# Immune Effector Cell-associated Hemophagocytic Lymphohistiocytosis-like Syndrome (IEC-HS)

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**KEYWORDS**

• Chimeric antigen receptor T-cell therapy • Adoptive cell therapy
• Immune effector cell • Hemophagocytic lymphohistiocytosis
• Cytokine release syndrome • Cytokine • Ferritin

**KEY POINTS**

- Hemophagocytic lymphohistiocytosis (HLH)-like manifestations are seen following adoptive cell therapy.
- Immune effector cell-associated HLH-like syndrome (IEC-HS) is the term used to describe iatrogenic HLH after IEC therapies and differs from cytokine release syndrome (CRS).
- IEC-HS is defined as the development of a pathologic and biochemical hyperinflammatory syndrome that manifests with features of macrophage activation/HLH, is attributable to IEC therapy and independent of CRS.
- Unlike primary HLH, IEC-HS generally does not recur; however, identification and best management practices are in evolution.

## INTRODUCTION

Immune effector cell (IEC)-associated hemophagocytic lymphohistiocytosis (HLH)-like syndrome (IEC-HS)[1] is a newly defined diagnosis used to describe a severe hyperinflammatory process that has emerged as a complication of IEC-based therapies,

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Hematol Oncol Clin N Am 39 (2025) 617–643
https://doi.org/10.1016/j.hoc.2025.02.005 **hemonc.theclinics.com**

| Abbreviations | |
|---|---|
| ASTCT | American Society for Transplantation and Cellular Therapy |
| axi-cel | axicabtagene autoleucel |
| B-ALL | B-cell acute lymphoblastic leukemia |
| BCMA | B-cell maturation antigen |
| BMB | bone marrow biopsy |
| B-NHL | B-cell non-Hodgkin lymphoma |
| brexu-cel | brexucabtagene autoleucel |
| BiTE | bispecific T-cell engager |
| CAR | chimeric antigen receptor |
| carHLH | chimeric antigen receptor T-cell-associated hemophagocytic lymphohistiocytosis |
| CARTOX | CAR-T-cell-therapy-associated TOXicity |
| cilta-cel | ciltacabtagene autoleucel |
| CR | complete response |
| CRS | cytokine release syndrome |
| DLBCL | diffuse large B-cell lymphoma |
| FDA | US Food and Drug Administration |
| G | grade |
| HG-CRS | high-grade cytokine release syndrome |
| HLH | hemophagocytic lymphohistiocytosis |
| HLH-LT | chimeric antigen receptor-associated hemophagocytic lymphohistiocytosis (HLH)-like toxicities |
| ICANS | IEC-associated neurotoxicity syndrome |
| ICU | intensive care unit |
| ide-cel | idecabtagene vicleucel |
| IEC | immune effector cell |
| IEC-HS | immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome |
| IFN-$\gamma$ | interferon-gamma |
| IL-1 | interleukin-1 |
| IL-6 | interleukin-6 |
| IV | intravenous |
| LBCL | large B-cell lymphoma |
| LDH | lactate dehydrogenase |
| LG-CRS | low-grade cytokine release syndrome |
| MAS | macrophage activation syndromes |
| MAS-L | macrophage activation syndrome-like disease |
| MM | multiple myeloma |
| NR | not reported |
| NRM | nonrelapse mortality |
| NS | not significant |
| ORR | overall response rate |
| OS | overall survival |
| PFS | progression-free survival |
| POD | progression of disease |
| RFS | relapse-free survival |
| tisa-cel | tisagenlecleucel |
| TNF-$\alpha$ | tumor necrosis factor-alpha |
| ULN | upper limit of normal |

such as chimeric antigen receptor (CAR) T-cell therapy, engineered T-cell receptor therapies, and other forms of adoptive cell therapies. While patients with severe cytokine release syndrome (CRS)—a known complication of CAR T-cell therapy—often will have clinical and laboratory characteristics of HLH,[2] IEC-HS was developed based on the critical need to harmonize emerging reports of patients that experienced secondary inflammatory processes mimicking HLH that occurred as CRS was

resolved/resolving following a variety of CAR T-cell therapies.[1] IEC-HS is a pathologic and biochemical hyperinflammatory syndrome that manifests with the features of macrophage activation/HLH, is attributable to IEC therapy and distinct from CRS, and is associated with the progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis (**Fig. 1**). IEC-HS mimics primary and secondary HLH in its clinical presentation and is associated with excessive immune activation, unregulated cytokine production, and a spectrum of systemic inflammation.

The pathogenesis of this HLH-like syndrome is linked to the iatrogenic overactivation of engineered T-cells redirected for anticancer activity that involves immune dysregulation driven by therapeutic interventions that amplify IEC function. Although distinct from primary or other forms of secondary HLH, the syndromes share overlapping cytokine profiles, including elevated levels of interleukin-1 (IL-1) and interferon-gamma (IFN-γ), which may be important to therapeutic strategies for IEC-HS. This cytokine storm underpins the clinical manifestations resembling HLH and necessitates careful differentiation from other immune-related toxicities, such as CRS, which commonly occurs in most patients receiving adoptive cell therapies. The precise mechanisms differentiating IEC-HS from these closely related conditions remain under investigation, emphasizing the need for early recognition and targeted intervention to reduce morbidity and mortality while preserving the therapeutic efficacy of IEC therapies. Moreover, as cell therapy-based strategies are further modified to enhance

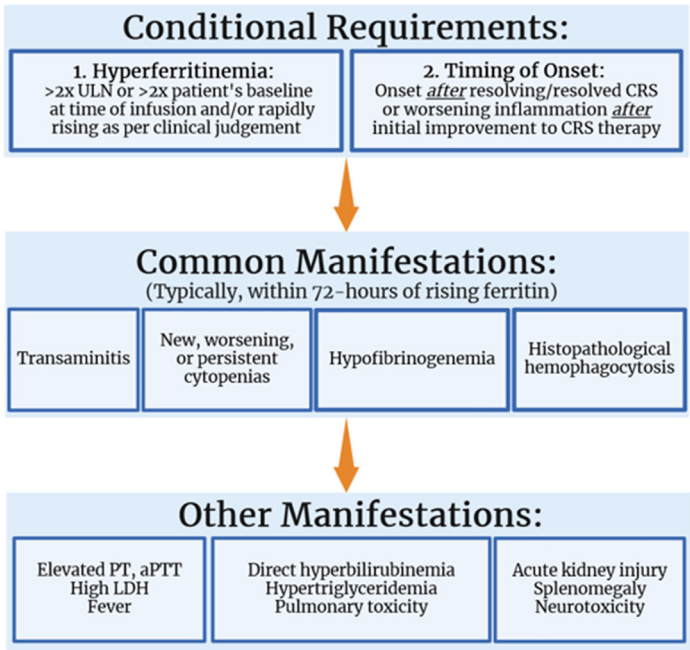


**Fig. 1.** The ASTCT Consensus IEC-HS Diagnostic Criteria. aPTT, activated partial thromboplastin time; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; LDH, lactate dehydrogenase; PT, prothrombin time; ULN, upper limit of normal. (*Created in* BioRender. Johnson, W. (2024) https://BioRender.com/r56u981.)

antitumor cytotoxicity, IEC-HS may be seen more frequently. In this article, we provide an overview of IEC-HS, review the known incidence, highlight diagnostic approaches, and discuss treatment strategies currently utilized or in evolution.

## OVERVIEW OF IMMUNE EFFECTOR CELL-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS-LIKE SYNDROME

### *Establishing Immune Effector Cell-associated Hemophagocytic Lymphohistiocytosis-like Syndrome*

With the rapid evolution of highly effective adoptive cell therapy-based approaches for refractory hematologic malignancies, establishing a framework for identifying and grading inflammatory toxicities was imperative. CRS and IEC-associated neurotoxicity syndrome (ICANS) were among the first to be formally harmonized across the cell therapy field.[3] With emerging reports of secondary inflammatory toxicities mimicking HLH—and particularly those that were temporally removed from CRS and not associated with severe CRS, it became clear that an initiative to better characterize this toxicity was essential. Previously established definitions for either primary or secondary HLH,[4,5] including those associated with malignancy,[6] were particularly challenging to apply in the context of patients with refractory malignancies receiving cell therapies. For example, baseline characteristics alone (eg, cytopenias and hepatosplenomegaly) or phenotypes associated with CRS (eg, rapidly rising inflammatory markers and fever) would already constitute several HLH criteria. In the context of emerging clinical experience, the US Food and Drug Administration (FDA) approvals for B-cell maturation antigen (BCMA)-and CD19-targeting products were also being labeled with HLH/macrophage activation syndromes (MAS) as potentially life-threatening toxicities, which further underscores the need to better understand these toxicities.

Accordingly, in 2022, a working group founded through the American Society for Transplantation and Cellular Therapy (ASTCT) was established with the following objectives: (1) unify the abundance of nomenclatures, definitions, and diagnostic criteria alluding to CAR T-cell-associated HLH-like syndromes (eg, carHLH or carMAS), (2) propose a preliminary grading scale of this entity, (3) provide consensus recommendations on the management options including supportive care, and (4) offer an accessible reference to the differential diagnosis and workup. It is within this working group that the nomenclature for and definition of IEC-HS was created.

These inaugural ASTCT IEC-HS consensus guidelines are now directly referred to in the National Comprehensive Cancer Network (NCCN) CAR T-cell-related toxicities guidelines for diagnosing and managing IEC-HS.[7] Likewise, recent consensus recommendations on the management of toxicities associated with CD3 $\times$ CD20 bispecific antibodies refer to these IEC-HS guidelines for managing atypical cases with HLH-like toxicities.[8]

Recognizing the notable limitations in referencing any robust outcomes-based IEC-HS data, compounded by the marked discrepancies in previously published diagnostic criteria and variations in laboratory-specific normal ranges, attaining a uniform agreement on IEC-HS diagnostic criteria was challenging and continues to evolve. At present, the ASTCT IEC-HS diagnostic criteria require a rapidly rising ferritin (ie, an increase at least twice the patient's baseline and/or the laboratory-specific upper limit of normal [ULN]). However, no minimal number of organ-specific toxicity manifestations is obligatory to be met to support an IEC-HS diagnosis and/or guide the subsequent initiation of directed treatment (see **Fig. 1**).

Similar challenges were encountered in establishing a clinically relevant grading scale specific to IEC-HS that could be applied after the definition and diagnostic

criteria were met. Additionally, the scarcity of high-level, evidence-based data supporting various treatments resulted in "expert opinion" being the highest level of evidence available when establishing treatment recommendations. Nevertheless, this inaugural ASTCT IEC-HS consensus effort, in concert with previously published and subsequent work, paved the path toward increasing recognition for this life-threatening phenomenon of IEC-HS.

### *Pathophysiology of Immune Effector Cell-associated Hemophagocytic Lymphohistiocytosis-like Syndrome*

The pathophysiology of IEC-HS is inferred from our understanding of primary and secondary HLH, as well as insights from CAR T-cell biology and CRS. HLH represents a hyperinflammatory state driven by dysregulated immune activation, typically involving a positive feedback loop between T-cells and macrophages. In the context of CAR T-cell therapy, engineered T-cells, designed to activate upon encountering specific antigenic triggers, initiate a robust cytokine cascade characteristic of CRS; this cascade includes the release of proinflammatory mediators such as interleukin-6 (IL-6), IFN-$\gamma$, and tumor necrosis factor-alpha (TNF-$\alpha$).[2] In IEC-HS, these cytokine signals become dysregulated and persist through mechanisms that remain incompletely understood. Persistent T-cell and macrophage activation overwhelms the body's regulatory feedback systems that typically suppress excessive inflammation. IFN-$\gamma$ directly drives macrophage activation and proliferation,[9] and damage-associated molecular patterns released from dying malignant or normal cells further amplify the inflammatory response.[10] This results in the recruitment of additional immune effectors (including endogenous T-cells) to fuel a self-perpetuating cytokine storm. In IEC-HS, the cytokine milieu is marked by endothelial activation and vascular permeability (driven by IL-6 and TNF-$\alpha$), a profound systemic inflammatory response with hyperferritinemia, and elevated levels of soluble interleukin-2 receptor-$\alpha$.[1] Thus, the hallmark of IEC-HS is the failure of regulatory mechanisms to resolve this hyperinflammatory state. This dysregulation is likely related to sustained and highly active CAR T-cell cytotoxicity, but other factors—such as hypomorphic genetic variants associated with HLH,[11] contributions from other immune cells involved in immune surveillance, and characteristics of the CAR construct itself—may also play significant roles. Together, these factors converge to produce a severe and refractory inflammatory syndrome.

### *Comparing Hemophagocytic Lymphohistiocytosis, Cytokine Release Syndrome, and Immune Effector Cell-associated Hemophagocytic Lymphohistiocytosis-like Syndrome*

The pathophysiologies of HLH, CRS, and IEC-HS exhibit significant overlap in cytokine-mediated inflammatory pathways and clinical features, though their mechanisms differ. HLH, as previously described, is a hyperinflammatory disorder resulting from unchecked macrophage activation and excessive cytokine production.[12] CRS, in contrast, arises from acute proinflammatory cytokine release, notably IL-6, triggered by IEC activation during CAR T-cell therapy or bispecific T-cell engagers (BiTEs). Unlike HLH, CRS typically responds to IL-6 blockade with tocilizumab, though not universally.[13] IEC-HS bridges HLH and CRS, often occurring after CRS during CAR T-cell therapy. Sustained CAR T-cell activation and expansion promotes macrophage proliferation and persistent cytokine signaling, involving a feedback loop with endogenous T-cells and innate immune cells. Cytokine elevations in IEC-HS, including IFN-$\gamma$, C-X-C motif ligand 9 (CXCL9), CXCL10, tumor necrosis factor (TNF)-$\alpha$, IL-6, and IL-18, resemble HLH.[14] Clinically, IEC-HS manifests with pancytopenia,

hepatotoxicity, and multi-organ dysfunction, which is less common in CRS—especially with increasing use of strategies for early toxicity mitigation or prevention.

The biological and temporal distinctions between CRS and IEC-HS reflect their different pathophysiology. IEC-HS often emerges as a "second wave" of inflammation following CRS resolution. In these cases, initial CAR T-cell-induced CRS may respond to IL-6 blockade, but persistently activated CAR T-cells may drive the subsequent recruitment and activation of diverse immune cell populations.[15–17] Severe CRS refractory to IL-6 blockade can present with HLH-like manifestations, but may not necessarily constitute IEC-HS, though the overlap in clinical signs raises questions as to whether IEC-HS represents a spectrum of CRS. Translational studies suggest the role of IL-10 in differentiating IEC-HS from severe CRS.[18] This distinction, however, is crucial as IEC-HS management differs, requiring HLH-like treatment, including lymphocytotoxic agents (ie, etoposide, corticosteroids) or multi-cytokine-targeted therapies beyond IL-6 such as ruxolitinib, anakinra, or emapalumab.[19] Such strategies suppress the broader inflammatory network driving IEC-HS, beyond the scope of single-cytokine blockade.

HLH-associated null mutations in cytotoxic lymphocyte function genes, such as *PRF1*, *UNC13D*, and *STXBP2*, predispose children to impaired clearance of hyperactive immune cells, causing familial HLH.[20] Emerging evidence may implicate hypomorphic genetic mutations in these genes in adult-onset HLH, although it is unknown whether they play a potential role in IEC-HS pathogenesis. While hypomorphic mutations have been identified in adults with HLH, it remains unclear if this leads to a cytotoxic defect.[11,21–23] In IEC-HS, mutations in HLH-related or other genes that predispose to immune dysregulation could exacerbate the intense inflammatory environment induced by CAR T-cell activation and tumor lysis.[24,25] CAR T-cell constructs themselves intensify the hyperinflammatory state by sustaining cytokine production and recruiting innate immune cells, particularly macrophages central to IEC-HS. Persistent macrophage activation perpetuates hemophagocytosis and systemic inflammation, mirroring HLH while remaining distinct due to its CAR T-cell association. Germline or somatically acquired single nucleotide polymorphisms may predispose to immune dysregulation, transforming an otherwise self-limiting CRS in one patient into severe, refractory IEC-HS in another, requiring targeted interventions addressing both lymphocyte and cytokine dysregulation. These insights highlight the need for further research into genotype-phenotype interactions in CAR T-cell therapy patients, which could guide risk stratification and enable early preventative or therapeutic interventions.

### *Grading*

Severity varies from patient to patient, ranging from laboratory abnormalities alone to multiple organ failure requiring ICU level of support.[1] The suggested ASTCT IEC-HS severity grading was developed based on the National Cancer Institute Adverse Event "Immune System Disorder, other" as a backbone with modifications based on expert clinical experience and consensus. Importantly, grading is independent of the number of therapies that are used to treat IEC-HS and based on clinical manifestations alone.

## A HISTORICAL OVERVIEW OF IMMUNE EFFECTOR CELL-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS-LIKE SYNDROME: INCIDENCE, DIAGNOSTIC CRITERIA, AND OUTCOMES

As the collective experience with CAR T-cell-associated toxicities evolved, it became increasingly evident that a subset of patients was emerging with what we now refer to

as IEC-HS. **Table 1** provides a summary of notable publications to date on HLH-like manifestations following CAR T-cell therapy.

### *B-cell Acute Lymphoblastic Leukemia*

Tisagenlecleucel (tisa-cel), the first CAR product approved by the FDA, pioneered the initial observations and management options for the CAR-related toxicities of CRS and ICANS in B-cell acute lymphoblastic leukemia (B-ALL) patients.[2,38] The University of Pennsylvania and Children's Hospital of Philadelphia first described an HLH-like syndrome in B-ALL patients with high-grade CRS following tisa-cel therapy.[2] They proposed a diagnostic criterion of postinfusion peak ferritin greater than 10,000 ng/mL, previously validated in children with primary HLH for its sensitivity and specificity.[39] This threshold formed the basis for subsequent diagnostic criteria.[27,30,35] A retrospective analysis of a large cohort ($n$ = 185) treated with tisa-cel identified HLH-like manifestations occurring in 14% of patients, linked to severe CRS and ICANS, higher relapse rates, and increased mortality, but were unable to distinguish between IEC-HS and severe CRS with HLH-like manifestations. Similarly, poor outcomes were seen in B-ALL cohorts when applying a higher ferritin threshold ($\geq$100,000 ng/mL).[15,26,40] Currently, tisa-cel and brexucabtagene autoleucel (brexu-cel) prescribing information include warnings for IEC-HS risks in B-ALL patients.[41,42]

### *B-cell Non-Hodgkin Lymphoma*

In 2017, the CAR-T-cell-therapy-associated TOXicity (CARTOX) group defined HLH in CAR T-cell recipients as a peak ferritin greater than 10,000 ng/mL during CRS accompanied by 2 or more grade (G)$\geq$3 organ toxicities (eg, liver, pulmonary, renal), or histologic hemophagocytosis.[30] In a cohort of 105 large B-cell lymphoma (LBCL) patients treated with axicabtagene autoleucel (axi-cel), 6% met CARTOX HLH criteria, correlating with inferior progression-free survival (PFS) and overall survival (OS).[29] Two subsequent retrospective, multi-institutional cohorts of LBCL patients treated with axi-cel or tisa-cel found that a peak ferritin level of greater than 5000 ng/mL, occurring in 18% to 19% of patients, was associated with significantly inferior PFS and OS.[28,33] Preexisting HLH criteria such as the HLH-2004 criteria and H-scores, established in primary and secondary HLH, have not been predictive of outcomes.[4,31,32]

More recently, the Mayo Clinic published their IEC-HS experience in a large cohort of B-cell non-Hodgkin lymphoma (B-NHL) and multiple myeloma (MM) patients (436 total patients).[35] Applying their own IEC-HS criteria (adapted from the CARTOX criteria), they reported an incidence rate of just 3%. Notably, IEC-HS was continuous with (rather than independent of) CRS in 62% of patients, and IEC-HS patients suffered a staggering overall mortality of 77% with most deaths related to IEC-HS complications. Based on the above experience with IEC-HS, all FDA-approved CD19-directed CAR-T-cell products disclose a warning for the risk of developing IEC-HS in their prescribing information,[41–44] with reporting incidence rates of 1% to 3.4% and mortality rates exceeding 67%.[34,37]

### *Multiple Myeloma*

BCMA-directed CAR-T therapies, idecabtagene vicleucel (ide-cel), and ciltacabtagene autoleucel (cilta-cel), also carry boxed warnings for IEC-HS risks, including reports of fatalities.[45,46] However, the real-world significance of IEC-HS in MM remains unclear due to inconsistent diagnostic criteria.[18,36,47–49] The University of California, San Francisco utilized a ferritin increase $\geq$100 ng/mL/h over 24 hours, plus a fibrinogen less than 150 mg/dL or a lactate dehydrogenase greater than 2 $\times$ the ULN, to define a MAS-like syndrome.[36] Using this approach, 22% of patients met IEC-HS criteria and

**Table 1**
**Definitions, incidence patterns, associations with cytokine release syndrome and immune effector cell associated neurotoxicity syndrome, and clinical significances of published immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome and other hyperinflammatory criteria**

| Histologies (year) | Product (s) (*n* = patients) | Applied IEC-HS/ Hyperinflammatory Criteria[a] and/or Reported Relevant Peak Ferritin Values | Incidence of Applied IEC-HS/ Hyperinflammatory Criteria[a] Association with CRS Association with ICANS | Median Time From Infusion to Onset | Clinical Significance of Applied IEC-HS/ Hyperinflammatory Criteria[a] |
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| B-ALL[2] (2016) | Tisa-cel (*n* = 51) | Evidence of CRS with a peak ferritin >10,000 ng/ mL. | 28% met their HLH diagnostic criteria.<br>100% of patients with ≥G4 CRS had a peak ferritin >10,000 ng/ mL.<br>59% of patients with ≤G3 CRS had a peak ferritin >10,000 ng/ mL.<br>Incidences and grades of ICANS were not reported. | NR | 4% of all patients died of severe CRS complications. |
| B-ALL[15] (2021) | CD22-directed (*n* = 59) | Shah et al. criteria: Evidence of CRS with a peak ferritin ≥100,000 ng/mL plus ≥2 of the following: ≥G3 hepatic, renal, and/ or pulmonary toxicity, and/or coagulopathy, and/or evidence of hemophagocytosis. | 36% met Shah et al. carHLH criteria.<br>Patients with carHLH: CRS G1-2 (71%); CRS ≥G3 (29%).<br>Patients without carHLH: CRS G1-2 (81%); CRS ≥G3 (19%).<br>Incidences and grades of ICANS were not reported for any cohort. | 14 d (range, 7–25) | CarHLH patients had similar ORR (91% vs 80%, *P* = NS).<br>CarHLH patients had similar rates of ≥G3 CRS (29% vs 19%, *P* = NS).<br>Survival data stratified by carHLH manifestations were not reported.<br>One carHLH patient died (sepsis). |

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| B-ALL[26] (2021) | Tisa-cel ($n$ = 12)<br>CD19-directed investigational ($n$ = 15) | Clinically diagnosed with carHLH in real-time.<br>Retrospectively per Shah et al. criteria.[15] | 15% met Shah et al. carHLH criteria.<br>Patients with carHLH: CRS G1-2 (25%); CRS ≥G3 (75%).<br>Patients without carHLH: CRS G1-2 (82%); CRS ≥G3 (18%).<br>Incidences and grades of ICANS were not reported for any cohort. | 11.5 d (range, 8–20) | All carHLH patients had prior or concurrent CRS.<br>CarHLH patients had similar max grades of CRS ($P$ = .09).<br>CarHLH patients had higher rates of ICU admissions (75% vs 18%, $P$ = .003).<br>CarHLH patients had less CR (0% [carHLH] vs 91% [CRS alone] vs 75% [no CRS], $P$ = .018).<br>CarHLH patients had inferior 2-mo OS (25% [carHLH] vs 91% [CRS alone] vs 100% [no CRS], $P$<.001).<br>All 4 carHLH patients died (1 carHLH, 3 POD). |
| B-ALL[27] (2023) | Tisa-cel ($n$ = 185) | Evidence of CRS with a peak ferritin ≥10,000 ng/mL plus ≥2 of the following:<br>Any grade hepatic, renal, pulmonary toxicity, coagulopathy, and/or evidence of hemophagocytosis. | 14% met their HLH-LT diagnostic criteria.<br>7% met HLH-LT when a higher (≥100,000 ng/mL) peak ferritin was applied.<br>Patients with HLH-LT: CRS G1-2 (12%); CRS ≥G3 (89%).<br>Patients without HLH- | 12 d (range, 4–21) | *HLH-LT vs HG-CRS without HLH-LT vs no/LG-CRS without HLH-LT*<br>HLH-LT patients had higher max CRS grades (median, 4 vs 3 vs 1, $P$<.0001).<br>HLH-LT patients had longer durations of |

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**Table 1**
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| Histologies (year) | Product (s) ($n$ = patients) | Applied IEC-HS/ Hyperinflammatory Criteria[a] and/or Reported Relevant Peak Ferritin Values | Incidence of Applied IEC-HS/ Hyperinflammatory Criteria[a] Association with CRS Association with ICANS | Median Time From Infusion to Onset | Clinical Significance of Applied IEC-HS/ Hyperinflammatory Criteria[a] |
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| | | | LT: CRS G1-2 (47%); CRS ≥G3 (11%).<br>Patients with HLH-LT: ICANS any grade (54%).<br>Patients without HLH-LT: ICANS any grade (17%). | | CRS (median, 11 d vs 5 vs 3, $P$<.0001).<br>HLH-LT patients had higher rates of any grade ICANS (54% vs 38% vs 14%, $P$<.0001).<br>HLH-LT patients had longer ICU admissions (median, 10 d vs 5. vs 0, $P$<.0001).<br>HLH-LT patients had higher rates of relapse (64% vs 29% vs 31%, $P$=.007).<br>HLH-LT patients had higher overall mortality rates (76% vs 18% vs 21%, $P$<.0001).<br>HLH-LT patients had higher NRM rates (28% vs 0% vs 4%, $P$=.0009).<br>(NRM = 1 CRS, 1 ICANS, 4 infection, 3 |

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| | | | | | cardiopulmonary failure).<br>HLH-LT independently associated with inferior RFS (HR 3.68, *P*<.0001) and OS (HR 4.61, *P*<.0001). |
| LBCL[28] (2020) | Axi-cel (*n* = 122) | IEC-HS/ Hyperinflammatory criteria were not applied.<br>18% of all patients had a peak ferritin >5000 ng/mL. | Not applicable.<br>All patients: CRS, any grade (93%); CRS ≥G3 (16%).<br>All patients: ICANS, any grade (70%); ICANS ≥G3 (35%).<br>Breakdowns of CRS/ ICANS by peak ferritin were NR. | NR | Patients with a peak ferritin >5000 ng/mL had higher rates of ≥G3 CRS (*P*<.001), ≥G3 ICANS (*P*<.001), inferior PFS (2.2 vs 6.8 mo, *P*=.020), and inferior OS (2.7 mo vs not reached, *P*<.001). |
| LBCL[29] (2021) | Axi-cel (*n* = 105) | HLH-04 criteria.[4]<br>CARTOX criteria[30]: Peak ferritin >10,000 ng/ mL during the CRS phase plus ≥2 of the following:<br>≥G3 hepatic, renal, and/ or pulmonary toxicity, and/or evidence of hemophagocytosis. | 6% met CARTOX HLH diagnostic criteria.<br>Patients with HLH: CRS ≤G2 (83%); CRS ≥G3 (0%).<br>Patients with HLH: ICANS ≤G2 (33%); ICANS ≥G3 (50%).<br>Patients without HLH: Incidences and grades of CRS/ICANS were not reported. | 11 d (range, 7–78) | HLH patients had inferior PFS (1 mo vs 8, *P*<.001).<br>HLH patients had inferior OS (2 mo vs NR, *P*=.001).<br>In total, 83% of HLH patients died (2 from HLH without POD, 2 POD, 1 respiratory failure).<br>The only surviving HLH patient had POD on day 30. |

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**Table 1**
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| Histologies (year) | Product (s) (*n* = patients) | Applied IEC-HS/ Hyperinflammatory Criteria[a] and/or Reported Relevant Peak Ferritin Values | Incidence of Applied IEC-HS/ Hyperinflammatory Criteria[a] Association with CRS Association with ICANS | Median Time From Infusion to Onset | Clinical Significance of Applied IEC-HS/ Hyperinflammatory Criteria[a] |
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| DLBCL[31] (2022) | CD19-directed (*n* = 75) | HLH-04 criteria.[4]<br>H-score.[32]<br>57% of all patients had a peak ferritin >500 ng/mL. | HLH-scores were applied only to patients with a peak ferritin >500 ng/mL (57%).<br>33% had a high H-score (≥169) and only 5% met HLH-04 criteria.<br>Patients with a high H-score (≥169): CRS ≤G1 (33%); CRS ≥G2 (67%).<br>Patients with a low H-score (<169): CRS ≤G1 (28%); CRS ≥G2 (72%).<br>Patients with a high H-score (≥169): ICANS ≤G1 (36%); ICANS ≥G2 (64%).<br>Patients with a low H-score (<169): ICANS ≤G1 (35%); ICANS ≥G2 (66%). | NR | The median H-scores were similar for patients with ≥G2 CRS (*P*=.63) and ≥G2 ICANS (*P*=.81).<br>A high H-score (≥169) had no impact on PFS (*P*=.77) or OS (*P*=.18).<br>4 patients were "clinically treated as HLH" and all died (1 thrombosis, 2 POD, 1 cerebral hemorrhage). |

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| LBCL[33] (2023) | Axi-cel ($n$ = 202)<br>Tisa-cel ($n$ = 149) | IEC-HS/HLH criteria were not applied.<br>14% of all patients had a peak ferritin >5000 ng/mL. | Not applicable.<br>Patients with a peak ferritin >5000 ng/mL: Any grade CRS (98%); CRS ≥G3 (NR).<br>All patients: CRS G1-G2 (66%); CRS ≥G3 (9%).<br>Incidences and grades of ICANS were not reported for any cohort. | NR | A peak ferritin >5000 ng/mL associated with inferior PFS (HR 2.61, $P$<.001).<br>A peak ferritin >5000 ng/mL associated with inferior OS (HR 2.38, $P$<.001).<br>CRS grade alone had no impact on CR rates, PFS, or OS. |
| LBCL, B-ALL[34] (2023) | Axi-cel ($n$ = 14,464)<br>Tisa-cel ($n$ = 29,366) | HLH events reported to the FDA Adverse Events Reporting System. | 136 HLH events were reported.<br>HLH was the sixth most common hematological toxicity reported. | NR | HLH reported events resulted in a mortality rate of 69.9%. |
| B-NHL, MM[35] (2024) | $N$ = 436 total patients<br>CD19-directed ($n$ = NR)<br>BCMA-directed ($n$ = NR) | A peak ferritin >10,000 ng/mL plus ≥2 of the following criteria:<br>≥G3 hepatic, renal, and/or pulmonary toxicity, ≥G3 cytopenia (new or unexplained), ≥G3 acidemia, and/or evidence of hemophagocytosis. | 3% met their carHLH diagnostic criteria.<br>Patients with carHLH: CRS, any grade (100%); CRS ≥G3 (39%).<br>Patients with carHLH: ICANS, any grade (100%); ICANS ≥G3 (69%).<br>Patients without carHLH: Incidences/grades of CRS/ICANS were not reported. | 7 d (range, 4–32) | CarHLH was continuous with CRS in 62% of patients and independent of CRS in 38%.<br>77% of carHLH patients died (5 carHLH, 1 POD, 1 neurotoxicity-related aspiration event, 1 bowel perforation with sepsis, 1 COVID, 1 unknown cause). |

(*continued on next page*)

**Table 1**
**(*continued*)**

| Histologies (year) | Product (s) ($n$ = patients) | Applied IEC-HS/ Hyperinflammatory Criteria[a] and/or Reported Relevant Peak Ferritin Values | Incidence of Applied IEC-HS/ Hyperinflammatory Criteria[a] Association with CRS Association with ICANS | Median Time From Infusion to Onset | Clinical Significance of Applied IEC-HS/ Hyperinflammatory Criteria[a] |
|---|---|---|---|---|---|
| MM[36] (2021) | BCMA-directed ($n$ = 55) | A ferritin rise of ≥100 ng/mL/hour within a 24-h period plus one of the following:<br>Fibrinogen <150 mg/dL or LDH >2x ULN. | 22% met their MAS-L diagnostic criteria.<br>18% met HLH-04 criteria.[7]<br>2% met CARTOX HLH criteria.[8]<br>Patients with MAS-L: CRS G1-2 (100%); CRS ≥G3 (0%).<br>Patients without MAS-L: CRS G1-2 (84%); CRS ≥G3 (0%).<br>Patients with MAS-L: ICANS G1-2 (25%); ICANS ≥G3 (17%).<br>Patients without MAS-L: ICANS G1-2 (12%); ICANS ≥G3 (2%). | NR | MAS-L patients had similar ORR ($P$=.05), RFS ($P$=.37), and OS ($P$=.16).<br>MAS-L patients had similar rates ($P$=.33) and max grades ($P$=.99) of CRS.<br>MAS-L-patients had longer durations of CRS (median 5.4 d vs 3.7, $P$=.03).<br>MAS-L patients trended toward higher rates of ICANS (42% vs 14%, $P$=.05).<br>MAS-L patients had longer hospitalizations (21 d vs 19, $P$=.009).<br>MAS-L patients had higher rates of ICU admissions (27% vs 2%, $P$=.02). |

| | | | | | |
|---|---|---|---|---|---|
| MM, B-NHL, B-ALL (2022)[37] | Axi-cel ($n$ = 3089)<br>Brexu-cel ($n$ = 312)<br>Tisa-cel ($n$ = 2329)<br>Liso-cel ($n$ = 176)<br>Ide-cel ($n$ = 110)<br>Cilta-cel ($n$ = 18) | HLH events reported to the FDA Adverse Events Reporting System and Vizient database. | A total of 6034 adverse events were reported.<br>The incidence rates per CAR-T cell product were the following:<br>Axi-cel (1.7%), Brexu-cel (1.6%), Tisa-cel (2.5%), Liso-cel (2.8%), Ide-cel (0%), Cilta-cel (0%). | NR | The mortality rates of HLH per CAR-T cell product were the following:<br>Axi-cel (75.5%), Brexu-cel (80%), Tisa-cel (60.3%), Liso-cel (40%), Ide-cel (0%), Cilta-cel (0%). |
| MM[18] (2023) | BCMA-directed ($n$ = 99) | CARTOX HLH criteria.[30] | 20% met CARTOX HLH diagnostic criteria.<br>Patients with carHLH: CRS $\leq$G2 (10%); CRS $\geq$G3 (80%).<br>Patients without carHLH: CRS $\leq$G2 (52%); CRS $\geq$G3 (28%).<br>Rates and grades of ICANS were not reported for any cohort. | 10.5 d (range 6–27) | Patients with carHLH had similar ORR and CR compared with patients with $\geq$G3 CRS without carHLH ($P$>.05).<br>Patients with carHLH had a 15% NRM rate (1 cerebral hemorrhage, 2 infections).<br>Patients with $\geq$G3 CRS without carHLH had a 4% NRM rate (1 infection). |

*Abbreviations:* Axi-cel, Axicabtagene ciloleucel; B-ALL, B-cell acute lymphoblastic leukemia; BCMA, B-cell maturation antigen; BMB, bone marrow biopsy; B-NHL, B-cell non-Hodgkin lymphoma; Brexu-cel, brexucabtagene autoleucel; carHLH, chimeric antigen receptor T-cell-associated hemophagocytic lymphohistiocytosis; CARTOX, CAR-T-cell-therapy-associated TOXicity Working Group; Cilta-cel, ciltacabtagene autoleucel; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; FDA, US Food and Drug Administration; G, grade; HG-CRS, high-grade cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; HLH-LT, chimeric antigen receptor-associated hemophagocytic lymphohistiocytosis (HLH)-like toxicities; ICANS, immune effector-associated neurotoxicity syndrome; ICU, intensive care unit; Ide-cel, idecabtagene vicleucel; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; LG-CRS, low-grade cytokine release syndrome; MAS-L, macrophage activation syndrome-like disease; MM, multiple myeloma; NR, not reported; NRM, nonrelapse mortality; NS, not significant; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POD, progression of disease; RFS, relapse-free survival; Tisa-cel, tisagenlecleucel; ULN, upper limit of normal.

[a] Terminologies used were taken from their respective published articles.

experienced longer hospital stays and higher intensive care unit (ICU) admission rates, although survival was unaffected. In a study of 159 ide-cel-treated patients, 42% had a pre-lymphodepletion ferritin greater than ULN, correlating with increased ICANS but not affecting response rates.[47] Another trial of BCMA-directed CAR-T therapy applied CARTOX HLH criteria and reported numerically higher nonrelapse mortality (15% vs 4%) in IEC-HS patients, although survival data were not disclosed.[18]

## TREATMENT OF IMMUNE EFFECTOR CELL-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS-LIKE SYNDROME

To date, no clinical trials have been specifically conducted to evaluate IEC-HS, likely due to its relative rarity, novelty as a clinical entity and variability in onset and presentation.[19] There remains a critical need for observational cohort studies to better define the incidence, risk factors, and natural history of IEC-HS across various IEC therapies—particularly the construction of a multicenter, prospective registry for systematic collection of clinical data, laboratory markers, and longitudinal outcomes. Coordinated, larger-scale efforts focusing on cytokine profiling and immune cell phenotyping could transform the ability to preempt and manage IEC-HS, ultimately improving patient outcomes and the safety profile of IEC therapies.

Despite these limitations and using best practice approaches, treatment of IEC-HS focuses on addressing 2 interrelated aspects of known HLH/MAS pathophysiology, including persistent, late, or prolonged CAR T-cell expansion and the associated hypercytokinemia, including elevations in IFN-$\gamma$, IL-1$\beta$, IL-12, IL-4, IL-8, IL-6, IL-18, IL-10, TNF-$\alpha$, and macrophage inflammatory protein (MIP)-1$\alpha$.[15,18,20] Importantly, patients who develop IEC-HS have often already received multiple doses of tocilizumab with or without steroids for antecedent CRS. Generally, additional doses of tocilizumab in the setting of IEC-HS are not recommended due to the potential to exacerbate IL-18, which may lead to further inflammation (**Fig. 2**).[50]

## SUPPORTIVE CARE CONSIDERATIONS FOR IMMUNE EFFECTOR CELL-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS-LIKE SYNDROME

### *Intensive Care Unit Considerations*

Patients with rapidly progressive IEC-HS are at risk for requiring ICU admission and organ support, including renal replacement therapy, vasopressor support, and respiratory support per standard of care.[26,35,51] Renal replacement therapy may be indicated for overt renal dysfunction or fluid overload. Cardiovascular dysfunction can occur, and echocardiography should be considered on a case-by-case basis. Respiratory failure in patients with IEC-HS can develop secondary to pulmonary edema and capillary leak. In addition, patients are at high risk for recurrent or prolonged cytopenias, coagulopathy with hypofibrinogenemia, and infection.[1]

### *Support of Cytopenias and Coagulopathy*

It is recommended that patients are monitored for cytopenias and development of coagulopathy with hypofibrinogenemia at least daily, with transfusion of blood products as needed. Bleeding can be life-threatening and prolonged.[1,34,51] Vitamin K supplementation should be considered for patients with an international normalized ratio (INR) greater than 1.5.

### *Infection*

In some studies, patients with IEC-HS have been found to have a higher risk of developing infection and prolonged neutropenia compared with patients with

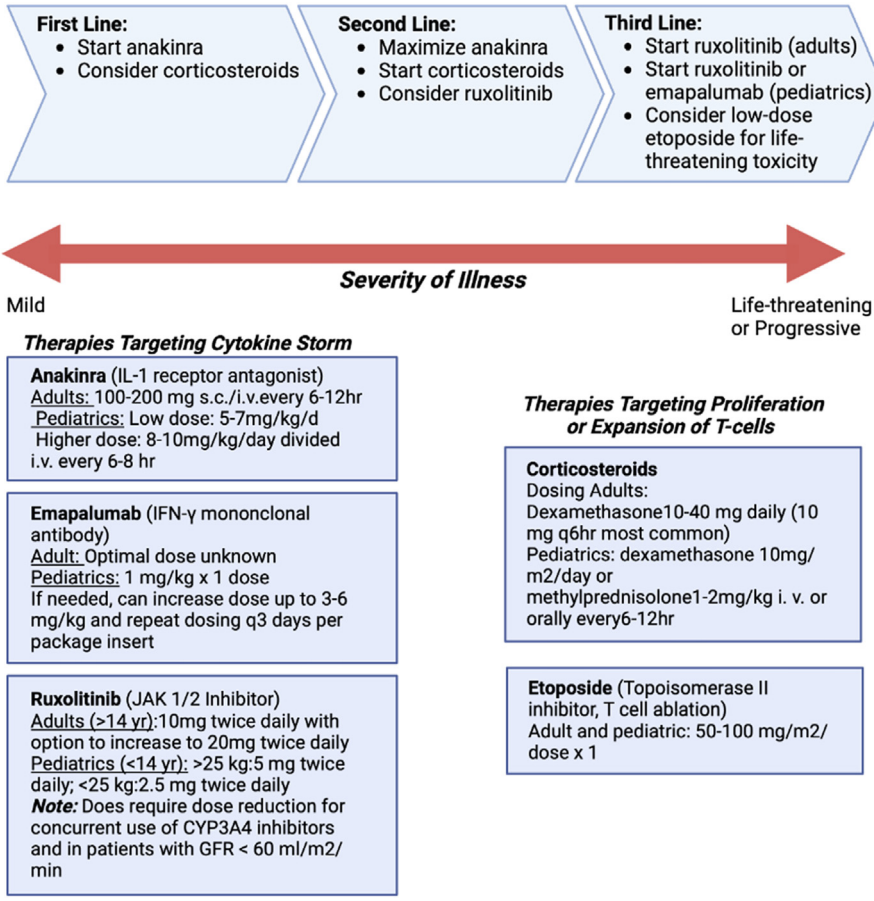


**Fig. 2.** IEC-HS therapies based on severity of illness. (*Modified from* Hines MR, Knight TE, McNerney KO, et al. Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome. *Transplant Cell Ther.* 2023;29(7):438.e1–438.e16. https://doi.org/10.1016/j.jtct.2023.03.006; *Data from* Rocco JM, Inglefield J, Yates B, et al. Free interleukin-18 is elevated in CD22 CAR T-cell-associated hemophagocytic lymphohistiocytosis-like toxicities. *Blood Adv.* 2023;7(20):6134–6139. https://doi.org/10.1182/bloodadvances.2023010708; Previously recommended dosing has been included and is based on current literature for IEC-HS when available, or for CRS or HLH when IEC-HS data is unavailable; Created using Biorender.) *Created in* BioRender. Hines, M. (2024) https://BioRender.com/y94l060.

CRS—especially when multiple immunosuppressants are used to temper the inflammatory process.[27] Evaluation for possible infection is crucial to determine if infection is driving the recrudescence of inflammation, or if the patient truly has IEC-HS that is independent of infection, as therapy will differ. If infection with inflammation is present, antimicrobial therapy should be prioritized while balancing the need for further immunosuppression or anticytokine-directed therapies.[1] Recommended testing for infection includes assessment for new bacterial, viral, and fungal infections, as well as viral reactivation, in blood and urine. Additional testing of other possible sources, such as sputum, bronchoalveolar lavage, and cerebrospinal fluid can be considered based on clinical presentation. Antifungal, antiviral, and anti-pneumocystis jiroveci

pneumonia (PJP) prophylaxis are recommended for patients who are neutropenic and/or lymphopenic and are often standard-of-care after lymphodepletion. For patients in whom multiple immunosuppressive therapies are implemented, infectious disease consultation is strongly encouraged.

### *Therapies Targeting the Cytokine Storm*

#### *Anakinra*

Anakinra is a recombinant IL-1 receptor antagonist that is available for subcutaneous or intravenous (IV) administration. Given significant elevations of IL-1β in patients with IEC-HS, anakinra is a reasonable targeted therapy with a wide therapeutic window (1.5 mg/kg/d up to 2 mg/kg/h continuous infusion) and a low side effect profile. The most common side effects include soft tissue infection, neutropenia, and hepatic transaminase elevation with prolonged use. There is documentation of the efficacy of anakinra for the treatment of refractory ICANS and CRS with doses up to 12 mg/kg/d IV, with higher doses associated with lower treatment-related mortality, and a good overall response, suggesting continued CAR efficacy.[52] In patients with neurologic manifestations of HLH, IV administration may be more beneficial due to higher achieved peak serum concentration to allow for better blood–brain barrier penetration.[53] The use of anakinra for IEC-HS has been described and has shown efficacy in case series and retrospective studies, but no interventional trials have been completed in IEC-HS.[15,26,27,35]

#### *Ruxolitinib*

Ruxolitinib is a Janus Kinase 1/2 inhibitor, which prevents the intracellular signaling and downstream transcriptional changes of multiple cytokines reported to be elevated in IEC-HS, including IFN-γ, IL-6, IL-4, IL-10, and IL-12. There has been documented efficacy using ruxolitinib in primary and secondary HLH, and case studies suggest efficacy in steroid-refractory CRS.[54–60] Based on current data, the potential efficacy of ruxolitinib in IEC-HS is likely multifactorial with evidence of reduced cytokine production from CAR T-cells, as well as other immune cells, and reduced CAR T-cell proliferation. Notably, there is in vivo and in vitro evidence that ruxolitinib likely causes dose-dependent reductions of CAR T-cell expansion and cytolytic effect, with restoration of cytokine production and cytolytic function once ruxolitinib is discontinued.[61] In the few studies where ruxolitinib has been used, there has not been a documented reduction in overall CAR T-cell efficacy.[58–61] The possible effect of ruxolitinib on CAR T-cell expansion may be less problematic in the setting of IEC-HS given the later timing after CAR T-cell infusion, and because persistent or prolonged CAR T-cell expansion may be part of the underlying pathophysiology of IEC-HS. Often patients with IEC-HS have transaminitis and worsening cytopenias at the start of therapy, and these findings are not considered a contraindication for starting ruxolitinib. Possible drug adverse effects should be considered in patients with persistent transaminitis and cytopenias in the setting of clinical improvement.

#### *Emapalumab*

Emapalumab is a monoclonal antibody that targets IFN-γ and has been FDA-approved for the treatment of adult and pediatric primary HLH.[62,63] IFN-γ is increased in IEC-HS, and whether INF-γ is a key driver of IEC-HS pathophysiology is under investigation. The side effect profile for emapalumab is favorable with only notable risks being infusion reactions and viral reactivation; however, there are no published clinical trials evaluating the use of emapalumab for treatment of secondary HLH or any other indications in adult patients. The effect of emapalumab on CAR T-cell function and expansion is unknown, although there is some evidence that IFN-γ inhibition

may decrease antileukemic function.[20] There are several case studies and series that have shown potential efficacy in severe, refractory CRS and IEC-HS in pediatric patients with maintained antileukemic CAR T-cell effect.[64–66]

### *Therapies Targeting Proliferation or Expansion of T-cells*

#### *Corticosteroids*

Part of steroid efficacy in both primary and secondary HLH is in their general immunosuppressive effect and cytotoxic effect, but it is unclear how much the cytotoxic effect of steroids occurs when used for CRS in CART-cell therapy. Steroids remain a mainstay of both CRS and IEC-HS therapy.[1,15,26,27,35] There is mixed data on the potential reduction of efficacy and expansion of CAR T-cells.[67,68] The majority of data suggests continued efficacy, with caution against high and early dosing of steroids.

#### *Etoposide*

In the setting of primary and secondary HLH, the mechanism of action is targeted ablation of activated $CD8^+$ T-cells.[69] There is very limited clinical experience with the use of etoposide in the setting of CAR T-cell therapy and generally has only been considered for refractory and life-threatening IEC-HS.[1,19,35] Dosing for this indication is lower than described for pediatric HLH per the HLH-94 and 2004 protocols and is typically given as a single dose.[19,70] As described by Scala and colleagues, there is some evidence that long-term CAR T-cell expansion and antitumor effect can be maintained even after etoposide dosing.[19] In the setting of hyperproliferation, etoposide could be considered as a way to mitigate the underlying pathology driving the inflammatory cascade.

#### *Other agents*

Alternative agents for CAR T-cell depletion have been described in a few cases including basiliximab, cyclophosphamide, and antithymocyte globulin.[35]

#### *Choice of therapy*

A stepwise approach to therapy has been recommended based on the severity of disease with the addition of a single agent for mild symptoms or the presence of laboratory abnormalities alone (see **Fig. 2**).[1] In select cases, observation alone has been sufficient as the hyperinflammation can be self-limited. However, as the trajectory can be hard to predict, close monitoring with daily evaluation is strongly advised. For moderate disease severity (ie, patients requiring supportive care such as transfusions), stepwise addition of agents is reasonable until there is clinical and laboratory stability. For severe, life-threatening, or refractory disease, multiple agents may need to be initiated together as described by Scala and colleagues.[19] Once there is clinical and laboratory stabilization, reassessment and stepwise weaning of therapy is imperative to reduce prolonged immunosuppression and infection risk. Similar to the evolving strategy of pre-emptive treatment of low-grade CRS to prevent more severe toxicities, we anticipate that earlier identification of IEC-HS will facilitate the use of pre-emptive treatment and offset more severe manifestations where multiple immunosuppressants are needed.

#### *Future directions in toxicity mitigation*

A growing arsenal of tools aimed at enhancing the safety and precision of CAR T-cell therapies, ensuring that the benefits of these transformative treatments are not undermined by severe treatment-emergent toxicities, is in evolution. Active efforts in CAR T-cell engineering and design strategies to allow for selective attenuation, gating, or elimination of hyperactive CAR T-cell responses are in development and summarized in **Table 2**.[71–79] Additional strategies to reduce the risk of severe hyperinflammation

**Table 2**
**Examples of novel engineering approaches in toxicity mitigation strategies for immune effector cell therapies**

| | System | Approach |
|---|---|---|
| Suicide switches | Herpes simplex virus (HSV)-thymidine kinase (TK) | Therapeutic T-cells engineered with HSV-TK are selectively depleted by nucleoside analogs.[71,72] |
| | Inducible caspase 9 (iCas9) | Transgenic T-cells, incorporating a modified iCasp9, undergo apoptosis upon exposure to a dimerizing drug.[73] |
| Epitope-based targeting | CD20 tags | Chimeric CD20 surface proteins on CAR T-cells enable killing by CD20 antibodies (rituximab).[74] |
| | Truncated epidermal growth factor receptor (EGFRt) | EGFRt-expressing CAR T-cells undergo selective depletion with an anti-EGFR antibody (cetuximab).[75] |
| Logic-gated systems | SynNotch receptors | CAR expression is a 2-step process requiring stimulation with an initial trigger antigen, which then results CAR expression (or another therapeutic payload); these enable customizable/context-dependent killing.[76] |
| | AND-Gate CARs | CARs are engineered to require 2 or more antigens for activation, enabling specificity.[77] |
| | Inhibitory CARs (iCARs) | CARs are designed to include an inhibitory signaling domain, which inhibit the T-cell upon antigen recognition, thereby decreasing off-tumor reactivity.[78] |

*Data from.*[71–79]

may also involve pharmacologic and dosing modifications, such as step-up dosing regimens, in which CAR T-cell therapies or other immune effectors like bispecific antibodies are administered in smaller, fractionated doses with close monitoring for adverse effects.[80] This approach, already employed in approved bispecific antibodies for lymphoma and myeloma,[81–85] enables gradual immune activation and limits the likelihood of overwhelming inflammatory responses.

***Considerations in emerging indications with novel forms of effector T-cell therapies***

As IEC therapies expand from hematologic malignancies to solid tumors, autoimmune conditions, and neurologic diseases, treatment-emergent acute hyperinflammation requires careful attention. Several IEC therapies approved for solid tumors represent significant progress, including tebentafusp (gp100 peptide-HLA-directed T-cell engager for uveal melanoma),[86] tarlatamab (DLL3-targeting BiTE for small cell lung cancer),[87] afamitresgene autoleucel (MAGE-A4 T-cell receptor gene therapy for synovial sarcoma),[88] and lifileucel (tumor-infiltrating lymphocyte therapy with interleukin-2 for immunotherapy-refractory melanoma).[89] Although pivotal studies report low rates of severe CRS, real-world data are limited. However, more potent CAR designs may be required for efficacy in solid malignancies and may thereby increase acute hyperinflammation risks.

For nonmalignant diseases, the risk-benefit balance differs, as potentially life-threatening toxicities like IEC-HS are unacceptable. Early studies in autoimmune diseases (eg, lupus, antisynthetase syndrome)[90–93] and neurologic conditions (eg, multiple sclerosis, myasthenia gravis)[94,95] show promising results with manageable safety profiles, though some cases required aggressive CRS management. These therapies aim to recalibrate immune dysregulation but carry a theoretic risk of systemic hyperinflammation. Ongoing trials will clarify their safety and therapeutic roles in nonmalignant conditions.

## DISCUSSION

Diagnosis of IEC-HS remains difficult and current diagnostic criteria, while based on some data, were selected by expert consensus.[1] Re-evaluation of these criteria needs to be performed to ensure that the proposed IEC-HS criteria are appropriately selecting patients with increased mortality and requiring IEC-HS directed therapy, as well as accurately identifying IEC-HS patients. IEC-HS diagnosis is often more straightforward in patients with a delayed presentation. However, in patients with IEC-HS that occurs as CRS is improving or when CRS has recently resolved and therapy for CRS is being weaned, it is often difficult to determine if continued CRS is being unmasked, or the patient is developing an infection, or the patient is now developing IEC-HS. In these cases, further determination of biomarkers specific to IEC-HS is desperately needed to ensure that effective immunomodulation for IEC-HS is started when appropriate while avoiding immunosuppression in patients with infection. Possible biomarkers of interest could be based on the predominance of certain cell populations by flow cytometry or specific cytokine panel patterns among others.

## SUMMARY

Some may argue that IEC-HS and severe or persistent CRS are within the same spectrum of disease. However, patients with severe CRS and patients with IEC-HS have distinct underlying pathophysiologies with different risks and responses to therapy, with IEC-HS often refractory to continued or reinstituted tocilizumab.[15,19,26,27,35]

High clinical suspicion for possible IEC-HS is imperative to ensure appropriate monitoring, particularly for the assessment of coagulopathy and associated bleeding risk, as well as initiation of IEC-HS-directed therapy.

## CLINICS CARE POINTS

- Distinct from cytokine release syndrome, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) can be seen after adoptive cell therapy and requires recognition to optimize the therapeutic approach to this potentially life-threatening complication.
- Supportive care measures, including optimization of blood coagulation parameters and prevention or early intervention for infectious disease complications, are especially imperative in the optimal management of patients who develop IEC-HS.
- A host of anticytokine or T-cell-directed therapies are available and based on patient-specific parameters can be considered for the treatment of IEC-HS.

## DISCLAIMER

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## DISCLOSURE

This work was supported in part by the Intramural Research Program, United States, Center for Cancer Research, United States, National Cancer Institute National Institutes of Health, United States (ZIA BC 011823, N.N. Shah). N.N. Shah receives research funding from Lentigen, VOR Bio, and CARGO Therapeutics. N.N. Shah has attended advisory board meetings (no honoraria) for VOR, ImmunoACT, and Sobi. N.N. Shah receives royalties from CARGO. J.C. Lee receives research funding from Incyte, United States. W.T. Johnson received consulting fees from BioNTech and served on an advisory board for Sobi and Electra Therapeutics.

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