refractory consider anakinra DOSE every 12 hours. To be suggested by hematology if required <p>Steroids</p> <ul style="list-style-type: none"> • Methylprednisolone 500 mg IV every 12 hours for 3 days • Consider following taper if improvement <ul style="list-style-type: none"> ○ 250 mg IV every 12 hours for 2 days ○ 125 mg IV every 12 hours for 2 days ○ 60 mg IV every 12 hours, stop when CRS improves to grade 1

* If concurrent ICANS/neurotoxicity see CRS + ICANS management chart for medication therapy

Immune Cell Associated Neurotoxicity Syndrome (ICANS)

Definition: (ICANS) is a clinical and neuropsychiatric syndrome involving pro-inflammatory cytokines, disrupted blood brain barrier, and neuronal injury.

Symptoms can occur in days to weeks following T cell therapies. Typically presents within 2-4 days after onset of severe CRS but can also develop independently of CRS. ICANS symptoms are diverse including dysgraphia, tremor impaired attention; however, expressive aphasia is a very specific symptom for patients who later develop severe neurotoxicity. ICANS is a clinical diagnosis of neurologic toxicity attributed to recent administration of an immune therapy. It is a diagnosis of exclusion after ruling out other potential causes of mental status changes or altered neurologic function.

ICE
<ul style="list-style-type: none"> • Orientation: orientation to year, month, city, hospital: 4 points • Naming: ability to name 3 objects (eg. point to clock, pen, button): 3 points • Following commands: ability to follow simple commands (eg. "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point • Writing: ability to write a standard sentence (eg. My name is ...): 1 point • Attention: ability to count backwards from 100 by 10: 1 point

Scoring: 10, no impairment; 7-9, grade 1 ICANS; 3-6, grade 2 ICANS; 0-2, grade 3 ICANS; 0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

ICANS GRADING

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score*	7-9	3-6	0-2	0 (patient 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 ICE score of 3 who had 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 medications)

‡Tremors and myoclonus associated with immune effector therapies may be graded according to CTCAE 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.

ICANS MANAGEMENT*

NEUROTOXICITY GRADING ASSESSMENT	TREATMENT
<p>Grade 1 Management on the floor ICE score 7 - 9 In-person evaluation by medical professional</p>	<p>Supportive care</p> <ul style="list-style-type: none"> • IV hydration • Aspiration precautions <p>Investigations</p> <ul style="list-style-type: none"> • ICE scoring every 2 hours until resolution of symptoms • Brain imaging (MRI) and EEG • SLP consult for swallowing precautions
<p>Grade 2 Management on the floor ICE score 3 - 6 In-person evaluation by medical professional</p> <p>Notify CCOT of grade 2 ICANS for potential transfer</p>	<p>Supportive care</p> <ul style="list-style-type: none"> • IV hydration • NPO <p>Steroids</p> <ul style="list-style-type: none"> • Dexamethasone 10 mg IV every 6 hours reassess in 12 hours <p>Investigations</p> <ul style="list-style-type: none"> • Blood glucose with meals and bedtime • ICE scoring every 2 hours until resolution of symptoms • Brain imaging (MRI) and EEG • Consider lumbar puncture
<p>Grade 3 Management in the ICU ICE score 0-2</p>	<p>Supportive care</p> <ul style="list-style-type: none"> • Levetiracetam 1000 mg IV every 12 hours • Lorazepam 4 mg IV q5 minutes for seizure activity • Avoid phenytoin due to drug interactions <p>Steroids</p> <ul style="list-style-type: none"> • Methylprednisolone 1 mg/kg IV every 12 hours. Continue until grade 1 ICANS then taper <p>Anticytokine therapy</p> <ul style="list-style-type: none"> • Consider anakinra 100 mg IV q6 hours <p>Investigations</p> <ul style="list-style-type: none"> • ICE scoring every 2 hours until resolution of symptoms • Brain imaging (MRI) and EEG • Complete lumbar puncture if not yet done
<p>Grade 4 Management in the ICU ICE score 0</p>	<p>Supportive care</p> <ul style="list-style-type: none"> • Levetiracetam 1000 mg IV every 12 hours • Lorazepam 4 mg IV q5 minutes for seizure activity • Avoid phenytoin due to drug interactions <p>Steroids</p> <ul style="list-style-type: none"> • Methylprednisolone 1 g IV every 12 hours. Hematology to provide taper when appropriate

	<p>Anticytokine therapy</p> <ul style="list-style-type: none">• Consider anakinra 100 mg IV q6 hours <p>Investigations</p> <ul style="list-style-type: none">• ICE scoring every 2 hours until resolution of symptoms
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* If CRS see CRS + ICANS management chart for medication therapy

Concurrent CRS ICANS MEDICATION MANAGEMENT

CRS GRADING ASSESSMENT	TREATMENT
Grade 2 - 4 CRS + any grade of ICANS	Follow ICANS chart for neurotoxicity supportive care and steroids Follow CRS chart for supportive care and steroids
Grade 1 ICANS with concurrent CRS	Anticytokine therapy <ul style="list-style-type: none"> • Tocilizumab 8 mg/kg IV every 8 hours (maximum dose 800 mg) for a maximum of 4 doses Steroids – if no improvement within 1 doses of tocilizumab add <ul style="list-style-type: none"> • Dexamethasone 10 mg IV every 12 hours. Reassess ongoing need after 2 doses.
Grade 2 ICANS with concurrent CRS	Anticytokine therapy <ul style="list-style-type: none"> • Tocilizumab 8 mg/kg IV every 8 hours (maximum dose 800 mg) for a maximum of 4 doses Steroids – if no improvement within 1 doses of tocilizumab add <ul style="list-style-type: none"> • Dexamethasone 10 mg IV every 6 hours OR • Methylprednisolone 1 mg/kg every 12 hours • Continue until improvement to grade 1 ICANS then taper
Grade 3 or 4 ICANS with concurrent CRS	Anticytokine therapy <ul style="list-style-type: none"> • Do not use tocilizumab as it does not cross blood brain barrier • Anakinra 100 mg IV q6 hours Steroids <ul style="list-style-type: none"> • Methylprednisolone 1 g every 12 hours, if no improvement escalate to 1 g every 8 hours

References:

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