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Review

When the Living Drug Strikes Back: Cytokine Release Syndrome and Neurotoxicity from CAR T-Cell and Bispecific Therapies

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Abstract: Chimeric antigen receptor (CAR) T-cell therapies and bispecific T-cell engagers have produced durable remissions in haematological malignancies that were previously considered refractory, and the bispecific class has now extended this approach to a solid tumour, extensive-stage small-cell lung cancer, through the delta-like ligand 3 engager tarlatamab. The shared mechanism of intense, sustained T-cell activation generates two characteristic and potentially fatal toxicities: cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). As bispecific agents shift toward subcutaneous and outpatient administration, an increasing proportion of treated patients present to emergency departments without immediate access to the treating cellular therapy centre, where the syndrome may not be recognised. This narrative review translates the consensus produced by haematology and cellular therapy societies into an operational framework for acute care. It synthesises the mechanism, epidemiology, grading, and initial management of CRS, ICANS, and related immune effector cell toxicities, drawing on the American Society of Transplantation and Cellular Therapy consensus, the American Society of Clinical Oncology guideline, the joint European recommendations, and pivotal and updated product trials. Recognition rests on a few disciplined habits: naming the therapy, treating fever in a recently treated patient as an emergency, grading CRS and ICANS while methodically excluding infection, and contacting the treating centre early. Management centres on tocilizumab for CRS, corticosteroids for ICANS, anakinra in refractory disease, and aggressive supportive care. Competence with these syndromes is becoming a general expectation of acute care rather than the exclusive concern of cellular therapy units.

Keywords: CAR T-Cell Therapy; Bispecific Antibodies; Cytokine Release Syndrome; Immune Effector Cells; Immunotherapy Toxicity

1. Introduction

A CAR T-cell is best thought of as a living drug. The patient's own T-cells are collected, genetically rewired to recognise a tumour antigen, and returned, after which they expand and can patrol the body for years [1]. In little more than a decade this idea travelled from first-in-human experiments to standard care for relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL), large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, and multiple myeloma [2,3]. The bispecific T-cell engagers reach a similar destination by a different route, and without any cell manufacturing: a single molecule grips a tumour antigen with one arm and CD3 on the patient's T-cells with the other, forcing the two together and triggering tumour lysis. Blinatumomab opened this class in B-cell

precursor ALL [4], and teclistamab and a lengthening list of successors followed in myeloma and lymphoma [5].

The same force that makes these agents work, intense and prolonged T-cell activation, is what makes them dangerous. Two syndromes dominate the acute presentation. Cytokine release syndrome (CRS) is a body-wide inflammatory storm; immune effector cell-associated neurotoxicity syndrome (ICANS) is a distinct encephalopathy that often follows it. Early trials produced enough variation in how these events were described that a common grading language became essential, and the 2019 American Society of Transplantation and Cellular Therapy (ASTCT) consensus now fills that role [6]. Severity covers the whole range, from a self-limited fever to multiorgan failure, status epilepticus, and death [7,8].

Where these patients are treated has shifted, and that shift is the reason this review exists. For years, the toxicities belonged to a handful of accredited centres, with intensive monitoring, tocilizumab on the shelf, and critical care through the next door. Bispecific antibodies broke that arrangement. They are increasingly given subcutaneously and in the outpatient clinic, and patients treated at a referral hospital go home to towns served by ordinary general hospitals [5]. A patient who turns febrile or confused a few days after a T-cell engaging therapy may therefore walk into any emergency department (ED), met by a team that has no link to the cellular therapy service and, on the surface, no reason to suspect what is unfolding. The ASCO guideline panel wrote emergency physicians into its audience for precisely this reason [7].

This review sets out a working approach for the front line: how to recognise and start treating CRS, ICANS, and the other immune effector cell toxicities most likely to reach the ED. The aim is to carry the consensus built by haematology and cellular therapy societies into a setting where time is short and the nearest subspecialist may be an hour away by telephone. The emphasis stays on the decisions that can be made before transfer and on the few questions that actually change what happens next.

2. Immune Effector Cell Therapies: A Brief Orientation

2.1. CAR T-Cell Products

A CAR is a synthetic receptor that combines an extracellular antigen-binding domain, a transmembrane segment, and intracellular signalling domains, typically CD3-zeta paired with a costimulatory module, either CD28 or 4-1BB, that shapes the kinetics and intensity of activation [9]. CD28-based constructs tend to expand rapidly and produce earlier, more intense toxicity, whereas 4-1BB-based constructs expand more gradually. Several products are in wide clinical use. For B-cell malignancies these comprise tisagenlecleucel [3,10], axicabtagene ciloleucel [2], brexucabtagene autoleucel [11], and lisocabtagene maraleucel [12], all directed at CD19. For multiple myeloma, idecabtagene vicleucel [13] and ciltacabtagene autoleucel [14] target B-cell maturation antigen (BCMA). This list reflects agents approved at the time of writing; the regulatory landscape moves quickly, and the inventory available in any given country should be assumed to change. Use has also expanded from heavily pretreated patients toward earlier lines, including the second-line setting for large B-cell lymphoma [15], which enlarges the population at risk of presenting acutely.

Toxicity differs by product and by construct. In its pivotal study, axicabtagene ciloleucel, a CD28 construct, produced CRS in 93% of patients, grade 3 or higher in 13%, with neurological events in 64%, grade 3 or higher in 28% [2]. Lisocabtagene maraleucel, a 4-1BB construct with a defined CD4 to CD8 ratio, produced lower rates, with CRS in 42%, grade 3 or higher in 2%, and neurological events in 30%, grade 3 or higher in 10% [12]. The BCMA products generate frequent but usually low-grade CRS; idecabtagene vicleucel produced CRS in 84%, grade 3 or higher in only 5% [13].

These numbers come with a caveat that matters at the bedside. They were generated in an early era, before earlier intervention and prophylaxis became routine, and they read worse than current practice warrants. Programmes now move sooner to corticosteroids and tocilizumab, and some give scheduled prophylaxis, so contemporary severe-toxicity rates sit well below the pivotal figures. In a dedicated safety cohort of axicabtagene ciloleucel, stepping in earlier with corticosteroids cut severe CRS and severe neurotoxicity without blunting efficacy [16], and prophylactic tocilizumab lowers severe CRS while, contrary to early fears, adding no measurable infection risk [17]. For the emergency physician this cuts both ways. The headline percentages overstate what a contemporary patient is likely to be carrying, yet severe events still happen, and the patient in front of the clinician may already have received immunomodulation that erases the textbook fever and flattens the classic picture.

2.2. Bispecific T-Cell Engagers

Bispecific agents are off-the-shelf molecules that require neither apheresis nor manufacturing. Blinatumomab (CD19 by CD3) is given as a continuous intravenous infusion for B-cell precursor ALL [4]. A newer generation is dosed subcutaneously or by short infusion with stepwise escalation designed to limit CRS. For lymphoma, glofitamab [18], epcoritamab [19], and mosunetuzumab [20] target CD20 by CD3. For myeloma, teclistamab [5] and elranatamab [21] target BCMA by CD3, and talquetamab targets GPRC5D by CD3 [22]. Tarlatamab, a delta-like ligand 3 (DLL3) by CD3 engager, was the first molecule of this class approved for a solid tumour, extensive-stage small-cell lung cancer [23]. That indication is directly relevant to the ED, because the affected population is large, frequently comorbid, and dispersed across general hospitals that rarely encounter cellular therapy.

Bispecific agents generally produce lower-grade CRS than CD28-based CAR T-cells, concentrated around the step-up and first full doses of the first cycle. Teclistamab produced CRS in 72% of patients, grade 3 or higher in less than 1% [5]. Glofitamab produced CRS in 63%, grade 3 or higher in roughly 4% [18]. Tarlatamab produced CRS in approximately half of recipients, predominantly grade 1 to 2; updated safety analyses from the DeLLphi-301 programme reported CRS in 53% of patients and neurological events, including ICANS, in around 10%, with most CRS confined to the first or second dose and managed with antipyretics, fluids, and glucocorticoids [23,24]. Neurological events occur with bispecific therapy but are less frequent than with CD19 CAR T-cells. The important caveat is that bispecific therapy is often delivered closer to home, so a higher proportion of any given event may first be assessed outside the treating centre.

Across all of these products, CRS and ICANS are graded identically using the ASTCT consensus, and management follows shared principles articulated in the ASCO guideline and in the joint European Society for Blood and Marrow Transplantation and European Hematology Association recommendations [6,7,25]. Representative products and their reported toxicity rates are summarised in **Table 1**.

Table 1. Representative immune effector cell therapies and reported cytokine release syndrome and neurological toxicity rates from pivotal or updated trials.

Product	Class and Target	Format/Costim.	Main Indication	CRS, Any (Grade 3+)	Neurological/ICANS, Any (Grade 3+)	Ref.
Axicabtagene ciloleucel	CD19 CAR	CD28	Large B-cell lymphoma	93% (13%)	64% (28%)	Neelapu et al. [2]
Lisocabtagene maraleucel	CD19 CAR	4-1BB	Large B-cell lymphoma	42% (2%)	30% (10%)	Abramson et al. [12]
Idecabtagene vicleucel	BCMA CAR	4-1BB	Multiple myeloma	84% (5%)	Low grade, infrequent	Munshi et al. [13]
Teclistamab	BCMA × CD3 bispecific	Subcutaneous, step-up	Multiple myeloma	72% (<1%)	Lower than CD19 CAR T	Moreau et al. [5]
Glofitamab	CD20 × CD3 bispecific	Intravenous, step-up	Large B-cell lymphoma	63% (~4%)	Lower than CD19 CAR T	Dickinson et al. [18]
Tarlatamab	DLL3 × CD3 bispecific	Intravenous, step-up	Extensive-stage SCLC	~53% (mostly G1–2)	~10%	Ahn et al. [23], Sands et al. [24]

Note: Representative agents for which CRS and neurological event rates are reported in the cited pivotal or updated trials. Rates are not directly comparable across products because grading criteria, monitoring intensity, prophylaxis use, and patient populations differ between studies, and most figures derive from early-era management; contemporary rates with prophylactic or pre-emptive strategies are generally lower (see Section 2.1). BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DLL3, delta-like ligand 3; G, grade; ICANS, immune effector cell-associated neurotoxicity syndrome; SCLC, small-cell lung cancer.

3. Shared Pathophysiology

CRS is what a self-amplifying inflammatory loop looks like in a patient. When the engineered or redirected T-cell locks onto its target, it fires, releasing interferon-gamma and tumour necrosis factor. Those signals rouse the nearby myeloid cells, the macrophages and monocytes, which answer with a flood of interleukin-6 (IL-6), interleukin-1 (IL-1), and nitric oxide. The first hard evidence came from animal models, which showed that monocyte-derived IL-6 and IL-1 drive the syndrome and that blocking IL-1 heads off both CRS and neurotoxicity, the rationale behind the drugs now reached for in the clinic [8,26,27].

That model has since been tested in patients rather than only in mice, and the translation has held. A phase 2 trial of prophylactic subcutaneous anakinra, an IL-1 receptor antagonist, in recipients of commercial anti-CD19

CAR T-cells reduced the rate of severe ICANS to roughly 10% in a population in which historical rates exceed 30%, without compromising response [28]. Single-cell and biomarker analyses of patients who developed breakthrough toxicity despite anakinra prophylaxis have refined the picture further, indicating that once-daily dosing is often insufficient to abolish the myeloid-driven inflammatory programme and helping to explain why intensified or risk-adapted schedules perform better [29]. These human data support, and partly recalibrate, the original murine framework, and they have moved IL-1 blockade from a mechanistic curiosity to a practical option in refractory disease. A complementary literature reframes the cytokine storm itself not as a uniform pathological overshoot but as a context-dependent immune response whose intensity reflects disease burden, target density, and host factors, a useful corrective when judging how aggressively to immunosuppress an individual patient [30].

IL-6 remains the principal therapeutic target in CRS, less because it is mechanistically superior than because tocilizumab, an anti-IL-6 receptor antibody already in wide rheumatological use, was readily available and effective. ICANS is mechanistically distinct from CRS, although the two frequently coincide. Current evidence implicates endothelial activation and disruption of the blood-brain barrier, which allows inflammatory cytokines and cellular infiltrate to reach the central nervous system; elevated cerebrospinal fluid protein, raised cytokine concentrations, and microvascular changes have all been documented [31,32]. This biology explains a point that recurs throughout management: tocilizumab, which does not cross the blood-brain barrier efficiently and may transiently raise central IL-6 concentrations, is effective for CRS but not for isolated ICANS, where corticosteroids are the mainstay [6,25].

Risk of severe toxicity rises with high disease burden, higher infused cell dose, CD28 costimulation, and the intensity of lymphodepletion [32–34]. The earliest framework for the diagnosis and management of these toxicities, which predates the ASTCT consensus, came from single-institution experience and remains a useful reference for the underlying concepts [32,35].

4. Cytokine Release Syndrome

CRS almost always begins with fever, which is the cardinal and usually the first sign. With CAR T-cells the median onset is two to three days after infusion, ranging from the day of infusion to roughly two weeks; with bispecific agents, onset clusters around the step-up doses of the first cycle [6,8,35]. Beyond fever, the syndrome progresses through hypotension and hypoxia and may extend to capillary leak, coagulopathy, hepatic and renal dysfunction, and cardiovascular collapse. The ASTCT consensus grades severity by the presence of fever and the intensity of support required for hypotension and hypoxia, deliberately excluding laboratory values and organ-specific findings from the grade itself (**Table 2**) [6].

Table 2. ASTCT consensus grading of cytokine release syndrome and corresponding acute management.

Grade	Hypotension	Hypoxia	Acute Management
1	None	None	Fever present. Antipyretics, fluids, full infection work-up; tocilizumab if prolonged or comorbid
2	Not requiring vasopressors	Low-flow nasal cannula (≤6 L/min) or blow-by	Tocilizumab 8 mg/kg IV (max 800 mg), repeatable; add corticosteroid if no response
3	One vasopressor (± vasopressin)	High-flow cannula (>6 L/min), facemask, or non-rebreather	ICU admission, vasopressors, tocilizumab plus corticosteroids
4	Multiple vasopressors (excluding vasopressin)	Positive pressure (CPAP, BiPAP, intubation)	ICU, organ support, tocilizumab plus high-dose corticosteroids; consider anakinra if refractory

Note: Fever (temperature ≥38 °C) is required for grade 1; once antipyretic or anti-cytokine therapy has been given, grade is driven by hypotension and hypoxia. Grade reflects the more severe of the hypotension and hypoxia columns. BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; ICU, intensive care unit; IL, interleukin; IV, intravenous. Adapted from Lee et al. [6].

One detail catches out the unwary. Once antipyretics or anti-cytokine therapy have been given, the fever can disappear, and grading then turns on hypotension and hypoxia alone [6]. A patient treated with tocilizumab at the referral centre, then deteriorating at home, can reach the ED entirely afebrile yet physiologically in grade 3. Consider a concrete case. A 64-year-old man with multiple myeloma receives a step-up dose of a BCMA bispecific and spikes to 39 °C six hours later; he is given tocilizumab and paracetamol, watched overnight, and sent home. The next afternoon he arrives at a community ED, normothermic, with a systolic pressure of 84 mmHg and a new oxygen requirement. The missing fever is falsely reassuring. By the ASTCT rules this is grade 3 CRS until proven otherwise, and the earlier tocilizumab neither rules out the diagnosis nor removes the need for vasopressors, a further dose

of anti-cytokine therapy, and critical care. Fixating on the thermometer is the single commonest reason the grade is called too low.

Initial assessment mirrors the sepsis pathway, because the two are clinically indistinguishable at the bedside and frequently coexist. Blood cultures, lactate, complete blood count, comprehensive metabolic panel, coagulation studies, C-reactive protein, and, where available, ferritin should be obtained, alongside chest imaging and a focused search for a source of infection. Empirical broad-spectrum antibiotics are appropriate in any febrile immune effector cell recipient until infection is excluded, given the profound immunosuppression of this population [7,36].

Management escalates with grade. Grade 1, fever alone, is managed with antipyretics, fluids, and the infection work-up described above; tocilizumab is considered for fever that is prolonged or accompanied by significant comorbidity. Grade 2, hypotension not requiring vasopressors or hypoxia requiring low-flow oxygen, warrants tocilizumab 8 mg/kg intravenously to a maximum of 800 mg, which may be repeated every eight hours to a usual limit of three to four doses in 24 h, together with intravenous fluids and supplemental oxygen. Corticosteroids, typically dexamethasone, are added when the response to tocilizumab is inadequate. Grade 3, the need for a single vasopressor or high-flow oxygen, and grade 4, multiple vasopressors or positive-pressure ventilation, require admission to an intensive care setting, vasopressor support, anti-IL-6 therapy combined with corticosteroids, and consideration of the IL-1 receptor antagonist anakinra in refractory cases [6,7,25,28,29].

Supportive care underpins every grade. Fluid resuscitation should be judicious, since capillary leak in higher-grade CRS makes these patients prone to pulmonary oedema, and a strategy that pairs measured boluses with early vasopressor support is often preferable to large-volume loading. Continuous or frequent monitoring of blood pressure, oxygen saturation, and temperature is warranted once grade 2 is reached, with a low threshold for cardiac monitoring given the risk of arrhythmia and, rarely, stress cardiomyopathy. Urine output, lactate clearance, and the coagulation profile track the adequacy of resuscitation and the emergence of complications. These are familiar acute-care skills, and their familiarity is the point: most of what a febrile, hypotensive immune effector cell recipient needs in the first hour is competent resuscitation, delivered while the specific anti-cytokine decision is made.

Two practical tensions deserve mention. First, corticosteroids, although central to higher-grade events, are not without cost: their early or prolonged use has been associated in some analyses with inferior CAR T-cell expansion and shorter survival, so the lowest effective exposure, rather than reflexive escalation, is the goal once the acute danger is controlled [37]. Second, the timing of escalation has shifted earlier over successive cohorts, on the principle that brief, decisive intervention prevents the deep physiological deficits that are harder to reverse [16]. Throughout, the treating cellular therapy centre should be contacted as early as possible, because product-specific protocols and the patient's prior course materially affect these decisions.

5. Immune Effector Cell-Associated Neurotoxicity Syndrome

ICANS typically follows CRS, with a median onset of four to ten days after CAR T-cell infusion, although it can appear later, can occur without preceding CRS, and may follow a biphasic course [6,31,32]. The earliest signs are often subtle: deteriorating handwriting, word-finding difficulty, hesitant speech, tremor, or mild disorientation. Progression can be rapid, through expressive aphasia, depressed consciousness, and seizures, to cerebral oedema in the most severe cases. Focal deficits are uncommon and should prompt a search for an alternative cause such as stroke or central nervous system infection.

Grading combines a structured cognitive assessment with level of consciousness, seizure activity, motor findings, and signs of raised intracranial pressure (**Table 3**). The cognitive component is the Immune Effector Cell-associated Encephalopathy (ICE) score, a ten-point bedside instrument assessing orientation, naming, command-following, writing, and attention [6]. The ICE score is easily performed in the ED and should be documented serially, because a falling score is the most sensitive early indicator of progression.

Management is built on corticosteroids rather than anti-IL-6 therapy, reflecting the pathophysiology described above. Grade 1 is managed supportively, with corticosteroids considered. Grade 2 and higher warrant dexamethasone 10 mg intravenously every six hours, or equivalent, escalating to high-dose methylprednisolone, for example 1 g daily, for grade 4 disease. Seizures are treated with benzodiazepines and levetiracetam, and some centres use levetiracetam as prophylaxis. Signs of raised intracranial pressure or cerebral oedema, including a Cushing response, papilloedema, or decerebrate posturing, constitute a neurological emergency requiring high-dose corticosteroids, hyperosmolar therapy, intensive care, and urgent neurosurgical and neurological consultation. Tocilizumab is added

only when CRS coexists; it has no role in isolated ICANS [6,7,25]. Neuroimaging and, where safe, lumbar puncture help exclude alternative diagnoses, and electroencephalography is indicated when non-convulsive seizures are suspected.

Table 3. ASTCT consensus grading of immune effector cell-associated neurotoxicity syndrome (ICANS) and corresponding acute management.

Grade	ICE Score	Consciousness	Seizure/Motor/ICP	Acute Management
1	7 to 9	Awakens spontaneously	None	Supportive; consider corticosteroids
2	3 to 6	Awakens to voice	None	Dexamethasone 10 mg IV q6h; ICU consideration
3	0 to 2	Awakens to tactile stimulus	Self-limited seizure; focal or local oedema on imaging	Dexamethasone; ICU; EEG if seizure suspected
4	0 (unarousable)	Unarousable or requires vigorous stimulus	Prolonged or repetitive seizures; deep weakness; diffuse cerebral oedema; raised ICP	High-dose methylprednisolone; ICU; hyperosmolar therapy; neurosurgery

Note: Final grade is determined by the most severe domain. The ICE score (maximum 10) assesses orientation to year, month, city, and hospital (4 points), naming of three objects (3 points), following one command (1 point), writing a sentence (1 point), and counting backward from 100 by tens (1 point). EEG, electroencephalography; ICP, intracranial pressure; ICU, intensive care unit; IV, intravenous. Adapted from Lee et al. [6].

6. The Diagnostic Crossroads: Distinguishing Toxicity from Sepsis

The hardest problem in the ED is also the most elementary: at first contact, CRS and severe infection look identical, and they frequently run together. These patients are deeply immunosuppressed. Lymphodepleting chemotherapy, the loss of normal B-cells, hypogammaglobulinaemia, long stretches of neutropenia, and corticosteroid exposure stack into a sustained vulnerability to bacterial, viral, and fungal infection [36]. Telling toxicity from sepsis does not change the opening move, because both demand cultures, empirical broad-spectrum antibiotics, and haemodynamic support without delay. The distinction earns its keep only at the next fork, when the question becomes whether to add tocilizumab and corticosteroids, which treat CRS but carry their own infectious price.

A few features tilt the odds without settling them. Timing helps: a syndrome that erupts in the first days after a CAR T-cell infusion, or around the step-up doses of a bispecific, is more likely to be toxicity than coincidental infection. A named pathogen pulls toward infection but never excludes concurrent CRS. C-reactive protein and ferritin usually climb in CRS, yet neither is specific. The safest stance is to refuse the either/or. Cover for infection, and grade and treat CRS at the same time, in conversation with the cellular therapy centre, rather than stalling on one path while trying to prove the other.

A few additional manoeuvres add value without delaying treatment. Serial rather than single measurements are more informative: a C-reactive protein or ferritin that is high but stable behaves differently from one rising steeply over hours, and the trend often clarifies whether an inflammatory process is accelerating. Repeating the vital signs and the lactate after initial resuscitation gives an early read on trajectory. Where the patient or family can provide it, the treating centre's record of the prior toxicity course is among the most useful pieces of information available in the ED, because a patient who developed grade 3 CRS with a previous dose is more likely to do so again, whereas one who tolerated several cycles uneventfully shifts the prior probability toward infection. None of these steps should hold up cultures, antibiotics, or anti-cytokine therapy when the clinical picture already warrants them; they refine an assessment that proceeds in parallel with treatment.

7. Other Immune Effector Cell Toxicities Relevant to Acute Care

7.1. Immune Effector Cell-Associated Haemophagocytic Lymphohistiocytosis-Like Syndrome

A subset of patients develops a hyperinflammatory state resembling haemophagocytic lymphohistiocytosis, now termed immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome (IEC-HS). It is characterised by rapidly rising ferritin, cytopenias, hepatic dysfunction, coagulopathy with hypofibrinogenaemia, and sometimes haemophagocytosis on marrow examination, typically emerging as CRS appears to be resolving [38]. The ED clue is a markedly elevated ferritin out of proportion to the clinical CRS grade. No single threshold is diagnostic, but a ferritin that climbs steeply and exceeds roughly 10,000 ng/mL, particularly when paired with a falling fibrinogen, rising triglycerides, transaminitis, and worsening cytopenias, should raise the possibility directly; values in the tens of thousands are common once the syndrome is established, and the trajectory matters as much as any single number.

Management, coordinated with haematology, may include corticosteroids, anakinra, and, in refractory cases, agents such as etoposide. The entity is important to recognise because it is readily mistaken for sepsis or for ongoing CRS.

7.2. Immune Effector Cell-Associated Haematotoxicity

Cytopenias after immune effector cell therapy are common, frequently severe, and often biphasic or prolonged well beyond the period of lymphodepletion, a pattern captured by the term immune effector cell-associated haematotoxicity (ICAHT) and graded by joint European consensus [39]. The ED relevance is twofold: neutropenia predisposes to the infections discussed above, and thrombocytopenia or anaemia may present as bleeding or symptomatic anaemia. A new or worsening cytopenia in a recently treated patient warrants a blood film, haematinics, and early haematology contact rather than reflexive attribution to chemotherapy.

7.3. B-Cell Aplasia, Hypogammaglobulinaemia and Infection

CD19 and BCMA-directed therapies deplete normal B-cells and plasma cells along with the malignant clone, producing prolonged B-cell aplasia and hypogammaglobulinaemia that can persist for months to years [40]. This underlies a durable risk of infection, including encapsulated bacteria and respiratory viruses, and supports a low threshold for investigation and treatment of suspected infection in the ED. Many patients receive immunoglobulin replacement and antimicrobial prophylaxis; a lapse in either, easily uncovered on history, can precipitate the presentation [41].

7.4. Tumour Lysis and On-Target Effects

Rapid tumour killing can precipitate tumour lysis syndrome, particularly in high-burden disease, with the attendant risks of hyperkalaemia, hyperphosphataemia, hyperuricaemia, and acute kidney injury that the ED manages by standard protocols. On-target, off-tumour effects depend on antigen distribution; the GPRC5D-directed agent talquetamab, for example, produces characteristic skin, nail, and oral toxicity that, while rarely an emergency, can prompt presentation and should not be mistaken for infection [22].

8. Particular Considerations for Bispecific Antibodies

Bispecific agents differ from CAR T-cells in ways that matter to the ED. Because they are administered repeatedly and often closer to home, the window of risk is longer and more dispersed than the defined post-infusion period of a single CAR T-cell treatment. CRS clusters around the step-up doses and the first full dose of the first cycle, so a patient presenting with fever within a day or two of an early dose deserves heightened suspicion, whereas events become uncommon in later cycles [5,18,19]. Many programmes hospitalise patients for the initial step-up doses, but the trend toward outpatient and subcutaneous administration means that the first medical contact for an early reaction may be the ED.

Tarlatamab deserves a paragraph of its own, because it drags CRS and neurological toxicity out of haematology and into solid-tumour oncology, and with them into general EDs that almost never see cellular therapy [23]. A patient with small-cell lung cancer who presents with fever, confusion, or hypotension days after a tarlatamab dose may not be recognised as having received a T-cell engaging therapy unless someone asks directly. The timing resembles that of the lymphoma and myeloma bispecifics rather than that of CAR T-cells: events cluster after the first and second doses, with onset and time to intervention usually measured in hours to a day or two from dosing, and severe events are uncommon [24]. What matters in the history is not simply whether tarlatamab was given but exactly when the last dose fell, since a presentation deep into an established cycle carries a different prior probability than one in the opening days of treatment. The principles of grading, infection exclusion, and early contact with the treating service hold unchanged.

Two further features of bispecific therapy bear on acute care. First, treatment is frequently interrupted and then re-initiated, for toxicity, infection, or logistics, and many protocols require the step-up sequence to be repeated when the gap exceeds a defined interval. A patient who has tolerated months of maintenance dosing can therefore re-enter a high-risk window after a pause, so the ED history should establish not only the date of the last dose but whether that dose was a re-escalation. Second, prolonged or indefinite dosing sustains the immunosuppression, hypogammaglobulinaemia, and infection risk discussed earlier for far longer than the defined post-infusion period

of a single CAR T-cell treatment, which means that a bispecific recipient presenting with fever months into therapy still warrants the full infective work-up rather than reassurance based on the time elapsed since initiation.

9. A Practical Framework for the Emergency Department

Four habits, made automatic, catch almost every case. The first is to ask. Put the question to every cancer patient directly: have you had CAR T-cell therapy, or a bispecific or T-cell engaging antibody, and when was the last dose? The generic question about chemotherapy will miss it. The second is to respect the fever. In a recently treated patient, treat fever as an emergency until both infection and CRS have been dealt with, because the patient who looks deceptively well at triage is the one who deteriorates sharply soon after. The third is to watch the writing and the speech. Perform an ICE score in any treated patient who is confused, dysphasic, or behaving out of character, and repeat it, since a faltering hand or a hesitant sentence is often the first crack of neurotoxicity to appear. The fourth is to phone early. Contact the treating cellular therapy centre the moment the suspicion forms, because the product-specific protocol, the patient's previous toxicity course, and the local supply of tocilizumab and intensive care all bend the plan [7,25]. **Figure 1** draws these steps together.

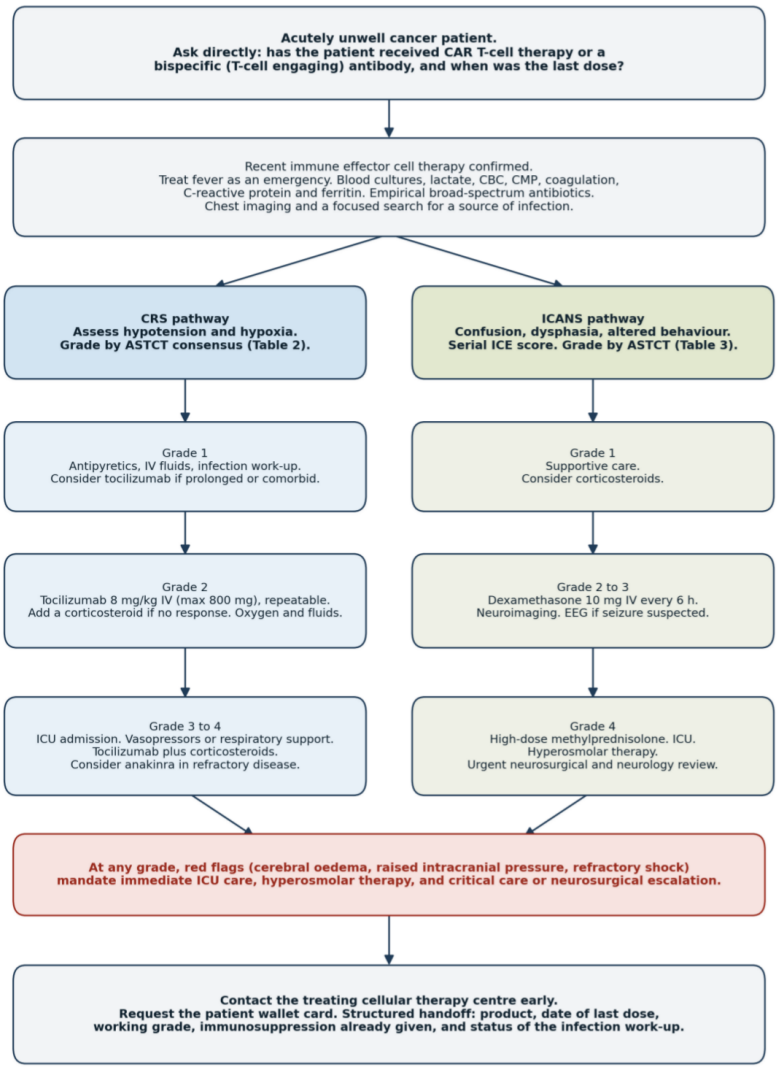

Figure 1. Emergency department evaluation and management of suspected cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Note: The pathway begins with direct questioning about CAR T-cell or bispecific (T-cell engaging) therapy and the date of the last dose, proceeds to parallel grading and treatment of CRS and ICANS by the ASTCT consensus, and emphasises early contact with the treating cellular therapy centre. ASTCT, American Society of Transplantation and Cellular Therapy; CBC, complete blood count; CMP, comprehensive metabolic panel; EEG, electroencephalography; ICE, immune effector cell-associated encephalopathy; ICU, intensive care unit; IV, intravenous.

Many centres issue patients a wallet card or equivalent documentation identifying the product received, the date of the last dose, the toxicities experienced, and a direct contact number for the treating service. When present, this card shortens the diagnostic process considerably, and asking for it should become a reflex in the assessment of any oncology patient who appears acutely unwell [42]. Where tocilizumab is stocked, the ED can initiate treatment for grade 2 or higher CRS without waiting for transfer, provided the decision is coordinated with the treating team. This last point carries an important caveat. Tocilizumab is widely available in hospitals with rheumatology or specialist inpatient services, and its stocking became more common during the period when it was used for severe COVID-19, but availability cannot be assumed. Smaller community and rural EDs, which together account for a large share of the general hospitals this review addresses, may not hold the drug or may stock only limited quantities, and confirming local availability in advance is a worthwhile piece of preparedness. Where tocilizumab is not immediately available, corticosteroids, supportive care, and expedited transfer become the operative plan.

Disposition follows grade. Grade 1 CRS and grade 1 ICANS may be observed, with rapid communication to the treating centre and clear safety-netting, although a low threshold for admission is prudent given the potential for rapid progression. Grade 2 events generally warrant admission. Grade 3 and grade 4 events, and any sign of cerebral oedema, raised intracranial pressure, or refractory shock, require intensive care and, where feasible, transfer to or close coordination with the treating cellular therapy centre. A structured handoff that states the product, the dose timing, the working grade, the immunosuppression already given, the status of the infection work-up, and the planned monitoring saves hours of subsequent uncertainty [6,7].

10. Future Perspectives

The trajectory of this field points toward wider exposure of acute care to immune effector cell toxicities, not narrower. Bispecific approvals are expanding across haematological and, with tarlatamab, solid-tumour indications, and administration continues to move toward subcutaneous dosing, abbreviated monitoring, and outpatient or community-based step-up schedules. As that diffusion continues, a growing fraction of first presentations for CRS and ICANS will occur in EDs without on-site cellular therapy expertise, which makes the operational competencies described here increasingly mainstream rather than specialised.

Several developments are likely to shape practice over the next few years. Prophylactic and pre-emptive immunomodulation, with early tocilizumab, risk-adapted corticosteroids, and IL-1 blockade through anakinra, is moving from trial cohorts toward routine protocols, and the net effect is a population whose severe-toxicity risk is lower but whose presentations are increasingly modified by prior treatment, as the afebrile patient described earlier illustrates. Newer targets and mechanisms, including agents directed at GM-CSF and other myeloid mediators, are under study and may further alter the toxicity profile. Biomarker-guided risk stratification, using early ferritin, C-reactive protein, and cytokine trajectories, may eventually allow more confident separation of CRS from infection and earlier identification of IEC-HS, although none of these is yet a bedside test. Finally, the dispersion of these therapies into general hospitals argues for structured cross-disciplinary pathways, shared between cellular therapy centres and their referring EDs, and for the incorporation of immune effector cell toxicity into emergency medicine training. Standardised wallet cards, accessible product registries, and direct contact lines are simple measures that would shorten the path to correct treatment.

Practical infrastructure will matter as much as new drugs. Remote monitoring during the highest-risk early cycles, using wearable temperature and heart-rate sensors with defined escalation thresholds, is being explored as a way to detect CRS before the patient reaches the ED, and telehealth links between community hospitals and cellular therapy centres can bring subspecialty judgement to the bedside in real time. At the level of the individual department, pre-built order sets that bundle the infection work-up, ASTCT grading prompts, weight-based tocilizumab dosing, and the treating-centre contact pathway reduce the cognitive load of a presentation that most emergency physicians still encounter rarely. Patient-facing education, ensuring that recipients and their families can name the product and carry the relevant documentation, complements these measures and is among the cheapest interventions available.

11. Limitations

This article is a narrative review and carries the limitations of that format. It does not rest on a systematic search or a formal quality appraisal, and selection of the literature, while intended to be representative and current, is inevitably influenced by the authors' judgment. The toxicity rates cited from pivotal and updated trials are not directly comparable across products, because grading definitions, monitoring intensity, prophylaxis use, and patient populations differ between studies, and the accompanying table should be read as indicative rather than as a basis for head-to-head ranking. Much of the management guidance is extrapolated from haematology and cellular therapy consensus rather than from emergency-department evidence, since prospective data generated specifically in the acute-care setting remain scarce. Finally, the field moves quickly: product approvals, prophylaxis strategies, and recommended thresholds are changing, and some specifics will date. The general approach, recognition by direct questioning, grading, parallel treatment of infection and toxicity, and early contact with the treating centre, is expected to remain stable even as particular agents and numbers evolve.

12. Conclusions

Immune effector cell therapies have rewritten the outlook for several cancers that were until recently almost untreatable, and they keep spreading into new diseases, earlier lines, and new places of care. The toxicities that travel with them, chiefly cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, are recognisable and treatable the moment they are considered. The moves that decide the outcome all sit within the reach of an emergency physician: name the therapy, treat fever as an emergency, grade with discipline, cover infection while treating toxicity in parallel, give tocilizumab for cytokine release syndrome and corticosteroids for neurotoxicity, hold anakinra in reserve for refractory disease, and get the treating centre on the telephone early. As these therapies move closer to the community, fluency with their complications is migrating from the specialist unit to the general ED, much as the prompt recognition of sepsis and stroke once did.

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Conflicts of Interest

The authors declare no conflict of interest.

AI Use Statement

During the preparation of this manuscript, the authors used a large language model (Anthropic Claude) to assist with drafting, language refinement, and formatting. No AI tools were used for data analysis or for the interpretation of clinical evidence. All scientific content, clinical recommendations, and references were verified, critically reviewed, and edited by the authors, who take full responsibility for the integrity and accuracy of the work.

Abbreviations

Abbreviation	Full Name
ALL	acute lymphoblastic leukaemia
ASCO	American Society of Clinical Oncology
ASTCT	American Society of Transplantation and Cellular Therapy
BCMA	B-cell maturation antigen
BiPAP	bilevel positive airway pressure
CAR	chimeric antigen receptor
CBC	complete blood count
CMP	comprehensive metabolic panel
CPAP	continuous positive airway pressure
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
DLL3	delta-like ligand 3
EBMT	European Society for Blood and Marrow Transplantation
ED	emergency department
EEG	electroencephalography
EHA	European Hematology Association
ES-SCLC	extensive-stage small-cell lung cancer
GPRC5D	G protein-coupled receptor class C group 5 member D
ICAHT	immune effector cell-associated haematotoxicity
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICP	intracranial pressure
ICU	intensive care unit
IEC-HS	immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome
IL	interleukin
IV	intravenous
LBCL	large B-cell lymphoma
MCL	mantle cell lymphoma

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