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## Diagnosis, grading and management of toxicities from immunotherapies in children, adolescents and young adults with cancer

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## Abstract

Cancer immunotherapies have been associated with remarkable response rates but are also associated with unique and severe toxicities, which can lead to rapid clinical deterioration. Novel immune effector cell (IEC) therapies and immune checkpoint inhibitors are under investigation in ongoing clinical trials and the use of standard of care cancer immunotherapies including chimeric antigen receptor (CAR) cells and immune checkpoint inhibitors, in paediatric patients continues to yield mature clinical follow-up. Herein, authors from the Pediatric Acute Lung

Injury and Sepsis Investigators (PALISI) Network Hematopoietic Cell Transplantation-Cancer Immunotherapy (HCT-CI) Subgroup, the Paediatric Diseases Working Party (PDWP) of the European Society of Blood and Marrow Transplantation (EBMT), the supportive care committee of the Pediatric Transplantation and Cellular Therapy Consortium (PTCTC) and the MD Anderson Cancer Center CAR T Cell Therapy-Associated Toxicity (CARTOX) Program have collaborated to provide updated comprehensive recommendations on the care of paediatric, adolescent young adult patients receiving cancer immunotherapies.

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## Introduction:

Cancer immunotherapy involves components of the immune system harnessed to induce long term cancer remission. These include immune checkpoint inhibitors (ICIs), Bispecific T cell engagers BiTEs and immune effector cell (IEC) therapies which have all revolutionized modern cancer medicine. Nevertheless, these therapies have been associated with unique and potentially life-threatening toxicities, which include cytokine-release syndrome (CRS), IEC-associated neurotoxicity syndrome (ICANS) and other severe immune-related adverse events (irAEs). Vigilance, prompt recognition and management of these toxicities, with attention to age appropriate considerations, can lead to optimized outcomes in children and in adolescents and young adults (AYAs) receiving these therapies. Paediatric populations are defined as those including patients aged <15 years, and AYA populations include patients aged 15–25 years<sup>1</sup>. We have previously published grading and management guidelines for paediatric patients receiving IEC- based therapy with chimeric antigen receptor (CAR) T cells<sup>2</sup>, and the American Society for Transplantation and Cellular Therapy (ASTCT) subsequently adopted key elements of the grading criteria that we developed but has not proposed management guidelines<sup>3</sup>.

In 2020, the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network Hematopoietic Cell Transplantation- Cancer Immunotherapy Subgroup and the MD Anderson Cancer Center CAR T Cell Therapy-Associated Toxicity (CARTOX) Program convened an interdisciplinary and international expert panel of key opinion leaders from leading academic centers and societies, including the Pediatric Diseases Working Party of the European Society of Blood and Marrow Transplantation, the Supportive Care Committee of the Pediatric Transplantation and Cellular Therapy Consortium and the Extracorporeal Life Support Organization, with three aims: (1) to assess the current state of cancer immunotherapy for paediatric patients; (2) to provide interdisciplinary supportive care guidelines for these patients; and (3) to develop proactive surveillance strategies for possible late effects related to these treatments. The panelists include physicians, fellows, trainees, nurses, pharmacists and basic and translational scientists with expertise in paediatric and adult immunotherapy, haematology, solid tumour, nephrology, critical care and infectious disease. New immunotherapies with unique toxicity profiles continue to emerge; herein, we provide recommendations applicable to the management of children and AYAs receiving these therapies (Box 1).

## Methods

Panelists conducted literature reviews using key specific search teams ('cancer immunotherapies', 'tumour-infiltrating lymphocyte', 'T cell receptor therapy', 'natural killer cell therapy', 'virus-specific cytotoxic lymphocyte', 'bispecific T cell engager', 'immune checkpoint inhibitor', 'chimeric antigen receptor T cell therapy', 'cytokine-release syndrome', 'immune effector cell-associated neurotoxicity syndrome', 'haemophagocytic lymphohistiocytosis', 'immune-related adverse event', 'pseudoprogression' and 'infection prophylaxis') that were summarized and reviewed by a writing committee (see Author contributions). The guideline panel comprised a multidisciplinary and interprofessional team, including physicians with expertise in paediatrics, IEC therapy, immunotherapy and ICIs. A modified Delphi method was used to vote until consensus was achieved by all panelists via electronic communications. The final manuscript was reviewed and approved by all authors as well as the Scientific Review Committee of the PALISI Network.

## Cancer immunotherapies

### CAR-transduced cell therapies

CAR T cells are generated through genetic modification of the patient's own (autologous) T cells or those of an allogeneic donor. In 2017, tisagenlecleucel was the first CAR T cell product to be approved by the FDA for the treatment of patients aged <25 years with relapsed and/or refractory (R/R) CD19<sup>+</sup> B cell acute lymphoblastic leukaemia (B-ALL)<sup>4</sup>. Shortly after, axicabtageneclisoleucel was also approved by the FDA for the treatment of adult patients with R/R large B cell lymphomas, and in 2020, brexucabtagene autoleucel was approved for the treatment of adult patients with R/R mantle cell lymphoma<sup>5,6</sup>. These therapies can result in remarkable clinical outcomes, but are also associated with unique and potentially fatal toxicities, such as CRS and ICANS<sup>7</sup>. Specific toxicity profiles can differ depending on: (1) the source cell type (typically T cells or natural killer (NK) cells); (2) the engineered product (including the target antigen, costimulatory domain and gene transfer technology); (3) the manufacturing process and reagents; (4) the primary disease; and (5) host factors, specific details of which are beyond the scope of this Consensus Statement<sup>8-10</sup>.

Resistance to CAR T cell therapy, including in the context of variations in antigen expression levels, warrants further research. Dual targeting of tumour cell-surface markers (such as CD19 and CD20) might help overcome treatment failure owing to downregulation of single antigen targets<sup>11</sup>. Fousek et al. created a trivalent CAR T cell product targeting CD19, CD20 and CD22 that was associated with promising preclinical results and is pending study in trials involving patients with CD19<sup>-</sup> relapsed B cell lineage disease<sup>12,13</sup>.

Next-generation IEC products, which could be used in new disease indications and could potentially be associated with more durable disease remissions and reduced toxicity, are the topic of investigation in current clinical trials, some involving children and AYAs (NCT04324996, NCT03056339 and NCT03448393)<sup>12,14,15</sup>. UCART19 is an allogeneic 'off-the-shelf' gene edited CD19-targeted CAR T cell product, in which *TRAR2* expression was deleted to abrogate the potential induction of graft-versus-host disease (GVHD) by

donor T cells<sup>16</sup>. In two multicentre phase I trials involving 7 children and 14 adults with R/R B-ALL, two patients treated with UCART19 developed GVHD (manifested as grade 1 skin toxicity). Other reported AEs included grade 3–4 CRS in three patients, grade 1–2 ICANS in eight patients and grade 4 prolonged cytopenias in six patients. Of the 21 patients, 14 had complete responses with or without incomplete haematological recovery at 28 days after infusion, with a median duration of response of 4.1 months. The use of allogeneic CAR NK cells has also been proposed to potentially minimize the risk of GVHD; one such approach is being tested in a trial including children with R/R CD19<sup>+</sup> haematological cancers<sup>14</sup>.

## TIL therapies

The tumour microenvironment (TME) typically contains tumour-infiltrating lymphocytes (TILs), including cytotoxic (CD8<sup>+</sup>) and helper (CD4<sup>+</sup>) T cells, B cells and NK cells, which can all influence metastasis, relapse and treatment response<sup>17–19</sup>. While most immune cells residing in the TME are functionally impaired, TILs can be harnessed as a form of adoptive cell therapy through the ex vivo expansion of resident T cells harvested from a patient's tumour<sup>20</sup>. TIL production typically takes several weeks using the existing rapid expansion protocols for selected TIL lines with the best in vitro tumour reactivity<sup>21</sup>. Lymphodepletion with fludarabine and cyclophosphamide, sometimes in conjunction with total body irradiation, potentiates the antitumour effect of TILs by limiting regulatory cells and eliminating cell subpopulations that compete with them for cytokines and T cell growth factors<sup>21–24</sup>. TILs are typically infused with high dose IL-2, an approach consistently associated with promising objective response rates in patients with metastatic melanoma<sup>24–26</sup>. Current research efforts in this field are focused on expanding indications, optimizing selection of T cell subsets, defining the choice of preparative lymphodepleting and/or IL-2 regimens.

A high neoantigen burden has been associated with increased presence of neoantigen-reactive TILs as well as improved responses to ICIs. Neoantigen burden has been suggested to be closely related to the presence of non-synonymous single-nucleotide variants (nsSNVs), which varies substantially across cancer types (from one nsSNV per tumour in paediatric tumours to >1,500 nsSNVs per tumour in tumours associated with high microsatellite instability)<sup>27,28</sup>. An enrichment in indel frameshift mutations has also been associated with a high burden of neoantigens that are distinct from self<sup>28</sup>. Identification of neoantigen-reactive TILs based on the presence of nsSNVs and indel mutations has improved and might constitute a promising approach to improving the efficiency of therapies involving TILs<sup>28</sup>.

TIL-based therapies have been explored in some cancers that predominantly affect children, such as neuroblastoma. TILs have been successfully expanded from tumour samples obtained through either biopsy or resection from children with neuroblastoma. Substantial numbers of NK T (NKT) cells and  $\gamma\delta$ T cells were identified alongside the mixed population of CD8<sup>+</sup> and CD4<sup>+</sup> T cells with either effector or central memory phenotypes<sup>29</sup>. Transduction of TILs with a second-generation CAR targeting GD2 enhanced elimination of neuroblastoma cells in vitro<sup>29</sup>. Researchers have hypothesized that neoadjuvant treatment with ICIs in children with neuroblastoma could result in enrichment of tumour tissue with

lymphocytes. These TILs could be expanded rapidly ex vivo during a short interval between surgery and infusion in order to achieve a suitable target cell dose for adoptive transfer<sup>29</sup>. Neoadjuvant treatment with anti-CTLA4 antibodies has been proven to be feasible and well tolerated in adults with metastatic melanoma<sup>30</sup>.

The presence of CD8<sup>+</sup> T cells in tumours does not guarantee tumour eradication because they might have an exhausted and/or inactive phenotype. The IFN $\gamma$ <sup>Hi</sup>CD8<sup>Hi</sup>FOXP3<sup>Low</sup>CD33<sup>Low</sup> immune profile in tumours has been shown to be an excellent prognostic marker for favourable overall survival (OS) across patients with various tumour types<sup>31</sup>. Treatment with tumour cell-surface vimentin-targeted IL-12 (ttIL-12) before surgery converted tumours to this favourable IFN $\gamma$ <sup>Hi</sup>CD8<sup>Hi</sup>FOXP3<sup>Low</sup>CD33<sup>Low</sup> immune profile, leading to prolonged OS compared with no treatment or treatment with wild-type IL-12 in both mouse and patient-derived xenograft models<sup>31</sup>. The levels of serum IL-12 were lower in mice receiving ttIL-12 than in those receiving IL-12, which might have been associated with reduced toxicity<sup>31</sup>. Similarly, IL-2 can enhance the inherent antitumour activity of CD8<sup>+</sup> T cells and the cytolytic function of NK cells, but is also associated with a variety of toxicities, including capillary leak syndrome (CLS), characterized by edema, hypotension and oliguria within hours of infusion, fevers, rigors, myalgia and nausea<sup>21,32</sup>. In a study involving paediatric patients with progressive or metastatic tumours treated with IL-2, two of ten patients had CLS, three patients had grade 3–4 hypotension and all had fever, headache and bone and muscle pain<sup>33</sup>. TIL-related toxicities are less common, but can include mostly transient, dyspnoea, rigors and fever shortly after infusion. Autoimmune sequelae, including panuveitis, hearing loss and vitiligo, have been reported with adoptive cell transfer of TILs targeting melanoma-associated antigens<sup>34</sup>.

### Engineered TCR therapies

Engineered T cell receptor (TCR) therapy involves the infusion of T cells previously extracted from the blood of a patient and genetically modified to express: (1) receptors that recognize cancer-specific antigens, improve T cell survival and migration and/or reduce tumour-induced immune escape; and/or (2) cytokines to enhance T cell survival and tumour infiltration. AEs might be dependent on the antigen targeted, the methods used to engineer the TCR and the affinity of the transduced TCR<sup>8,9</sup>.

In a phase I trial, a TCR targeting a HLA-A\*0201- restricted NY-ESO-1 epitope, a highly immunogenic protein aberrantly expressed in several tumour types, OS at 3 and 5 years was 38% and 14% in adults and AYAs with synovial cell sarcoma, respectively, and 33% at both time points in those with melanoma<sup>35</sup>. All patients had transient toxicities, which were deemed to be associated with administration of the conditioning regimen and/or IL-2. A treatment-related death occurred 3 days after T cell infusion in a patient who had developed neutropenia and had septic shock from *Escherichia coli* bacteraemia<sup>35</sup>.

Severe central nervous system (CNS) toxicities, including necrotizing leukoencephalopathy, coma and treatment-related mortality, have been reported in adults and AYAs with melanoma receiving T cells with engineered TCRs targeting MAGEA3, owing to cross-recognition of MAGEA12 expressed in the CNS<sup>36</sup>. Cross-recognition of an unrelated epitope also resulted in cardiogenic shock and death in two adults (one with melanoma

and the other with multiple myeloma) who received T cells with engineered TCRs targeting MAGEA3 (reF.<sup>37</sup>). In another trial involving adults with metastatic melanoma, treatment with T cells expressing engineered TCRs targeting MART-1 and gp100 led to ‘on-target, off-tumour’ effects including skin rash (requiring treatment with local steroid injections), uveitis, hearing impairment and CRS (that led to respiratory failure and required the use of systemic steroids)<sup>38</sup>. No serious AEs occurred in eight adult patients with acute myeloid leukaemia or myelodysplastic syndrome who received T cells with engineered TCRs targeting WT1 (reF.<sup>39</sup>). Ongoing clinical trials are testing engineered TCR therapies in children with haematological malignancies (NCT03326921) or solid tumours (NCT03240861).

### NK cell therapies

Infusion of NK cells has emerged as a promising immunotherapy approach because these highly cytotoxic immune effector lymphocytes are capable of eliminating their target cells in an HLA-unrestricted fashion<sup>40</sup>. NK cells can either directly kill tumour cells through the release of cytoplasmic granules that contain perforin and granzyme, which results in target cell apoptosis, or through the expression of membrane-bound ligands that trigger NK cell cytolytic activity upon interacting with their receptors on target cells<sup>40–42</sup>. Khatua et al. reported the feasibility of locoregional administration of expanded NK cells in nine children with R/R medulloblastoma or ependymoma<sup>41</sup>. Among these patients, eight had AEs defined as grade 1–2 according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, including headache, fatigue and thrombocytopenia. One patient had CTCAEv5.0-defined grade 3 slurred speech that resolved with a short course of steroids and was unlikely to have been related to NK cell administration<sup>41</sup>. In a study involving 18 children and AYAs with R/R ALL, NK cells from haploidentical donors were well tolerated, with no reported GVHD<sup>43</sup>. In that cohort, ten patients proceeded to haematopoietic stem cell transplantation (HSCT) and, at the time of writing, almost half had achieved a durable remission<sup>43</sup>. Other studies of NK cells in patients with leukaemia have shown promising results and suggest that NK cell dosing might be an important determinant of therapeutic response and disease outcome<sup>44,45</sup>.

Cell lines derived from paediatric solid tumours, such as osteosarcoma, Ewing sarcoma and rhabdomyosarcoma, are sensitive to NK cells<sup>46,47</sup>. In a first-in-human trial of donor-derived NK cells after allogeneic HSCT in AYAs and adults with solid tumours, acute GVHD occurred in five of nine patients, and four patients had a durable remission following HSCT<sup>48</sup>. Pérez-Martínez et al. reported a possible graft versus tumour effect from donor NK cell populations among six children with solid tumours who underwent haploidentical HSCT with a reported disease-free survival of 50% after a median follow-up duration 14 months<sup>49</sup>.

The efficacy of NK cell therapy might be constrained by the finite lifespan of NK cells, the immunosuppressive nature of the TME of solid tumours and, until the last decade, limitations of ex vivo large-scale NK cell expansion methods<sup>50,51</sup>. These obstacles could be overcome through genetic modification to introduce co-stimulatory domains and/or antigen specificity through CAR. Additionally, cord blood-derived NK cells might be a readily available source of off-the-shelf products. In a phase I/II study of ex vivo expanded

allogeneic cord blood-derived NK cells in children and AYAs with solid tumours, no dose-limiting toxicities and/or GVHD have been reported to date ([NCT03420963](#)).

### Virus-specific cytotoxic lymphocytes

Studies of multiple malignancies, including melanoma and lymphoma, have provided clear evidence that cytotoxic lymphocytes (CTLs; CD8<sup>+</sup> cells) are involved in clinical progression<sup>52</sup>. Van Pel and Boon demonstrated that the lack of immunogenicity of a tumour reflects an inability to activate the immune system rather than the absence of tumour antigens<sup>53</sup>. CD8<sup>+</sup> CTLs alone or in combination with CD4<sup>+</sup> cells help to mount an antitumour immune response<sup>54</sup>. Epstein–Barr virus (EBV)-associated lymphoproliferative disorders unequivocally result from T cell dysfunction in immunosuppressed individuals, in particular, after HSCT and/or relapse after standard-of-care therapies (such as rituximab); expanded EBV-specific CTLs present a promising new therapy for these patients<sup>55–57</sup>.

Rituximab is the de facto standard first-line treatment for EBV<sup>+</sup> post-transplant lymphoproliferative disorders despite not being approved for this indication owing to an acceptable risk to benefit ratio, with responses reported in the range of 44–66%. Up to 50% of patients with a response, however, have disease relapse after rituximab therapy. Prockop et al. used off-the-shelf, allogeneic EBV-specific CTLs from HSCT donors without cancer to treat patients with R/R EBV-associated post-transplantation lymphoproliferative disorders. Complete or sustained partial remissions occurred in 68% of HSCT recipients and 54% of solid-organ transplant recipients, with a 1-year OS of >80% among patients with complete or partial remissions or stable disease after cycle 1 (reFs<sup>56,58,59</sup>). The use of autologous EBV-specific CTLs in patients with nasopharyngeal carcinoma or EBV<sup>+</sup> Hodgkin lymphoma is also associated with promising antitumour activity<sup>60,61</sup>. Other ongoing studies are seeking to determine whether EBV-associated antigens, such as those expressed by Hodgkin lymphoma and nasopharyngeal carcinoma cells, are amenable to EBV-specific CTL therapy ([NCT03769467](#) and [NCT01333046](#)).

Human cytomegalovirus (CMV) antigen can be expressed in glioblastoma multiforme, which led to testing autologous CMV-directed CTLs as a consolidative treatment for patients with this malignancy. This approach was deemed safe and tolerable<sup>62</sup>.

Virus-specific T cells (VSTs) have also been used to treat severe and/or intractable viral infections after HSCT (from EBV, CMV or adenovirus), with a low incidence of de novo GVHD (2 of 50 patients)<sup>63</sup>. Similarly, VSTs targeting EBV ([NCT01535885](#) and [NCT02900976](#)), CMV ([NCT01535885](#) and [NCT02210078](#)), BK virus ([NCT02479698](#)), human poliovirus 2 ([NCT02479698](#)), human herpesvirus 6 and adenovirus ([NCT01535885](#) and [NCT03425526](#)), as well as multi-virus VSTs ([NCT02108522](#)), are under investigation in trials involving adults, AYAs and children<sup>64</sup>. Off-the-shelf VSTs targeting BK virus have been used successfully to treat patients with progressive multifocal leukoencephalopathy and haemorrhagic cystitis, complications both seen after HSCT<sup>65,66</sup>. In the studies described, VST selection and/or expansion has been optimized to maximize viral cytotoxicity while minimizing alloreactivity, largely eliminating the risk of GVHD.

## BiTEs

BiTEs can target a range of tumour-associated antigens and thus can be used to treat a variety of haematological and solid tumours<sup>67</sup>. The CD3–CD19-targeted BiTE blinatumomab has single-agent efficacy in children and adults with R/R B-ALL and minimal residual disease (MRD)-positive B-ALL, and a favourable toxicity profile. Treatment with blinatumomab has been associated with CRS and ICANS<sup>68</sup>.

## ICIs

Immune checkpoints, including PD-1 and CTLA4, negatively control T cell-mediated immunity and have crucial roles in immune homeostasis and preventing autoimmunity<sup>69,70</sup>. Thus, immune checkpoints typically act as dependable mechanisms by which aberrant activation of the immune system is avoided, although they are frequently exploited by neoplastic cells to avoid antitumour T cell responses and thereby facilitate immune escape<sup>71</sup>.

The anti-CTLA4 antibody ipilimumab is an ICI approved by the FDA for the treatment of advanced-stage melanoma in patients aged >12 years<sup>72–74</sup>. The spectrum of irAEs in younger patients seems similar to that described in adults, although toxicities can present earlier in children, after even a single dose<sup>73</sup>. In a phase I trial of ipilimumab in children and AYAs with solid tumours, OS outcomes were more favourable among those who had irAEs than in those who did not<sup>73</sup>. In an open-label, single-arm phase II trial, 12 adolescents with previously treated or untreated unresectable stage III–IV melanoma received ipilimumab (3 or 10 mg/kg every 3 weeks), with no treatment-related deaths reported<sup>74</sup>. The study was discontinued owing to slow accrual, highlighting the challenges facing trials involving children with rare diseases and the importance of inclusion in future trials of adolescents with cancer types that occur predominantly in adults<sup>74</sup>.

The anti-PD-1 antibody nivolumab is also tolerated by children, although a phase II trial revealed limited single-agent activity in patients with common paediatric malignancies<sup>75</sup>. In this trial, the incidence of pleural or pericardial effusions was 15%, mostly occurring during the first cycle and simultaneously<sup>75</sup>. Nivolumab, alone or combined with low-dose ipilimumab, has antitumour activity and is approved for use in adults and children with mismatch repair-deficient or microsatellite instability-high metastatic colorectal cancer that is resistant to chemotherapy<sup>76,77</sup>. Pembrolizumab, another anti-PD-1 antibody, is approved for the treatment of adults and children with R/R classic Hodgkin lymphoma and seems to be well tolerated in children; although potentially treatment-related deaths (pneumonitis with pleural effusion, and pulmonary edema with sepsis) have been reported<sup>78</sup>. Reported AEs with pembrolizumab in adults include acute kidney injury (AKI), colitis, gastritis, adrenal insufficiency, hypertension, proteinuria, thrombocytopenia and hypokalaemia<sup>79,80</sup>.

The safety profiles of ICIs seem similar in children and adults, although close monitoring for earlier and more pronounced toxicities is warranted among younger children, particularly those aged <12 years<sup>73</sup>. Studies of combinations of ICIs with other immunotherapy agents to promote an immunogenic TME or directly provide a T cell infiltrate might lead to the identification of ideal combinations, although monitoring for toxicities will be important<sup>81</sup>.

## Toxicity grading and management

IEC therapy is associated with CRS, ICANS and other systemic organ dysfunctions, such as cardiotoxicity<sup>82</sup>, and treatment with ICIs can result in severe irAEs<sup>83,84</sup>. In 2019, the ASTCT developed a grading system for IEC toxicity, which adopted key elements from the previously published, widely used CARTOX guidelines<sup>2,3,85</sup>, and the American Society of Clinical Oncology (ASCO) has developed guidelines for the management of irAEs in adults receiving ICIs<sup>86</sup>. Herein, we provide important considerations for the diagnosis, grading and management of toxicities associated with immunotherapies in children and AYAs (Table 1).

### CRS

CRS has specific symptoms that can develop when immune cells are activated and release large amounts of cytokines following the administration of immunotherapies, especially those involving T cells. The incidence of CRS is variable, and occurred in almost half of children and AYAs with R/R B-ALL receiving blinatumomab and 77% of those receiving tisagenlecleucel in the phase II ELIANA study<sup>87,88</sup>. CRS is typically diagnosed by the presence of: (1) fever (temperature  $\geq 38$  °C) that is not attributable to any other cause as a defining symptom; (2) hypotension; and/or (3) hypoxia<sup>3</sup> (Fig. 1). The ASTCT guidelines for the diagnosis of CRS are applicable to adults and children alike; however, high vigilance for diagnosis might be especially important among children and AYAs.

Patients with fever and/or hypotension should be assessed for signs and/or symptoms of sepsis (for example, with cultures and/or imaging), and empirical antimicrobial coverage should be initiated. Hypotension in young patients is defined by age-specific physiologically normal ranges and/or in comparison with the individual's baseline values<sup>89</sup>. Prompt recognition of hypotension in young patients should be followed by intensive management. Patients with CRS are at risk of AKI, which can occur in 46% of patients after CAR T cell therapy, owing to direct inflammatory injury, fluid shifts, hypoperfusion and shock<sup>90,91</sup>.

Renal tissue damage is associated with adverse outcomes even without a decrease in glomerular filtration rate, and thus in this context serum creatinine is not a sensitive biomarker of renal function. Cystatin C could be a more reliable functional biomarker that is not affected by age, muscle mass or tubular secretion, although it is affected by the use of steroids<sup>92</sup>. An acute rise in the levels of filtration markers can reflect either a physiological response to an altered haemodynamic state (functional AKI, previously called prerenal azotaemia) or renal tissue damage (intrinsic AKI). Tubular injury biomarkers, such as neutrophil gelatinase-associated lipocalin and a combination of metalloproteinase inhibitor 2 and insulin-like growth factor-binding protein 7, might enable more precise AKI prediction<sup>93,94</sup>. In the absence of complications, the optimal timing to start renal replacement therapy remains largely unknown and poorly supported by quality evidence-based research; this uncertainty translates into wide variation in treatment patterns and practices. Renal replacement therapy might be considered when fluid overload is  $>10$ – $15\%$  or to manage electrolyte imbalances refractory to maximal recommended therapy. Additionally, prospective studies should address the effect of haemoadsorption with cartridge columns in combination with continuous renal replacement therapy on serum cytokine levels and the efficacy of CAR T cell therapy<sup>95</sup>. Overall, early recognition and

management of CRS might be associated with reduced incidence of AKI and functional recovery within 30 days<sup>96</sup>. In addition to AKI, hyponatraemia (sodium serum levels <130 mEq/l), hypokalaemia (potassium serum levels <2.0 mEq/l) and hypophosphataemia (phosphorus serum levels <2.5 mg/dl) are not uncommon after CAR T cell therapy and might result from the release of cortisol, intravascular volume depletion or IL-6-mediated increases in vasopressin secretion in the context of CRS<sup>97</sup>.

The use of normal saline solution might be associated with increases in hyperchloraemic metabolic acidosis, the occurrence of AKI and possibly mortality compared with balanced solutions<sup>98</sup>. Alternatively, albumin administration might be favourable in patients with CRS, especially in those with CLS and hypoalbuminaemia. CLS has been described in patients with CRS and might be more common in patients with severe CRS; albumin administration might reduce the duration of treatment with vasopressors and decrease respiratory, cardiovascular and neurological organ failure scores<sup>99–101</sup>. In patients who are critically ill, albumin administration is associated with reductions in endothelial dysfunction during inflammatory processes similar to those that occur after CAR T cell therapy<sup>99,100</sup>. While the optimal choice of resuscitation fluid for patients with CRS is undefined, acute fluid overload in patients with capillary leak (especially infants, children and those weighing <20 kg, who might have lower ability to tolerate substantial fluid shifts) is a major concern and might contribute to respiratory failure<sup>90</sup>. Preparation for initiation of therapy with vasopressors, cytokine blockade (such as anti-IL-6 antibodies) and/or steroids (discussed below) should occur at the onset of hypotension and should not be delayed in favour of more than two consecutive fluid boluses. Among patients likely to have adrenal insufficiency (such as those treated per paediatric ALL protocols), administration of stress-dose hydrocortisone can precede the initiation of therapy with vasopressors and/or cytokine blockade therapy.

Children and AYAs at risk of hypoxia from CRS should be vigilantly observed for signs or symptoms of respiratory distress. CRS severity grading for hypoxia is based upon the amount of support the patient requires, which in part relies on appropriate recognition of age-appropriate signs or symptoms of respiratory distress. Tachypnoea and/or use of accessory muscles might be associated with fever, and can lead to high energy expenditure and resultant acute respiratory failure<sup>89,102</sup>. The tidal volume of each breath and the peak inspiratory flow rate both increase with patient age. Conversely, extrathoracic dead space can be up to two to three times greater in children than in adults. Furthermore, the peripheral airway resistance in healthy children <5 years of age can be up to four times higher than that in adults. Inflammatory pathologies can further exacerbate this difference, with a reduction in the diameter of the airway of up to 50% and a 16-fold increase in airway resistance<sup>102,103</sup>.

Low-flow supplemental oxygen via a nasal cannula (typically 2–4 l/min in children; oxygen flow rates via a high flow nasal cannula (HFNC) of >6 l/min by ASTCT consensus criteria) can improve hypoxaemia in children, although the precise fraction of inspired oxygen at each flow rate is difficult to determine because of the dilution of oxygen with entrained air and variability in the degree of dilution with variations in tidal volume, minute volume, respiratory rate, inspiratory and expiratory times and flows, anatomical dead space and the effect of an open or closed mouth<sup>104</sup>. Therefore, low-flow supplemental oxygen might not

provide the same level of respiratory support in a 10-year-old child as it does in a 1-year-old; this difference should be considered when assessing a child with CRS. HFNC can benefit patients with respiratory symptoms from CRS by reducing energy expenditure, increasing carbon dioxide washout of nasopharyngeal dead space, facilitating mucociliary function with clearance of secretions and preventing atelectasis<sup>102,105</sup>. HFNC flow rates of 1.5–2.0 l/kg/min have been associated with a reduction in breathing effort, unloading of accessory muscle use and generation of positive pressure with a mean pharyngeal pressure of 4 cmH<sub>2</sub>O in children<sup>106,107</sup>.

In children with grade 3 CRS in whom low-flow oxygen and HFNC are insufficient, noninvasive ventilation with continuous or bilevel positive airway pressure might be a viable option. If indicated, non-invasive positive pressure ventilation should be administered in the paediatric intensive care unit and should not delay intubation. When triggered by patient inspiration, non-invasive ventilation can augment tidal volumes and thereby a patient's minute ventilation. Non-invasive ventilation can deliver higher pressures to overcome airway resistance, enhance ventilation and prevent atelectasis more effectively than HFNC; however, it requires a tight-fitting mask that can be uncomfortable. In addition, the forced air entering the upper airway with non-invasive ventilation can cause distension of the stomach placing susceptible patients at risk of emesis and aspiration<sup>108</sup>. Both HFNC and non-invasive ventilation can be sufficient to alleviate the respiratory symptoms of CRS, although failure rates of 26.9% and 28%, respectively, have been reported<sup>108,109</sup>. Therefore, clinicians must rigorously monitor paediatric patients with CRS to observe the evolution of their respiratory status.

In general, first-line therapy for diagnosed CRS involves administration of IL-6 blockers, such as the anti-IL-6R antibody tocilizumab, which can be considered in patients with grade 1–2 CRS and should be administered in those with grade 3–4 CRS (Fig. 1). In patients with grade 2–4 CRS, stress-dose hydrocortisone should be considered if hypotension from adrenal insufficiency is a possible cause of symptoms. Corticosteroids (methylprednisolone or dexamethasone) can be administered for persistent hypotension, vasopressor need, hypoxia and/or ICANS. In patients with grade 4 CRS, higher dosing of methylprednisolone should be considered. Corticosteroids should be tapered or discontinued once CRS improves to grade 1. In the rare patients in whom these interventions do not improve outcomes, additional therapies to consider include activation of 'safety switches' to directly curtail IEC activity. These approaches include dasatinib as a pharmacological on/off switch, the recombinant IL-1R antagonist anakinra, cyclophosphamide and anti-thymocyte globulin<sup>2,3,14,85,110,111</sup>.

Early initiation of therapy with anti-IL-6 antibodies and/or corticosteroids (within 24 hours) has been associated with reduced severity of CRS without affecting CAR T cell efficacy<sup>112,113</sup>. Although individual institutional algorithms, FDA labels and research protocols vary regarding specific management strategies, prompt recognition and mitigation of severe CRS remains a common goal. Trials are underway to explore the use of the JAK1 selective inhibitor itacitinib to prevent CRS induced by tisagenlecleucel or axicabtagene ciloleucel (NCT04071366), and anakinra for the prevention of CRS and neurotoxicity in patients with B cell lymphomas receiving axicabtagene ciloleucel (NCT04359784).

Prospective studies might provide information on optimal prophylaxis and mitigation strategies across a variety of CAR T cell products and among various disease indications.

## ICANS

ICANS is a pathological process involving the CNS following any immunotherapy that activates or engages endogenous or infused T cells and/or other IECs<sup>3</sup>. ICANS can be progressive and includes a wide range of symptoms, such as headache, pain, meningismus, short-term memory loss, altered mental status, impaired speech (dysarthria and/or aphasia), impaired cognitive skills, motor weakness, movement disorders (tremor, myoclonus and/or facial automatisms), seizures, encephalopathy and cerebral edema<sup>3,85,114</sup>. Following tisagenlecleucel treatment, 40% and 39% of patients with ALL and non-Hodgkin lymphoma (NHL), respectively, had neurological toxicities within the first 8 weeks, with a median duration of symptoms of 6 days and 14 days, respectively<sup>87,115</sup>. The incidence of reported neurological toxicities (64%) was higher and the median duration of neurological toxicity was longer (17 days) in patients with B cell malignancies receiving axicabtagene ciloleucel<sup>116</sup>. In all groups, the median time to onset of symptoms was 4–6 days<sup>87,115,116</sup>.

The Immune Effector Cell-Associated Encephalopathy (ICE) score is an encephalopathy assessment tool used for grading of ICANS in patients aged >12 years, with the highest score (ten) suggesting no cognitive impairment<sup>3</sup>. The ASTCT Consensus Grading adopted our recommendation<sup>3</sup> of using the Cornell Assessment of Paediatric Delirium (CAPD) for encephalopathy screening in children and AYAs for ICANS assessment<sup>3</sup>. CAPD is routinely used for delirium screening in patients aged 12 years and in those aged >12 years in whom this tool is developmentally appropriate<sup>117</sup>. A CAPD score of nine or more suggests delirium. A rising CAPD score from a patient's baseline is also relevant; for example, a patient with a CAPD score of four who later has a score of seven might be at increased risk of delirium and warrants more frequent monitoring. During the expected high risk period for ICANS, CAPD and ICE scores should be evaluated at least twice daily in patients receiving IEC therapies, with an increased frequency of monitoring if the patient experiences any neurological event, such as decreased level of consciousness, rising CAPD score above the patient's baseline, seizures or focal neurological findings.

Consideration of the child's chronological as well as developmental age can ensure that the appropriate developmental screening tool is used initially. ICANS grade is determined by the most severe event (ICE or CAPD score, level of consciousness, seizure occurrence, motor findings or raised intracranial pressure and/or cerebral edema) not attributable to any other cause<sup>3</sup>. Hence, the diagnostic work-up can include neuroimaging, neurology consultation and/or electroencephalography, and diagnostic lumbar puncture, if other causes of encephalopathy are suspected or if ICANS persists. Diffuse background slowing on electroencephalography was reported in 83.3% of paediatric and AYA patients with seizures due to grade 3 ICANS<sup>118</sup>. Similar findings of background showing abnormalities on electroencephalography have been reported in up to 76% of adults receiving CAR T cells possibly indicating clinical or subclinical seizure<sup>119,120</sup>. In these patients, neuroimaging (usually brain CT and/or MRI) typically produced physiologically normal results, although 43% of patients underwent acute MRI scans, that revealed severe neurotoxicity in

~30%, and thus a clear imaging pattern has not been described<sup>119,120</sup>. The spectrum of imaging findings ranges from the most severe and often fatal diffuse cerebral edema pattern to reversible, oftentimes symmetrical periventricular white matter T2 hyperintensity, with or without involvement of the deep grey matter<sup>119,120</sup>. Intracranial haemorrhages, infarcts, leptomeningeal enhancement, posterior reversible encephalopathy syndrome and excitotoxicity-related injury patterns affecting the mesial temporal lobes and splenium have also been reported<sup>119,120</sup>.

Transfer to a paediatric intensive care unit is indicated in patients with grade 3 ICANS, with progressive ICANS or ICANS that is non-responsive to tocilizumab and steroids. Aspiration precautions, avoidance of medications that cause CNS depression, blood pressure control with the goal of maintaining a mean arterial pressure within 20–25 mmHg of baseline, control of raised intra-cranial hypertension, correction of uraemia and coagulopathy (if present) and initiation and/or continuation of prophylactic anti-seizure medication is recommended in patients with ICANS and should be initiated as early as possible upon transfer to the intensive care unit. Nonpharmacological measures, such as agitation with careful monitoring, or low doses of haloperidol, precedex, olanzapine or resperidol, can be used.

Specific management includes the addition of tocilizumab for all grades of ICANS if concurrent with CRS. If no response to tocilizumab occurs or if ICANS is isolated, dexamethasone or methylprednisolone can be administered and dose escalated as needed. For focal edema or grade 4 ICANS, methylprednisolone is recommended. Continuation of corticosteroids is recommended until ICANS is reduced to grade 1. However, if grade 4 ICANS is refractory for > 24 hours, additional therapies, such as those recommended for CRS, and activation of safety switches should be considered (Fig. 2).

### **Secondary CAR T cell-related HLH**

Secondary CAR T cell-related haemophagocytic lymphohistiocytosis (HLH) is a rare and diagnostically challenging complication of IEC therapy. A diagnosis of secondary HLH diagnosis should be considered in patients with a maximum serum concentration of ferritin of >10,000 ng/ml during the high-risk period for CRS and who develop any two of the following organ toxicities after IEC therapy: grade 3 liver, kidney or lung toxicities (per CTCAEv5.0) and/or haemophagocytosis determined by morphology assessment and/or CD68-positivity in the bone marrow or other organs on immunohistochemistry<sup>2,85</sup>. Analysis of the serum levels of fasting triglycerides and soluble IL-2R should be considered in patients with suspected secondary HLH.

Secondary HLH that develops in children receiving IECs is generally responsive to cytokine blockade therapies (tocilizumab and/or corticosteroids). Patients with suspected CAR T cell-related HLH without grade 3 organ toxicities as mentioned above should be closely monitored, with appropriate supportive care. We recommend monitoring serum levels of ferritin, lactate dehydrogenase, fibrinogen, transaminases, bilirubin and creatinine while patients are receiving cytokine blockade therapies. If no improvement occurs after 48 hours, continue treatment or consider anakinra. Successful treatment of 12 children with rheumatic disease-related macrophage-activation syndrome with anakinra and

various combinations of conventional therapy (including corticosteroids, cyclosporine A, intravenous immunoglobulin (IVIG) and etoposide and etanercept) has been described<sup>121</sup>. In the rare event of treatment-refractory CAR T cell-related HLH, etoposide (150 mg/m<sup>2</sup> intravenously twice weekly during weeks 1 and 2, then once weekly) can be used. If concurrent ICANS occurs, the use of intrathecal cytarabine (30 mg in children 1–2 years of age, 50 mg in those 2–3 years of age, and 70 mg in those ≥ 3 years of age) with or without intrathecal hydrocortisone (15 mg, 25 mg and 50 mg, respectively) can also be considered<sup>85,122</sup>.

### **Allogeneic IEC-associated acute GVHD**

Compared with autologous IEC products, the use of allogeneic IEC products might reduce impediments to successful leukapheresis and manufacturing times. Yet, these products might also be associated with potentially life-threatening GVHD<sup>123</sup>. We outline staging, grading and suggested management approaches for IEC-associated acute GVHD, with specific paediatric considerations (Supplementary Table 1). Treatment of allogeneic IEC-associated GVHD could be product-dependent and include the use of topical or systemic steroids along with consideration of activation of safety switches as needed. Of note, body surface area (BSA) based on age and stool output quantification based on the patient's body weight (milligrams per kilogram) provide information on GVHD severity in children and AYAs<sup>124–126</sup>.

### **Severe irAEs**

The TME includes regulatory T cells, myeloid-derived suppressor cells (MDSCs),  $\gamma\delta$ T cells, tumour-associated macrophages and other cell types expressing inhibitory immune checkpoints. Consequently, ICIs can disrupt TME homeostasis, often with beneficial antitumour effects, but can also promote autoimmune AEs<sup>127,128</sup>. Anti-CTLA4 antibodies have generally been associated with more severe irAEs than anti-PD-1 antibodies. Common irAEs include rash, pruritus, fatigue, nausea, diarrhoea, anorexia, hypothyroidism, hyperthyroidism and pneumonitis<sup>129–131</sup>. Diarrhoea occurs in ~50% of adults receiving anti-CTLA4 ICIs. PD-1 and PD-L1 are expressed on cardiomyocytes, and thus anti-PD-1 antibodies can cause chest pain, shortness of breath, pulmonary edema, syncope, cardiogenic shock or death<sup>86,130</sup>. In a trial involving a small cohort of paediatric patients receiving anti-PD-1 treatment following CAR T cell infusion, irAEs included acute pancreatitis, hypothyroidism, arthralgia, urticaria and grade 3–4 cytopenias, with no grade 5 toxicities or GVHD observed<sup>132</sup>. Cerebral edema, infusion reactions, rash and diarrhoea have also been reported in children receiving ICIs<sup>133–138</sup>.

ASCO clinical practice guidelines provide important information that can be used for general diagnosis and management of irAEs in children and AYAs receiving ICIs<sup>86</sup>. Indeed, close monitoring is warranted among young children particularly those aged <12 years because earlier and more pronounced toxicities might be observed in this population<sup>73</sup>. Broadly, the management of irAEs relies on the use of steroids as first-line therapy when holding administration of ICIs is insufficient<sup>139,140</sup> (Table 2). Generally, ICIs can be continued with close monitoring in patients with grade 1 toxicities, with the exception of some neurological, haematological and cardiac toxicities. ICIs are usually held in

patients with grade 2 irAEs until resolution; corticosteroids can be administered. High dose corticosteroids should be initiated and ICI therapy held in the event of grade 3 irAEs. Corticosteroids should be tapered over the course of at least 4–6 weeks. If symptoms do not improve within 48–72 hours of high dose corticosteroids, the anti-TNF antibody infliximab can be considered. When symptoms and/or laboratory values show reversion to grade 1 irAEs, rechallenging with ICIs is an option, although caution is needed among patients with early onset irAEs. Dose adjustments are not recommended. Grade 4 toxicities usually warrant permanent discontinuation of ICIs, with the exception of endocrinopathies, which can be managed with hormone replacement<sup>86,141</sup>.

The ASCO guidelines<sup>86</sup> are useful but were developed for adults. Detailed anticipatory guidance to patients and caregivers, with attention to age-appropriate and weight-based considerations, could be important in the monitoring of children and AYAs receiving ICIs. The severity grading for dermatoses is based on the estimated BSA that is affected<sup>86</sup>. While the ‘rule of nines’ was designed to estimate BSA in adults, it might be less accurate in young children owing to their proportionally larger head and smaller mass in the legs and thighs<sup>142</sup>. A ‘rule of nines for children’ assigns 18% BSA to the head while each leg is 13.5%; the remaining body parts retain the same BSA percentages used in adults, with the anterior and posterior trunk each comprising 18% BSA, each individual upper extremity comprising 9% BSA and the perineum 1% BSA<sup>142</sup>. Similarly, gastrointestinal toxicities might be best graded in patients aged <18 years following the same approach as for GVHD staging (where severity is determined by volume of stool in millilitres per kilogram)<sup>124–126</sup> (Supplementary Table 1). Hypophysitis, a rare inflammatory disease of the pituitary gland, can present with non-specific symptoms including headache, mild fatigue, loss of libido and mood changes, which can be difficult to recognize in children. Careful age-appropriate and standardized symptom assessments, including screening for sexual development and health, might be important<sup>143</sup>. Endocrine complications can be reversible with hormone replacement therapy. The incidence of thyroid storm and myxoedema coma, while both rare in the general paediatric population, should be considered in the differential for children receiving ICIs<sup>84</sup>. Moreover, new onset of diabetes-related complications, such as diabetic ketoacidosis and hyperosmolar hyperglycaemia, can also be the first sign of irAEs<sup>144,145</sup>. Serial monitoring of the serum levels of corticotropin, thyrotropin, luteinizing hormone and follicle-stimulating hormone might be indicated in children receiving ICIs, possibly at baseline, 2 weeks after initiation of ICIs and then every 4–6 weeks. Deviation from age-appropriate physiologically normal values could indicate the need for radiographic imaging, hormone replacement, administration of steroids and/or beta blockers, paediatric endocrinology evaluation and/or inpatient admission for more intensive clinical assessment<sup>128</sup>. Immune-related pneumonitis can be serious and potentially fatal but often presents with nonspecific features, including dyspnoea, chest discomfort, cough and/or, less commonly, fever<sup>146</sup>. Clinical manifestations can be quite difficult to distinguish from disease-related discomfort or other treatment-related complications, such as infection or anaemia, and/or can mimic asthma or allergic bronchopulmonary aspergillosis.

CT scans, particularly with high resolution CT, can be helpful to detect radiographic patterns suggestive of cryptogenic organizing pneumonia, nonspecific interstitial pneumonia, hypersensitivity pneumonitis and bronchiolitis (such as ground-glass opacities,

consolidations, bronchiectasis, interlobular septal thickening and pleural effusions)<sup>147</sup>. Organizing pneumonia can appear as pulmonary nodules, thoracic (including hilar and mediastinal) adenopathy or granulomatosis in the setting of autoimmune pulmonary toxicity, which can be confused with new or worsening metastatic disease. The ‘reversed halo’ sign, which indicates central alveolar septal inflammation and cellular debris surrounded by granulomatous tissue within distal airways, can also be observed in patients with pulmonary irAEs. This sign appears as a central ground glass opacity surrounded by a more dense region of consolidation, which is distinct from the halo sign associated with pulmonary haemorrhage typically seen in angioinvasive aspergillosis<sup>128,148</sup>. As discussed, attention to age-appropriate and weight-based clinically normal ranges for respiratory status in children can ensure prompt recognition of immune-related pneumonitis. Among patients who develop renal toxicities, paediatric grading should be based on age-appropriate Kidney Disease: Improving Global Outcomes Work Group (KDIGO) consensus criteria to define AKI<sup>149</sup>. Patients might present with sterile pyuria or subnephrotic-range proteinuria, but neither finding is sufficiently sensitive or specific to confirm or rule out ICI-related AKI. When present, eosinophilia can be helpful as a sign that confirms that AKI is ICI-mediated<sup>150</sup>.

## Pseudoprogression

Pseudoprogression is a distinct response pattern best defined as radiological tumour progression from baseline that is not confirmed as progression on subsequent radiological assessment. Pseudoprogression has been described following administration of cancer immunotherapies, including IEC and ICIs, as a consequence of treatment-activated immune-cell infiltration into the TME<sup>151,152</sup>. Current radiographic response assessment criteria, such as Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, have been adapted for assessment of response to immunotherapies, resulting in the irRECIST, irRC or iRECIST criteria<sup>153–157</sup>. These methods are based on serial imaging to monitor disease progression, with the introduction of an additional follow-up scan to confirm or refute ‘unconfirmed’ tumour progression after an initial increase in lesion size<sup>154,156</sup>. Differentiation of pseudoprogression from disease progression is clinically important to avoid continuation of ineffective treatment. Clinical diligence is imperative as the average time to response in patients with pseudoprogression is 6 months in children and adults<sup>158,159</sup>. State-of-the-art biomarkers, such as circulating tumour DNA, could help distinguish between pseudoprogression and true progressive disease<sup>158</sup>. A tissue biopsy, when feasible and safe, might more definitively enable an accurate diagnosis. For example, the presence of CD3<sup>+</sup>, CD8<sup>+</sup>, TIA1<sup>+</sup> and granzyme B<sup>+</sup> lymphocyte infiltrates suggests T cell activation induced by treatment, and thus indicates pseudoprogression<sup>160–162</sup>. In some patients, discontinuation of immunotherapy can be recommended if symptomatic pseudoprogression occurs, while other patients with clinical deterioration might benefit from continued treatment. Limited evidence is currently available to direct standard management recommendations and thus, the risk of clinically significant deterioration should be determined by the treating team until further evidence-based recommendations are available<sup>163</sup>.

## Nursing and critical care considerations

Interdisciplinary and frontline clinical staff must demonstrate competency in prompt recognition of immunotherapy-associated complications and the use of the available clinical care algorithms to facilitate rapid escalation of care when indicated<sup>2,85</sup>. Consideration of important differential diagnoses are vital and assessment algorithms should be updated with emerging data. For example, distinction of blood transfusion reactions from CRS can be challenging if a patient develops signs or symptoms during the expected CRS window<sup>164</sup>. In the USA, IEC centre accreditation by the Foundation for the Accreditation of Cellular Therapy (FACT) is recommended as a means to ensure optimal outcomes. Additionally, interprofessional education and simulation-based training can help cultivate a collaborative approach to patient-centred care in a safe and non-threatening environment<sup>165,166</sup>.

As the availability of and indications for cancer immunotherapies continue to expand, institutions might need to revise their clinical algorithms, admission policies, therapeutic strategies and staff training requirements<sup>98,167</sup>. Commonly reported reasons for critical care admission include grade 3–4 toxicities, organ failure, a need for closer monitoring, increasing oxygen requirements concerning for noncardiogenic pulmonary edema, rapid clinical deterioration owing to large tumour burden, concurrent ICANS and CRS, and/or lack of availability of a unit delivering intermediate care. In a phase I/IIa study in which 75 children and AYAs with B-ALL received tisagenlecleucel, the critical care admission rate was 47%; 25% of these patients required high dose vasopressors, 44% oxygen supplementation, 13% mechanical ventilation and 9% dialysis<sup>87</sup>. In a retrospective study of adults with lymphoma who received axicabtagene ciloleucel, the critical care admission rates were high, but overall resource utilization was not disproportionate when compared with other patients with lymphoma who required critical care support during the same time period<sup>168</sup>. The availability of standardized clinical algorithms in conjunction with the presence of an interdisciplinary team can ensure the best possible patient outcomes<sup>98</sup>. An interdisciplinary expert panel, in which some authors of this Consensus Statement are involved, is currently assessing the role of extracorporeal therapies, such as extracorporeal membrane oxygenation, in paediatric patients receiving immunotherapies.

## Infection prophylaxis and treatment

Considerations regarding infectious disease management (Supplementary Table 2) and prophylaxis (Supplementary Table 3) are important for teams administering immunotherapies to children and AYAs<sup>169</sup>. Patients with an increased risk of opportunistic infection owing to preexisting neutropenia and/or hypogammaglobulinaemia (following prior treatments and/or lymphodepletion) would benefit from infectious disease surveillance screening and/or prophylaxis for viral, fungal and bacterial infections<sup>170,171</sup>. Additionally, patients receiving therapies targeting B cells could be at increased risk of infection, notably sinopulmonary infection with encapsulated bacteria<sup>172</sup>. Patients who develop CRS and/or receive immunosuppressive cytokine blockade therapies might have longer-term immune dysfunction and benefit from prophylaxis for infections<sup>173</sup>. An important goal of common immunization programmes to prevent childhood infections is the induction of persistent protective levels of pathogen-specific antibodies<sup>174</sup>. Repletion of IVIG might

be particularly important for paediatric patients with hypogammaglobulinaemia following cancer immunotherapy, given the smaller plasma volume and lower number of plasma cells in younger children and hence their decreased pathogen-specific immunity compared with adults<sup>173,175</sup>.

Further evidence is required before specific guidelines on vaccination after IEC therapy can be proposed, although we recommend that all patients are offered the seasonal influenza vaccine regardless of the level of immunosuppression, unless known contraindications exist. Other routine vaccines can be delayed in patients with platelet counts <30,000 cells/ $\mu$ l, those with active bleeding issues and those who have received B cell-targeted antibodies and/or ICIs within the past 6 months. At present, no further standard recommendations regarding vaccination of children and AYAs receiving CAR T cell therapies are available. The use of live vaccines is not recommended within 5 months of receiving IVIG or plasma transfusion. Owing to the risk of long-term B cell aplasia (BCA), careful assessment of immune reconstitution and specific antibody responses to vaccines is recommended to help guide revaccination decisions<sup>176</sup>.

During the COVID-19 pandemic, protocols for cancer immunotherapy eligibility and SARS-CoV-2 infection prevention, screening and management should be established locally and reviewed regularly in the context of infectious epidemiology and available resources<sup>177</sup>. Testing for SARS-CoV-2 infection should be considered before leukapheresis and initiation of lymphodepletion and/or cancer immunotherapy. From 2020, donors who have travelled to areas with prevalent SARS-CoV-2 infection, had known exposure to the virus and/or are actively infected, should have their cell collections postponed if possible<sup>177</sup>. Allogeneic products and/or products that are cryopreserved for manufacture are preferable to shipment of fresh products during periods of uncertain travel restrictions. While the data available are limited, children with cancer receiving immunotherapies might present with delayed and/or atypical and/or mild symptoms of SARS-CoV-2 infection<sup>178</sup>. High vigilance to distinguish primary disease progression from SARS-CoV-2 infection on radiological images is important. In some cases, repeat upper airway testing and/or lower airway testing might be indicated if a high degree of suspicion exists<sup>179</sup>. Antibody testing might not be reliable to establish a prior infection and/or determine immunity from reactivation and/or recurrence if the patient has BCA<sup>180</sup>. Prompt and accurate diagnosis of SARS-CoV-2 infection is important to ensure adequate infection control.

## Considerations on late effects

Cancer immunotherapies have improved the likelihood of durable remission, especially among children with high risk, R/R malignancies. To maximize clinical outcomes, sufficient attention must be paid to screening, diagnosis and management of potential late effects starting as early as 1 month after treatment initiation. Patients should be screened for secondary malignancies, ectopic tissue formation, immune reconstitution, organ dysfunction and endocrinopathies. Ruark et al. found that 37.5% of 40 AYAs and adults had one or more cognitive difficulties at a median of 3 years (range 1–5 years) after CAR T cell therapy; these neurological effects along with other long-term psychological and quality-of-life outcomes need further evaluation<sup>181</sup>. Additionally, we recommend screening for primary

disease recurrence, and/or consideration of consolidative therapies as available and when appropriate. For example, following CD19-targeted directed CAR therapies, up to 30% of patients can experience grade 3–4 cytopenias, not resolved by day 28 after therapy<sup>87</sup>. Thus, transfusions and/or growth factor support might be indicated, as well as a diagnostic bone marrow assessment to rule out other causes (such as myelodysplasia, malignancy, CAR T cell-related HLH or infection). Serial evaluation with bone marrow aspiration and MRD assessment by flow cytometry, quantitative PCR or next-generation sequencing at 3-month intervals might be appropriate. The presence of CD19<sup>+</sup> haematogones can precede a rise in the number of peripheral CD19<sup>+</sup> B cells and raise concern for loss of BCA<sup>182</sup>. Loss of BCA before 6 months after starting therapy is associated with increased risk of relapse and thus, further consolidative therapy should be strongly considered, including allogeneic HSCT<sup>183</sup>. BCA has been associated with progressive multifocal leukoencephalopathy and, therefore, patients should be monitored for neuropsychological, visual and motor deficits along with progressive dementia, which is suggestive of this condition, until BCA resolves<sup>184</sup>.

## Future directions

As the landscape of paediatric cancer immunotherapies continues to rapidly evolve, involved parties must remain prepared to adapt accordingly. Payors and regulatory agencies have the ethical responsibility to promote early inclusion of children and AYAs in clinical trials of cancer immunotherapies to ensure access of these populations to potentially life-saving therapies. Given the rarity of paediatric and AYA cancers, whenever possible, all patients should be treated in a well-designed clinical trial<sup>185</sup>. Planned and ongoing clinical trials have the potential to radically alter the standard-of-care treatment for some childhood cancers. For example, the current duration of standard chemotherapy in children and AYAs with high risk ALL is ~2–3 years. Patients with persistent MRD after induction and consolidation therapies are candidates for remission consolidation with high dose chemoradiotherapy and allogeneic HSCT. An ongoing phase II clinical trial is testing upfront treatment with tisagenlecleucel after two or three cycles of chemotherapy in newly diagnosed children and AYAs with high-risk disease and persistent MRD after induction and consolidation chemotherapy (NCT03876769). The ZUMA-4 trial is testing axicabtagene in children and AYAs with precursor B cell malignancies R/R after one or more lines of systemic therapy, including those with MRD-positive disease (NCT02625480). The use of CAR T cells in patients with very high risk disease after a few cycles of systemic chemotherapy might be associated with durable remissions and less cumulative exposure to cytotoxic agents (including intrathecal chemotherapy and radiation) that could have substantial long-term developmental effects, including on neurocognitive function<sup>186,187</sup>. CD19<sup>-</sup> relapse remains an important problem following immunotherapy with the CD19-targeted CAR T cell products. CD22 is a surface molecule expressed by most blasts in a majority (60–90%) of patients with B-ALL and is a reasonable target in B lymphoid malignancies<sup>188–190</sup>. Many ongoing preclinical and clinical strategies targeting molecules other than CD19, such as CD22, are being evaluated in these patients; however, a discussion of these approaches is beyond the scope of this Consensus Statement.

## Conclusions

Rapidly emerging cancer immunotherapies continue to positively and dramatically alter treatment paradigms in children and AYAs. These therapies are associated with promising outcomes in patients with high risk disease, but also with unique and potentially lethal complications. The use of interdisciplinary clinical algorithms that recognize physiological and developmental characteristics of paediatric and AYA patients is required to optimize both short-term and long-term patient outcomes.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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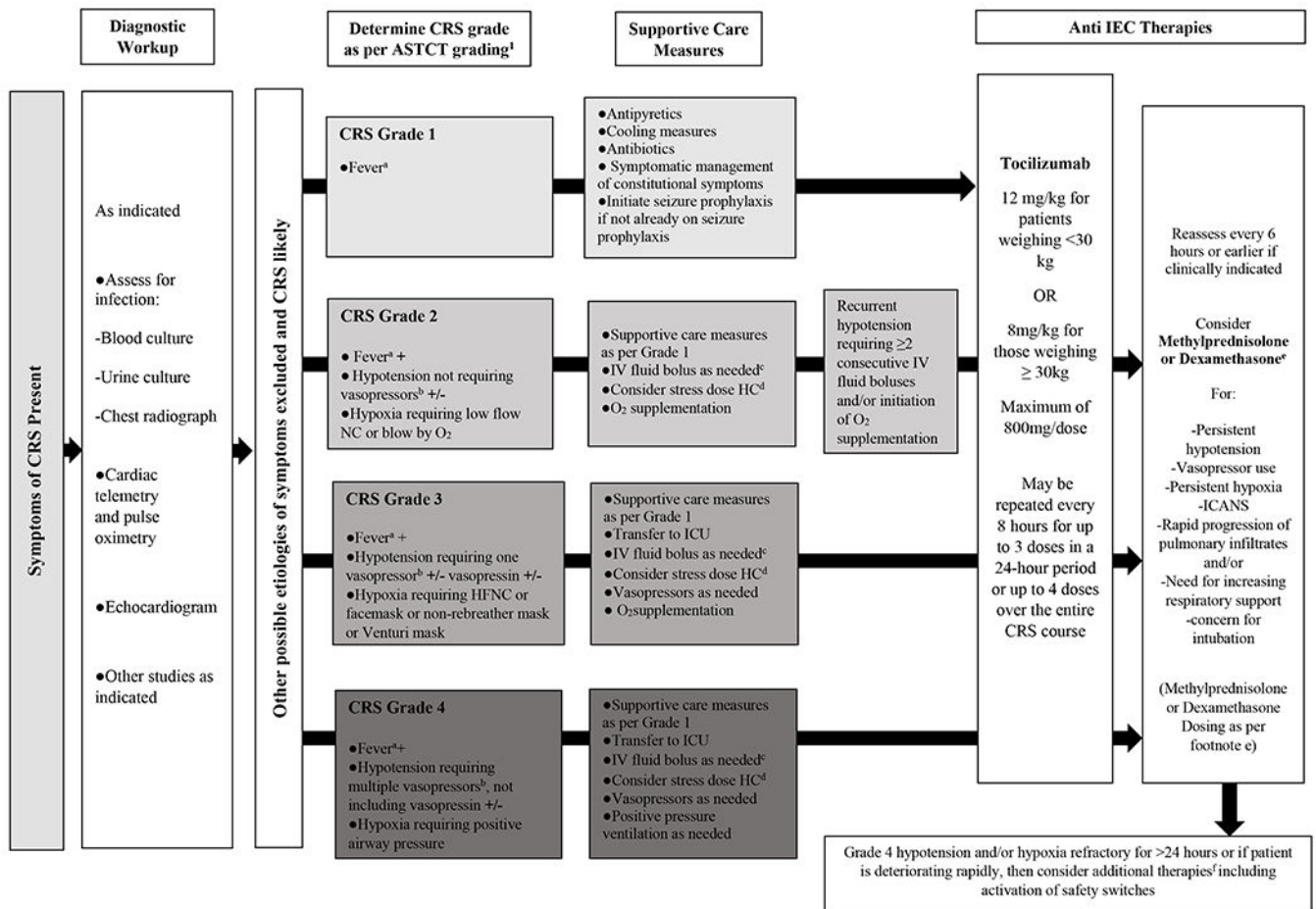
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**Box 1 |****Key consensus recommendations**

- By definition, cancers in children and in adolescents and young adults (AYAs) are rare cancers and, therefore, these populations should be included in well-designed clinical trials at the earliest time point possible. We encourage researchers, sponsors, institutions, regulatory agencies and payors to facilitate enrolment of these patients in trials.
- Cytokine-release syndrome (CRS) and immune effector cell- associated neurotoxicity syndrome (ICANS) should be graded following American Society for Transplantation and Cellular Therapy (ASTCT) criteria<sup>3</sup>. Health-care institutions are encouraged to regularly review management guidelines on the basis of current evidence, as well as host and product variables. Early initiation of cytokine blockade therapies to mitigate toxicity should be considered (Figs 1 and 2).
- Characterization of baseline organ function according to discipline- specific guidelines could facilitate monitoring of outcomes as well as toxicities from immunotherapy and foster collaborative research aimed at enhancing long-term outcomes. When possible, baseline comprehensive organ assessments should be performed, including neuroimaging, neurodevelopmental assessment, Cornell Assessment of Paediatric Delirium (CAPD) scoring, Kidney Disease: Improving Global Outcomes Work Group (KDIGO) renal assessment, and cardiac and pulmonary assessments.
- Serial monitoring of corticotropin, thyrotropin, luteinizing hormone and follicle stimulating hormone might be indicated in children receiving immune- checkpoint inhibitors (ICIs), ideally at baseline, 2 weeks after treatment initiation and then every 4-6 weeks. Deviation from age- appropriate physiologically normal values might indicate the need for radiographic imaging, hormone replacement, steroid administration, beta blockers, paediatric endocrinology evaluation and/or inpatient admission (for more extensive clinical assessments).
- Consider critical care assessment as early as possible, in particular in patients with grade 3 toxicities.
- Reversibility of underlying pathology, and not organ failure scores, should guide decisions about limiting critical care support.
- Monitoring of graft- versus- host disease (GVHD) in patients receiving allogeneic immune effector cell (IEC) products should follow paediatric grading, staging and management guidelines (Supplementary Table 1).
- Age- appropriate criteria should be used to assess toxicities from IEC or other immunotherapies in children. Aspects to assess include age- appropriate vital signs, estimation of body surface area (using methods such as Lund- Browder charts), renal (KDIGO) and endocrine function, and stool output.

Age- appropriate mood disorder and libido assessment should be performed to screen for hypophysitis (Table 2).

- High vigilance for early toxicities is warranted in children and AYAs receiving ICIs (as early as the first cycle).
- Children and AYAs receiving cancer immunotherapies should have baseline infectious disease evaluations and receive appropriate prophylaxis, with attention to age- appropriate monitoring of response to therapy (Supplementary Tables 2 and 3).
- All patients should be offered seasonal influenza vaccinations unless a specific contraindication exists (Supplementary Table 2).
- Revaccination or antibody titre testing should be considered 6 months after administration of antibodies targeting B cell markers or ICIs. At present there are no standard recommendations regarding vaccination of paediatric and AYA patients treated with CAR T cell therapy (Supplementary Table 2).
- Protocols for cancer immunotherapy eligibility and COVID-19 prevention including vaccination, screening and management should be established locally and reviewed regularly in the context of infectious epidemiology and available resources.
- Interdisciplinary and frontline staff should demonstrate and maintain competency in prompt recognition and management of complications from immunotherapy in children and AYAs, with clinical algorithms available for rapid escalation of care when indicated. Interprofessional simulation training might help to cultivate a collaborative team approach, and to establish and maintain competency.



### Figure 1. Grading and Management of Cytokine Release Syndrome (CRS)

Cytokine release syndrome (CRS) is a potentially life-threatening complication of immunotherapy. Patients post immunotherapy should be vigilantly monitored for this complication, incorporating paediatric considerations like age appropriate vital signs to facilitate the early recognition and prompt management of CRS.

ASTCT: American Society for Transplantation and Cellular Therapy, NC: Nasal Cannula, O<sub>2</sub>: Oxygen, HFNC: High Flow Nasal Cannula, ICU: Intensive Care Unit, IV: Intravenous, HC: Hydrocortisone, IEC: Immune Effector Therapy. ICANS: Immune Effector Cell-Associated Neurotoxicity Syndrome

<sup>a</sup>For patients who have CRS and have received antipyretic or anti-cytokine therapy, fever is no longer required to subsequently grade CRS but rather, grading is driven by hypotension and/or hypoxia and is determined by the more severe event

<sup>b</sup> Hypotension is defined by age-specific normal ranges and/or in comparison to their baseline values. When baseline systolic blood pressures (SBPs) are unknown, hypotension may be determined as follows: (a) term neonates (0-28 days) SBP <60 mm Hg; (b) infants (1-12 months) SPB <70 mm Hg; (c) children 1-10 years SBP <70 mm Hg + (age in years x 2) mm Hg and (d) children > 10 years SBP <90mm Hg

<sup>c</sup>10-20 mL/kg (maximum 1,000 mL) normal saline. Repeat once as needed to maintain normal BP above baseline or within normal range for age as defined above

<sup>d</sup>For hypotension consider hydrocortisone 12.5 – 25 mg/m<sup>2</sup>/day divided every 6 hours  
<sup>e</sup>**Grade 2 hypotension:** methylprednisolone 1 –2 mg/kg for one dose or dexamethasone 0.15 –0.5 mg/kg/dose (maximum 10 mg) IV for 1 dose

**Grade 2 hypoxia:** methylprednisolone 1 -2 mg/kg for one dose or dexamethasone 0.5 mg/kg/dose (maximum 10 mg) IV for 1 dose

**Grade 3 hypotension:** If on one vasopressor: methylprednisolone 1-2 mg/kg/day divided every 6 to 12 hours or dexamethasone 0.5 mg/kg/dose (maximum 10 mg) IV every 6 hours. If on two vasopressors methylprednisolone 1-2 mg/kg/day divided every 6 to 12 hours or dexamethasone 1 mg/kg/dose (maximum 20 mg) IV every 6 hours. If vasopressin and norepinephrine equivalent is 15 mcg/minute, follow as in Grade 4 CRS

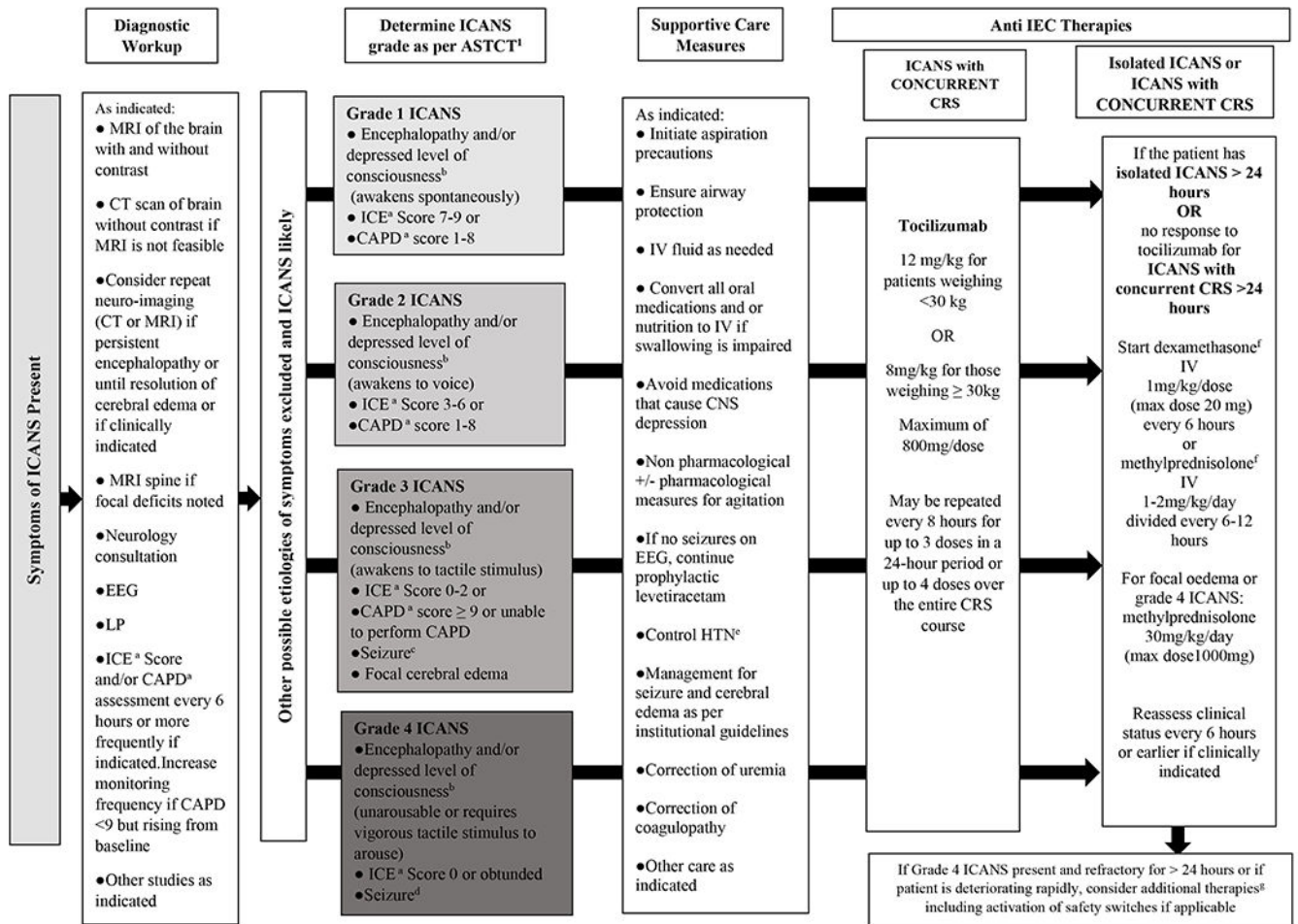
**Grade 3 hypoxia:** methylprednisolone 1 –2 mg/kg/day divided every 6 to 12 hours or dexamethasone 0.5 mg/kg/dose (maximum 10 mg) IV every 6 hours. If there is no improvement in hypoxia within 24 hours or there is rapid progression of pulmonary infiltrates or sharp increase in FiO<sub>2</sub> requirements, methylprednisolone 1-2 mg/kg/day divided every 6 to 12 hours or dexamethasone 1 mg/kg/dose (maximum 20 mg) IV every 6 hours

**Grade 4 hypotension or hypoxia:** Methylprednisolone 30 mg/kg/day (maximum 1,000 mg/day) in divided doses IV for 3 days followed by rapid taper as per clinical situation For grade 2-4 ,once CRS improves to Grade 1 or less, taper and/or stop corticosteroids depending on clinical situation

<sup>f</sup>Siltuximab 11mg/kg IV once, anakinra: Children 2 years and Adolescents: 1 mg/kg (maximum 100 mg) subcutaneously daily for 7 days , cyclophosphamide 1500mg/m<sup>2</sup> IV once(with mesna), anti-thymocyte globulin (rabbit)- 1 to 2 mg/kg IV daily for 3 days

References:

1 Lee, D. W. *et al.* ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant* 25, 625-638, doi:10.1016/j.bbmt.2018.12.758 (2019).



**Figure 2. Grading and Management of Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)**

Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) is a potentially life-threatening complication of immunotherapy. Patients receiving immunotherapy should be vigilantly monitored for ICANS, incorporating paediatric considerations (e.g. age-appropriate vital signs and use of pediatric delirium scores) to facilitate the early recognition and prompt management of ICANS.

ICANS: Immune Effector Cell-Associated Neurotoxicity Syndrome; MRI: Magnetic Resonance Imaging; CT: Computer Tomography; EEG: Electroencephalogram ; LP: Lumbar Puncture; ICE: Immune Effector Cell-associated Encephalopathy; CAPD: Cornell Assessment of Pediatric Delirium; ASTCT: American Society for Transplantation and Cellular Therapy; IV: Intravenous, CNS: Central Nervous System; HTN: Hypertension; IEC: Immune Effector Cell; max: maximum

<sup>a</sup>Depressed level of consciousness not attributable to any other case

<sup>b</sup>ICE score: For patients > 12 years of age; CAPD for patients > 12 years of age and/or for children > 12 years of age for whom this is developmentally appropriate

<sup>c</sup> Any clinical seizure (focal or generalized) that resolves rapidly (< 5 minutes) or non-convulsive seizures on EEG that resolve with intervention

<sup>d</sup>Life-threatening prolonged seizure ( ≥ 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between

<sup>e</sup>Control blood pressure with the goal of maintaining mean arterial pressure(MAP) within 20-25 mmHg of baseline MAP

<sup>f</sup>Dexamethasone can be started at 0.5mg/kg/dose (maximum 10 mg) and repeated up to every 6 hours as needed or methylprednisolone 1-2mg/kg/day divided every 6-12 hours. If grade 3 ICANS is persistent for > 24 hours, dexamethasone 1mg/kg/dose (maximum dose 20 mg) every 6 hours or methylprednisolone 1-2mg/kg/day divided every 6-12 hours. For focal oedema or grade 4 ICANS, methylprednisolone 30mg/kg/day (maximum dose 1000mg)

<sup>g</sup>Siltuximab 11mg/kg IV once, Anakinra Children ≥ 2 years and Adolescents: 1 mg/kg (maximum 100 mg) subcutaneously daily for 7 days , cyclophosphamide 1500mg/m<sup>2</sup> IV once(with mesna), anti-thymocyte globulin (rabbit)- 1 to 2 mg/kg IV daily for 3 days

References:

1 Lee, D. W. *et al.* ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant* **25**, 625-638, doi:[10.1016/j.bbmt.2018.12.758](https://doi.org/10.1016/j.bbmt.2018.12.758) (2019).

**Table 1:** Toxicities Associated with Immunotherapy in Paediatric, Adolescent and Young Adult Patients<sup>1-7</sup>

Immunotherapy Product	Acute toxicities (within 30 days of immunotherapy)	Management of acute toxicity	Late Effect Toxicity
<b>IEC Therapies</b>			
CAR-T	Autologous CAR T cells: CRS, ICANS Organ dysfunction, Infection, Infusion Reactions Allogeneic: CRS, ICANS, GVHD Infection, Infusion Reactions	Supportive Care Corticosteroids, Tocilizumab Additional therapies to be considered: Dasatinib, Anakinra, Cyclophosphamide, ATG, Activation of safety switches	Grade 3-4 Cytopenia, B Cell Aplasia, and/or hypogammaglobulinaemia Progressive multifocal leukoencephalopathy Malignancy Clonality Reactivation of hepatitis B and C. Theoretically, potential for insertional oncogenesis, secondary malignancies. Replication competent viral vectors. Reactivation of hepatitis B and C. Potential immunogenicity and anti mouse antibodies against CAR T <sup>7</sup>
TILs	Infusion reactions including capillary leak syndrome, Myalgia, Nausea, Fever, Rigors “On-target, off-tumour” toxicities including: autoimmune sequelae such as rash, uveitis, vitiligo in patients receiving TILs that recognize melanoma-associated antigens	Supportive Care Corticosteroids	Autoimmune sequelae
Engineered TCR therapy	“On-target, off-tumour” toxicities including: leukoencephalopathy, coma and death, all reported in patients with melanoma receiving TCR- engineered T cells targeting MAGEA3 Cardiogenic shock, death, reported in patients with multiple myeloma or melanoma receiving TCR- engineered T cells targeting MAGEA3 Rash, uveitis and hearing impairment, all reported in patients with melanoma receiving TCR- engineered T cells targeting MART-1 or gp100	Supportive Care Corticosteroids	None reported
NK Cells	Infusion Reactions Headache, Fatigue, Slurred speech Thrombocytopenia, Neutropenia, GVHD, Pulmonary Toxicity	Supportive Care Corticosteroids	None Reported
VSTs/CTLs	Infusion Reactions, GVHD, Pseudo progression, Pulmonary Toxicity,	Supportive Care Corticosteroids Serial imaging to monitor for pseudo progression	None reported
<b>Other Immunotherapies</b>			
BITEs	CRS, ICANS, infusions reactions, cytopenias, disseminated intravascular coagulation	Supportive Care Corticosteroids, Tocilizumab	B cell aplasia and Hypogammaglobulinaemia
ICI	CRS, infusion reaction, pruritus, fatigue, rash, Pseudo progression <b>Neurological:</b> Neurotoxicity, encephalitis <b>GI:</b> ↓ appetite, Nausea, Colitis, Pancreatitis <b>Hepatic:</b> Hepatitis, Transaminitis <b>Cardiac:</b> Myocarditis, Syncope <b>Pulmonary:</b> Oedema, Pneumonitis <b>Renal:</b> AKI <b>Endocrinopathies:</b> ACTH Insufficiency.	Supportive care Corticosteroids Serial imaging to monitor for pseudo progression Discontinuation of checkpoint inhibitor for Grade 4 toxicity Additional therapies to be considered if steroid resistant: Infliximab	Endocrinopathy Autoimmune sequelae

Immunotherapy Product	Acute toxicities (within 30 days of immunotherapy)	Management of acute toxicity	Late Effect Toxicity
	Hypothyroidism or Hyperthyroidism, Hypophysitis <b>Rheumatological:</b> Arthralgia, arthritis, myositis, Sicca syndrome, other autoimmune phenomena (such as nephritis) <b>Haematological:</b> HA, ITP, Neutropenia		

<sup>1</sup> Presence of antibodies on the efficacy and/or persistence of CAR-T cells remains to be determined

<sup>2</sup> When TILs given in conjunction with Interleukin 2

CAR-T: Chimeric Antigen Receptor T Cells, IEC: Immune effector Cell therapy, TCR: T Cell Receptor, CRS: Cytokine Release syndrome, PML: Progressive Multifocal Leukoencephalopathy, ICANS: Immune effector Cell Associated Neurotoxicity Syndrome, GVHD: Graft Versus Host Disease, ATG: Anti Thymocyte Globulin TILs: Tumor Infiltrating Lymphocytes, NK: Natural Killer, VSTs: Virus-Specific T-cells, CTLs: Cytotoxic Lymphocytes, BiTEs: Bispecific T cell engagers ICI: Immune Checkpoint Inhibitors, AKI: Acute Kidney Injury, ACTH: adrenocorticotrophic hormone, HA: Hemolytic Anaemia (HA), ITP: Immunological Thrombocytopenia Purpura MMF: Mycophenolate Mofetil, CSA: Cyclosporine

**Table II:**

**Key Considerations for the Management of Immune Related Adverse Events by Grade in Paediatric, Adolescent and Young Adult Patients Receiving Immune Checkpoint Inhibitors<sup>4,10,11</sup>**

Toxicity Grade	Paediatric Considerations	Management Guidelines	Future Administration of ICI
Grade I	Use age appropriate ranges for vital signs Use of the Lund-Browder chart for estimation of BSA Kidney injury reported as per KDIGO guidelines: urine output in mL/Kg/h and change in creatinine from baseline measurement	-Continue ICI therapy / -Close monitoring for progression of toxicity	Consider carefully rechallenging with ICI when toxicity reverts to Grade I <sup>2</sup> Dose adjustment not recommended
Grade II	Stool volume to be measured in mL/Kg Use of age appropriate reference ranges for laboratory tests (including TSH and Free T4) Careful assessment for nonspecific symptoms related to mood changes and libido which might be difficult to recognize in children	-Consider holding ICI until toxicity resolved -Close monitoring for progression of toxicity -Consider corticosteroids at a daily initial dose 0.5 to 1 mg/kg/d of prednisone or prednisone equivalent	
Grade III		-Hold ICI until resolution of symptoms -Close monitoring for progression of toxicity -High dose corticosteroids: Prednisone or prednisolone 1-2mg/kg/d -Consider infliximab if no resolution of symptoms within 48-72 hours of high dose corticosteroids	
Grade IV		-Discontinue ICI -Management as in Grade III	Permanent discontinuation <sup>3</sup>

BSA: Body Surface Area, ICI: Immune Checkpoint Inhibitors, d: day; KDIGO: Kidney Disease: Improving Global Outcomes. TSH: **Thyroid Stimulating Hormone**

<sup>1</sup>With the exception of transverse myelitis and some other neurological, haematological and cardiac toxicities

<sup>2</sup>Caution advised, especially in those patients with early-onset irAEs

<sup>3</sup>With the exception of Grade IV endocrinopathies that have been controlled by hormone replacement