Cytokine Release Syndrome (CRS) and Immune Cell Associated Neurotoxicity Syndrome (ICANS)

Presented by:
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Sajad Khazal, MD

Critical Care Management of Pediatric HSCT and Cell Therapy Patients Workshop
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Disclosures

The presenters have no financial relationships to disclose
Objectives

• Provide an overview of immune effector cell (IEC) therapy including chimeric antigen receptor cell therapy (CAR-T)
• Describe current clinical indications
• Define unique toxicities of IEC
• Discuss the role of nurses in the assessment and management of IEC therapy and its toxicities
• Discuss evidence-based algorithms for the management of IECs related toxicities
Emily Whitehead-
A Pioneer for CAR-T Therapy

Currently utilize the patients own T-cells (autologous)
Genetically engineered in the lab (viral or non viral)
Target the surface antigen of interest (e.g. CD19)
CAR T cells will destroy the cells expressing the target antigen
CAR T Cells have the potential for lifelong anti-tumor effect

Chimeric Antigen Receptor (CAR) T Cell Therapy Overview
Chimeric Antigen Receptor T-Cell Therapy: How it works

1. Apheresis catheter placement
2. T-cells are collected from the patient through apheresis
3. T-cells are genetically engineered in a laboratory to manufacture “Chimeric Antigen Receptor (CAR) T-cells”
4. The CAR T cells are then expanded
5. CAR T-cells are then infused into the patient
6. CAR T-cells recognize and kill tumor cells

Current FDA Approved CAR-T Cell Therapy

- **Agent**: Tisagenlecleucel (Kymriah™)
- **Indication**: treatment of relapsed (second or later) or refractory B-cell acute lymphoblastic leukemia (ALL) (pediatric and young adults up to 25) and relapsed or refractory large b-cell lymphoma (adults >18 years)

- **Agent**: Axicabtagene ciloleucel (Yescarta™)
- **Indication**: treatment of relapsed or refractory large B cell lymphomas

*CAR-T cell therapy, a cellular product, has been approved by the FDA as a drug, described as a “living drug”, the first of its kind*
IECs Therapy-Associated Toxicities

Mechanisms of Toxicity in Patients Receiving IEC Therapy

- Target cell destruction and IEC expansion
- Release of cytokines associated with IEC expansion
- Inflammatory response throughout organ systems (including the CNS)
### Unique IEC Toxicities

<table>
<thead>
<tr>
<th>Cytokine Release Syndrome (CRS)</th>
<th>Immune Cell Associated Neurotoxicity Syndrome (ICANS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Elevation in circulating cytokines in response to the infused IEC</td>
<td>• Associated with elevated cytokines in the CSF including IL-6 (passive diffusion from the blood)</td>
</tr>
<tr>
<td>• <strong>Characteristics:</strong> fever, hypotension, hypoxia</td>
<td>• <strong>Characteristics:</strong> confusion, delirium, encephalopathy, seizures and cerebral edema</td>
</tr>
</tbody>
</table>

- Pathophysiology poorly understood
- CRS/ICANS can occur concurrently or with no apparent association
- Nearly half of patients require intensive monitoring/critical care support
- Generally reversible but can be fatal
CRS Clinical Signs

One or more of the following:

• Fever ≥ 38°C
• Hypotension
  • Ages 1-10yr: SBP < (70+2 x age in years)
  • Greater than 10yr: SBP < 90
• Hypoxia
  • $O_2 < 92\%$ on room air

CRS Risk Factors

• High disease burden
• Comorbidities
• Active Inflammatory Process
• Early onset of CRS (within 3 days)
Grading CAR-T Related CRS

<table>
<thead>
<tr>
<th>CRS Parameter</th>
<th>Grade 1</th>
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<td>Hypoxia</td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring a vasopressor with or without vasopressin</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
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ICANS Clinical Signs

- Impaired expression affecting language and handwriting
- Delirium
- Seizures
- Age appropriate assessments are imperative for early recognition in young children
ICANS Risk Factors

- There are currently no known risk factors for ICANS

Grading Immune Effector Cell Associated-Neurotoxicity Syndrome

<table>
<thead>
<tr>
<th>Neurotoxicity Domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICE score⁴</td>
<td>7-9</td>
<td>3-6</td>
<td>0-2</td>
<td>0 (patient is unarousable and unable to perform ICE)</td>
</tr>
<tr>
<td>Depressed level of consciousness¹</td>
<td>Awake spontaneously</td>
<td>Awake to voice</td>
<td>Awake only to tactile stimuli</td>
<td>Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma</td>
</tr>
<tr>
<td>Seizure</td>
<td>N/A</td>
<td>N/A</td>
<td>Any clinical seizure focal or generalized that resolves rapidly or nonconvulsively on EEG that resolve with intervention</td>
<td>Life-threatening prolonged seizure (≥5 min), or repetitive clinical or electrical seizures without return to baseline in 6 weeks</td>
</tr>
<tr>
<td>Motor findings¹</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Deep focal motor weakness such as hemiparesis or paraparesis</td>
</tr>
<tr>
<td>Elevated ICP/cerebral edema¹</td>
<td>N/A</td>
<td>N/A</td>
<td>Focal/local edema on neuroimaging²</td>
<td>Diffuse cerebral edema on neuroimaging: Uncal herniation or decorticate posture: or Cranial nerve VI palsy; or Papilledema; or Cushing’s triad</td>
</tr>
</tbody>
</table>

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.

¹ A patient with an ICE score of 0 may be classified as grade 2 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

² Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).

³ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

⁴ Intracranial haemorrhage 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.
Management of CRS & ICANS

CRS

- Tocilizumab
  - IL-6 receptor antagonist
  - FDA approved for treatment of CRS
  - Must have 2 doses per patient on site
- Siltuximab
  - Binds to both soluble and membrane bound IL-6
  - Used as off label indication for CRS
  - Must have consent signed prior to infusion

ICANS

- Corticosteroids
  - believed to be associated with suppression of CAR-T cell expansion and unfavorable patient outcomes
  - Should not be used as premed for cell infusion or blood transfusions
  - Should be easy to identify CAR-T patients in electronic Medical Record to avoid accidental administration

Management of CRS

<table>
<thead>
<tr>
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<th>Grade 4 CRS</th>
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<tbody>
<tr>
<td>Management</td>
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<td>Management</td>
<td>Management</td>
</tr>
<tr>
<td>- Acetaminophen, as needed, for fever</td>
<td>- Manage according to recommendations for grade 1 CRS (if applicable)</td>
<td>- Manage according to recommendations for grades 1 and 2 CRS</td>
<td>- Manage according to recommendations for grades 1 and 2 CRS</td>
</tr>
<tr>
<td>- Evaluate for infectious aneologies (blood and urine cultures and chest radiography)</td>
<td>- Administer i.v. fluid bolus of 10–20 mL/kg normal saline; repeat as necessary to maintain SBP above baseline or age-specific normal range</td>
<td>- Transfer patient to PICU and obtain echocardiogram, if not performed already</td>
<td>- Administer i.v. fluids, anti-IL-6 therapy, corticosteroids, and vasopressors and perform hemodynamic monitoring as described for grades 1, 2, or 3 CRS</td>
</tr>
<tr>
<td>- Consider broad-spectrum antibiotics and filgrastim (if patient is neutropenic)</td>
<td>- For hypotension refractory to fluid boluses or hypoxia, consider anti-IL-6 therapy with i.v. tocilizumab 1.12 mg/kg for patients weighing &lt;30 kg or 8 mg/kg for those weighing ≥30 kg, to a maximum of 800 mg per dose; repeat dose every 6 hours for 3 doses within 24 hours (but titrate frequency according to response)</td>
<td>- If patient is refractory to lower dose alternatively, methylprednisolone 1–2 mg/kg per day divided every 6–12 hours can be used *</td>
<td>- If clinical improvement, consider high-dose methylprednisolone (1 g daily for 3 days, followed by taper of 10 mg per day divided every 6–12 hours)</td>
</tr>
<tr>
<td>- Assess for adequate hydration</td>
<td>- If hypotension persists after two fluid boluses and anti-IL-6 therapy, start vasopressors, transfer patient to PICU, and obtain echocardiogram</td>
<td>- Use supplemental oxygen as needed</td>
<td>- Use supplemental oxygen, including high-flow oxygen delivery and non-invasive positive pressure ventilation</td>
</tr>
<tr>
<td>- Consider anti-IL-6 therapy for persistent or refractory fever *</td>
<td>- Use supplemental oxygen as needed</td>
<td>- If patient is at high risk of severe CRS: hypotension persists after anti-IL-6 therapy, or there are signs of hypoperfusion or rapid deterioration, use stress-dose hydrocortisone 12.5–37.5 mg/m² per day divided every 6 hours; i.v. dexamethasone 0.5 mg/kg (maximum 10 mg per dose) every 6 hours; or methylprednisolone 1–2 mg/kg per day divided every 6–12 hours</td>
<td>- Administer i.v. fluids, anti-IL-6 therapy, corticosteroids, and vasopressors and perform hemodynamic monitoring as described for grades 1, 2, or 3 CRS</td>
</tr>
<tr>
<td>- Symptomatic management of constitutional symptoms and organ toxicities</td>
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</tbody>
</table>

\* Recommend high-dose methylprednisolone (1 g daily) for up to 3 days, followed by rapid taper of 10 mg per day divided every 6–12 hours.
### Management of ICANS

<table>
<thead>
<tr>
<th>Grade 1 CRBS</th>
<th>Grade 2 CRBS</th>
<th>Grade 3 CRBS</th>
<th>Grade 4 CRBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- Vigilant supportive care with explanation and is hydration</td>
<td></td>
<td></td>
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<tr>
<td>- Without oral intake of food, milk (cocoa, and fruit) and fluids</td>
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<td></td>
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<tr>
<td>- Substitute all oral medications and/or nutrition with i.v. fluids if swallowing is impaired</td>
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<tr>
<td>- Avoid medications that cause CNS depression</td>
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<tr>
<td>- Use doses of leucovorin (200 mg/kg, maximum 1 mg per dose), daily, or methylprednisolone (80 mg/kg, maximum 1 mg per dose, every 6 hours in children, with careful monitoring, for agitated patients)</td>
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<td></td>
<td></td>
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<tr>
<td>- Neurology consultation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Funduscopic examination for papilledema</td>
<td></td>
<td></td>
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<tr>
<td>- MRI of the brain with and without contrast and diagnostic lumbar puncture with measurement of opening pressure (normal pressure for a child)</td>
<td></td>
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</tr>
</tbody>
</table>

**Hypersensitivity Reactions**

- Supportive care and neurological work up as per grade 1 CRBS
- Administration of anti-IL-6 therapy if associated with concurrent CRBS
- Desmopressin 0.5 mcg/kg every 6 hours or methylprednisolone 1-2 mg/kg per day divided every 6-8 hours for CRBS that is not associated with concurrent CRBS or is refractory to prior anti-IL-6 therapy
- Consider transfer to PICU associated with grade 2 CRBS (Table 2)

**B-cell aplasia/Hypogammaglobulinemia**

- Supportive care and neurological work up as per grade 1 CRBS
- Administration of anti-IL-6 therapy if associated with concurrent CRBS
- Desmopressin 0.5 mcg/kg every 6 hours or methylprednisolone 1-2 mg/kg per day divided every 6-8 hours for CRBS that is not associated with concurrent CRBS or is refractory to prior anti-IL-6 therapy
- Consider transfer to PICU associated with grade 2 CRBS (Table 2)

**Other Side Effects**

- Hypersensitivity Reactions
- B-cell aplasia/Hypogammaglobulinemia
- Prolonged cytopenias
- Increased risk of infection
- Tumor lysis syndrome (TLS)
Assessing Neurotoxicity in Patients Receiving IEC Therapies

Nursing Assessment

Encephalopathy Assessment Tools for Grading of ICANS

<table>
<thead>
<tr>
<th>CARTOX-10 [12]</th>
<th>ICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation: orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points</td>
<td>Orientation: orientation to year, month, city, hospital: 4 points</td>
</tr>
<tr>
<td>Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points</td>
<td>Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points</td>
</tr>
<tr>
<td>Writing: ability to write a standard sentence (eg, “Our national bird is the bald eagle”): 1 point</td>
<td>Following commands: ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”): 1 point</td>
</tr>
<tr>
<td>Attention: ability to count backwards from 100 by 10: 1 point</td>
<td>Writing: ability to write a standard sentence (eg, “Our national bird is the bald eagle”): 1 point</td>
</tr>
<tr>
<td>Attention: ability to count backwards from 100 by 10: 1 point</td>
<td>Attention: ability to count backwards from 100 by 10: 1 point</td>
</tr>
</tbody>
</table>

CARTOX-10 (left column) has been updated to the ICE tool (right column). ICE adds a command-following assessment in place of 1 of the CARTOX-10 orientation questions. The scoring system remains the same.

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.
Handwriting Assessment

Pediatric Specific Nursing Documentation

- Cornell Assessment of Pediatric Delirium (CAPD)
  - All CAR-T patients <18 years old
  - Documented at 0600 and 1800
  - Assessed 11 hour period to provide accurate assessment
  - Notify provider if score is 9 or greater

- Pediatric Early Warning Score (PEWS) Algorithm
  - Uses objective data to predict patient deterioration early
  - Uses baseline and age appropriate vital signs, age appropriate behavior and clinical judgment
CAPD Documentation Template

Cornell Assessment of Pediatric Delirium: Criteria by Age

Developmental Anchor Points For Youngest Patients

<table>
<thead>
<tr>
<th>Age (in months)</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the child make eye contact with the caregiver?</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2. Are the child's actions purposeful?</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>3. Is the child aware of his/her surroundings?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4. Does the child communicate needs and wants?</td>
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<td></td>
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</tr>
<tr>
<td>5. In the child's eyes?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. In the child's head?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. In the child's body?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. In the child's voice?</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

TOTAL

2/18/2019
Pediatric Early Warning Score (PEWS)

Nursing Management: Key Considerations

- Quick & subtle changes require frequent and standardized assessment
- The use of handwriting samples can identify changes that may be related to underlying neurotoxicity
- Have a plan - Who to Call & What to Expect
- Thorough documentation is important to support identification of changes, toxicities
- Communication between nurse and patient/interprofessional colleagues is critical
- Holistic care of and education for patients is fundamental
Case Study #1

- 25 year old female, multiply relapsed ALL, Day +7 post Kymriah Infusion
  - Persistent, refractory fevers
  - Persistent headache
  - SBP <90mmHg, required fluid bolus and low dose norepinephrine
  - SpO2<90% on room air, requiring oxygen
Grading CAR-T Related CRS

<table>
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<tr>
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<th>Grade 1</th>
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<tr>
<td>Fever* With Hypotension</td>
<td>Temperature ≥ 38°C</td>
<td>Temperature ≥ 38°C</td>
<td>Temperature ≥ 38°C</td>
<td>Temperature ≥ 38°C</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring a vasopressor with or without vasopressin</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td>And/or† Hypoxia</td>
<td>None</td>
<td>Requiring low-flow nasal cannula or blow-by</td>
<td>Requiring high-flow nasal cannula, ECMO, nonrebreather mask, or Venturi mask</td>
<td>Requiring positive pressure (eg, CPAP, BIPAP, intubation and mechanical ventilation)</td>
</tr>
</tbody>
</table>

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 antipyretics 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.

Treatment of CRS

- Transferred to ICU
- Complete infectious work up to rule out sepsis
- Hypotension responded to low dose vasopressors
- Given tocilizumab x3 doses
ICANS Assessment

- Hallucinations
- Confused/ Disoriented
- Handwriting changes
- CARTOX-10 score 5/10
- No seizures

Grading Immune Effector Cell Associated-Neurotoxicity Syndrome

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<td>ICE score</td>
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<td>3-6</td>
<td>0-2</td>
<td>0-5</td>
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<td>Awake to voice</td>
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<td>N/A</td>
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N/A indicates not applicable.

¹ 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.

² Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).

³ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

⁴ 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.
Treatment of ICANS

- Previously transferred to ICU
- Corticosteroids given
- Symptoms resolved in ---- days

Case Study #2

- 19 year old female, multiply relapsed ALL, post infusion Day +5

- Tachycardia
- Persistent Fever
- Hypoxia requiring 2L NC
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<td>None</td>
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<td>Requiring a vasopressor with or without epinephrine</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td>And/or Hypoxia</td>
<td>None</td>
<td>Requiring low-flow nasal cannula or blow-by</td>
<td>Requiring high-flow nasal cannula, face mask, nonbreather mask, or CPAP, BIPAP, intubation and mechanical ventilation</td>
<td>Requiring positive pressure (e.g., CPAP, BIPAP, intubation and mechanical ventilation)</td>
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† 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.

Treatment of CRS

- Tocilizumab x2 doses
ICANS Assessment

• AOx3
• CARTOX-10 score of 10/10
• Headaches

References

Many Thanks To:

TEAM Pedi SCTCT at MD Anderson
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- Lindsay Robusto, BCOP

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- Shea Simon, MS, RN, OCN
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- Janet Smith, BSN, RN, CPON
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