Sepsis vs Inflammation Challenges After CART

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Outline

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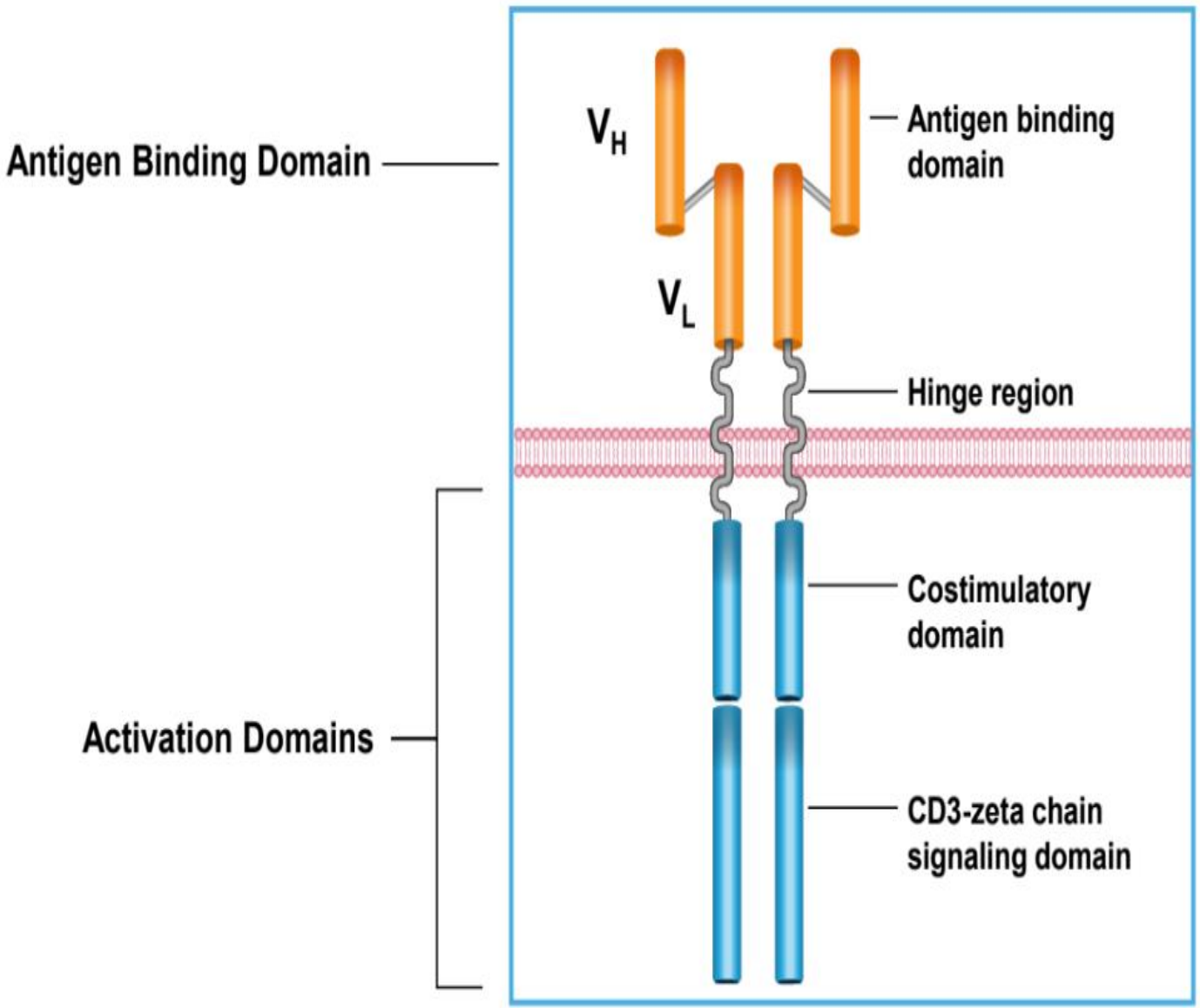
- What is CART
- CRS
- ICANS
- HLH
- B-cell aplasia and hypogammaglobulinemia
- Sepsis/Infections



scFv

Single-chain variable fragment (scFv) bypa MHC antigen presentation, allowing direct activation of T cell by cancer cell antigens

Hinge region

Essential for optimal antigen binding

Costimulatory Domain: CD28 or 4-1BB

Enhances proliferation, cytotoxicity and persistence of CAR T cells

Signaling Domain: CD3ζ chain

Proliferation and activation of CAR T cells
CAR T-cell-mediated killing of tumor cells

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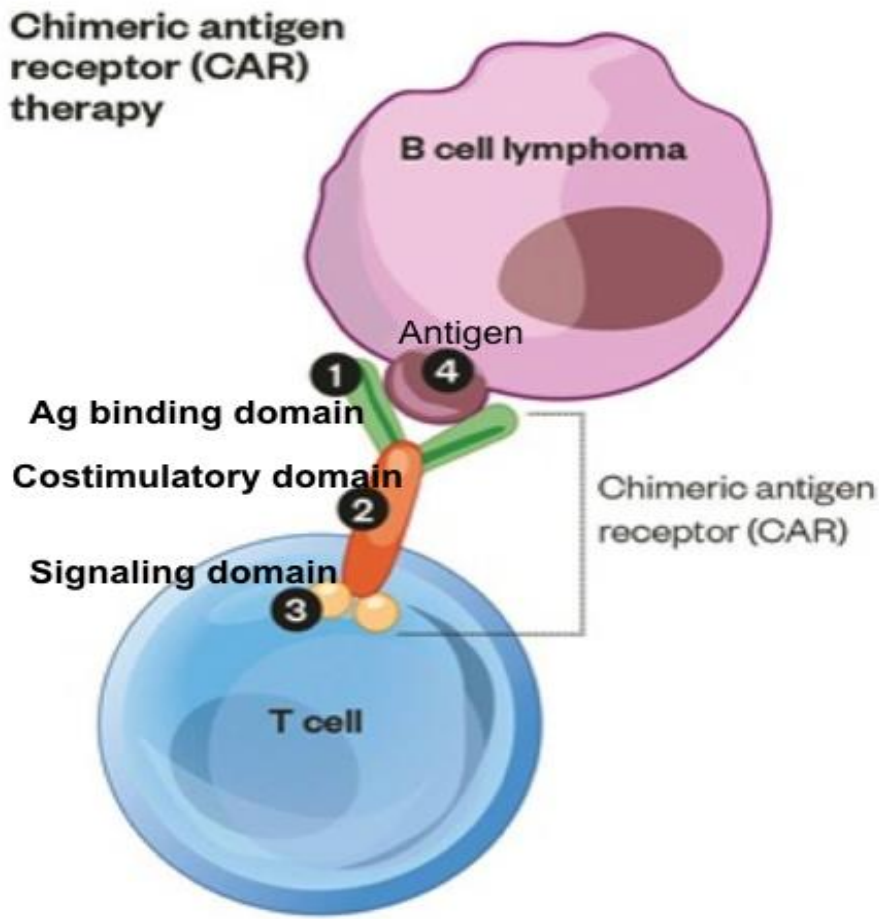

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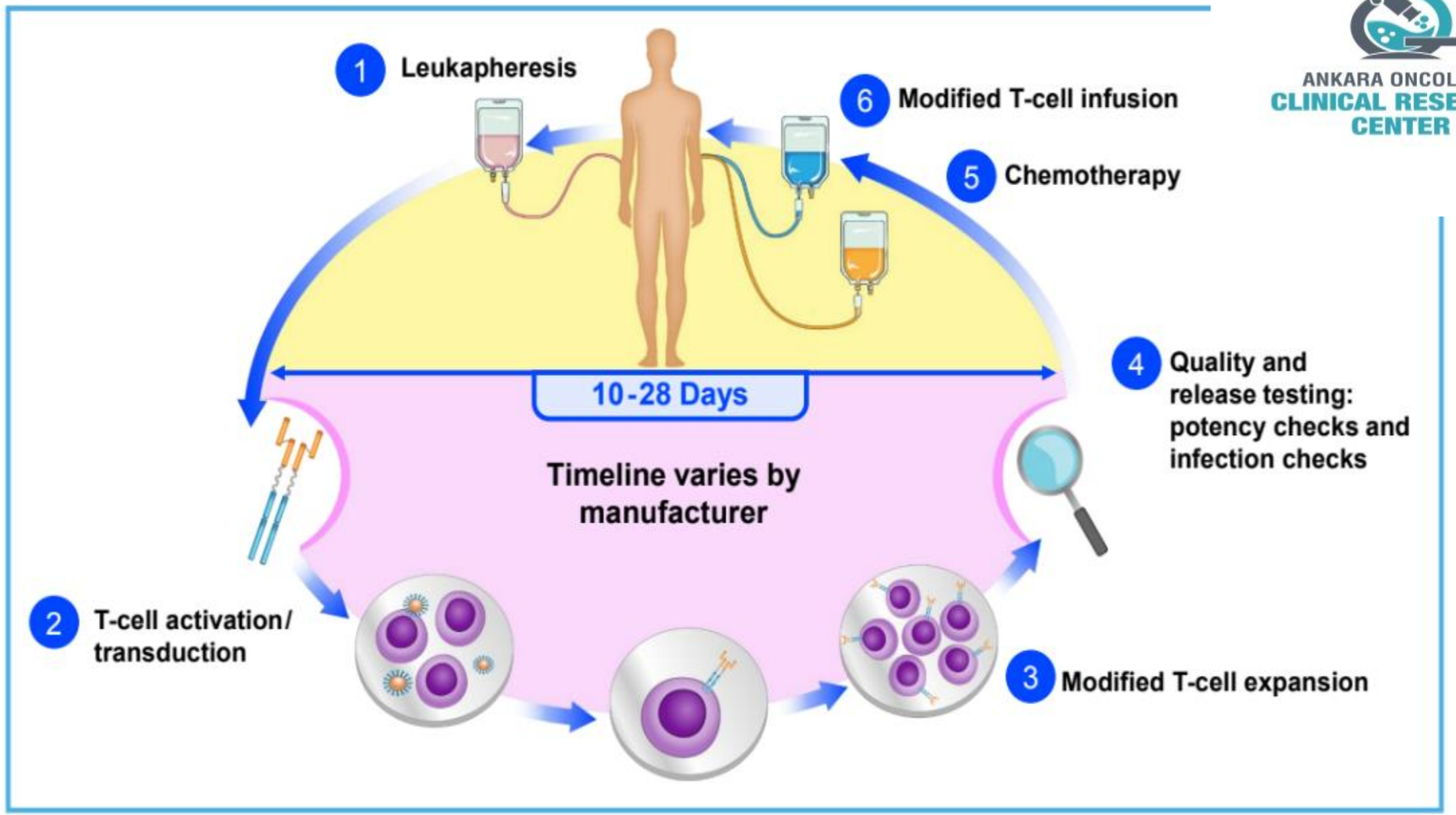

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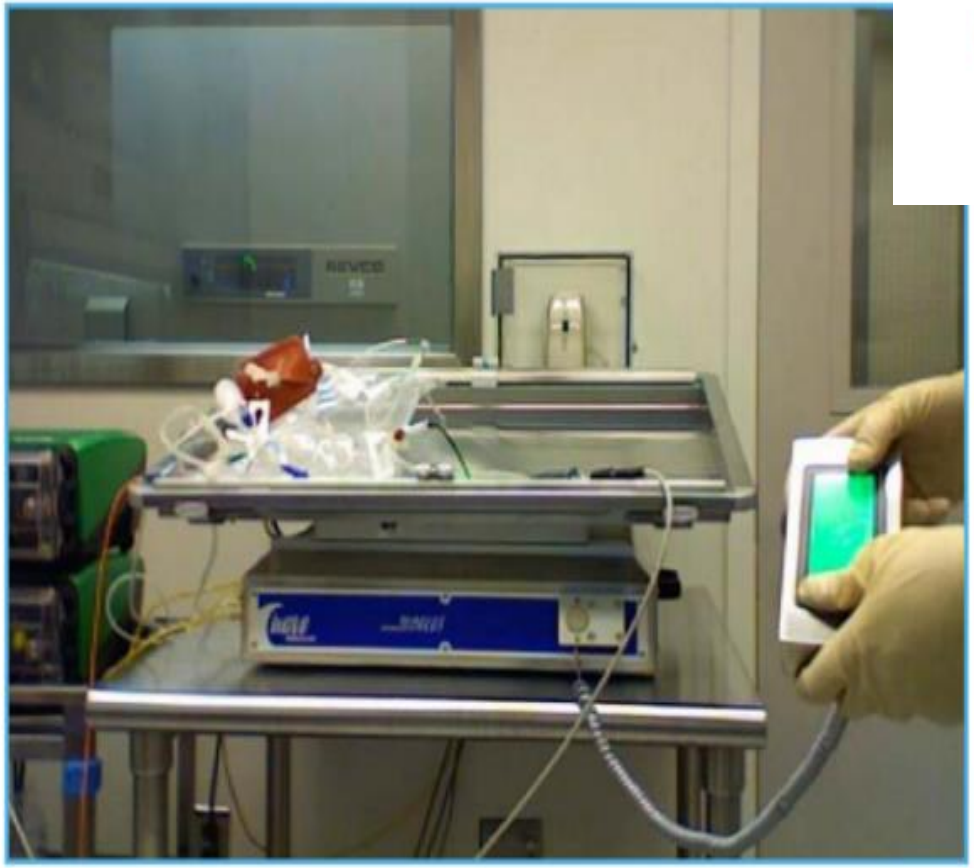
Generation of GMP-grade 19-28z retroviral vector stocks for clinical application



Ex vivo expansion of 19-28z transduced patient T cells under GMP conditions on the Wave® Bioreactor

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Drug	Disease	Trial
Axicabtagene ciloleucel[1,2]	DLBCL	ZUMA-1
	FL	ZUMA-5
Brexucabtagene autoleucel[3]	MCL	ZUMA-2
Ciltacabtagene autoleucel[4]	MM	CARTITUDE-1
Idecabtagene vicleucel[5]	MM	KarMMa
Lisocabtagene maraleucel[6]	DLBCL	TRANSEND NHL 001
Tisagenlecleucel[7,8]	DLBCL	JULIET
	B-ALL	ELIANA

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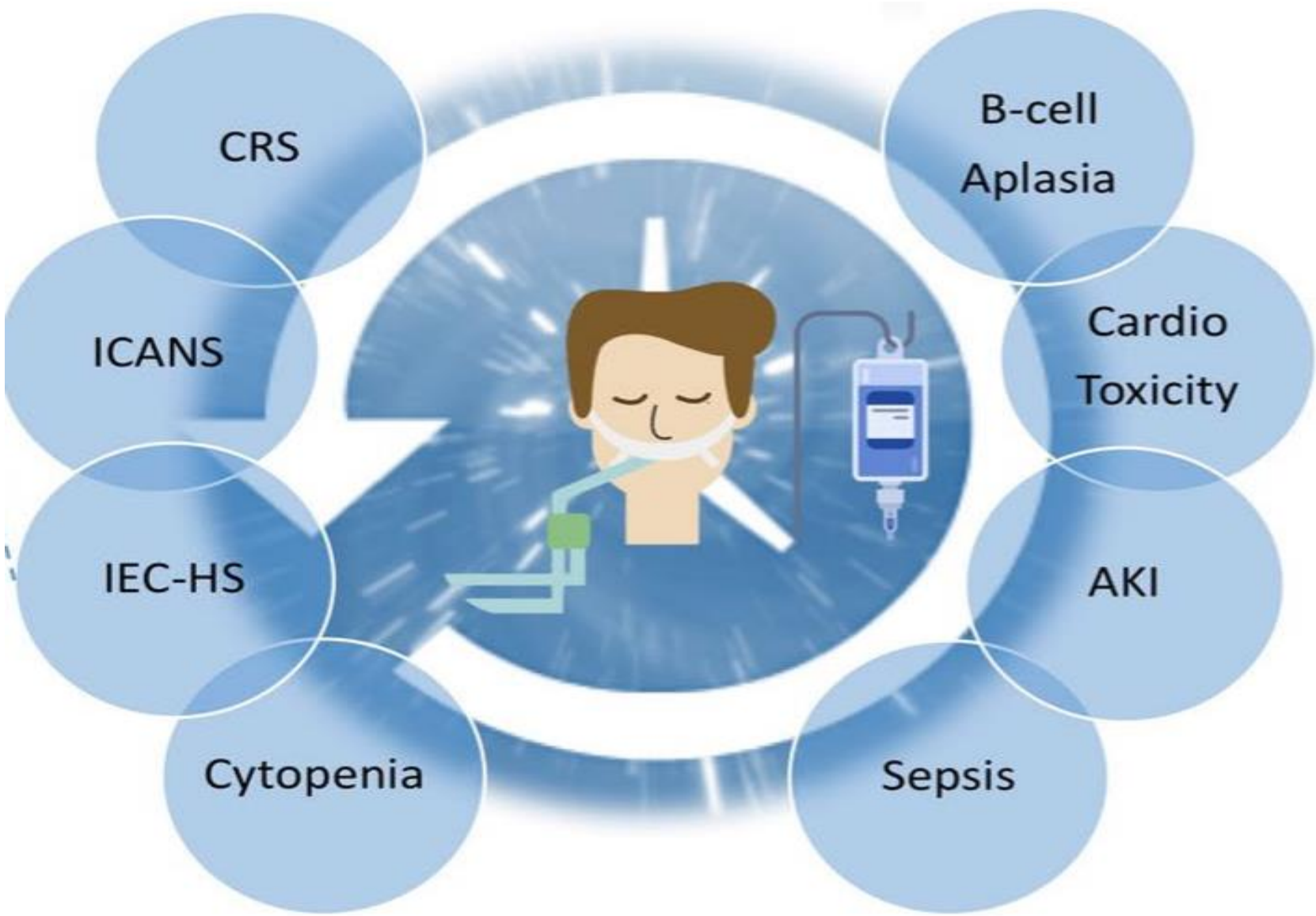

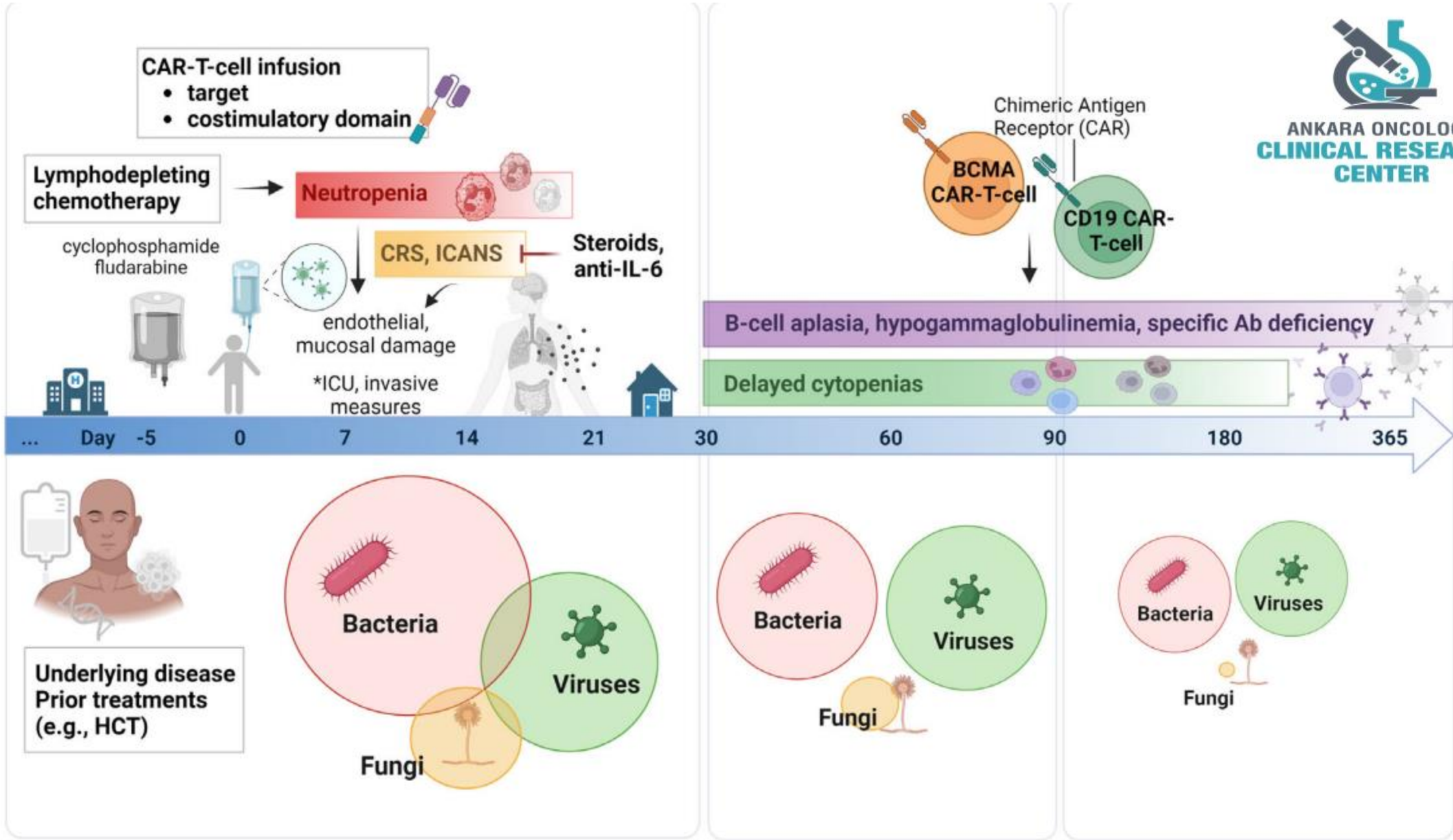

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CRS

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Risk factors: tumor burden, active infection, baseline inflammation, the CAR-T dose and product, and the intensity of lymphodepletion conditioning

- Overall, grade > 2 is reported in 10–30%

CRS Is a Systemic Inflammatory Disease

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Multiple cytokines may be responsible for this circulatory cascade, including interleukins, interferons, tumor necrosis factor, lymphokines, monokines, and chemokines

- Promotion or inhibition of cell growth
- Activation of immune effector cells
- Mediation for destruction of cells targeted by monoclonal antibodies
- Mediation of inflammatory response

CRS is a systemic inflammatory disease with a broad range of mediators and/or clinical indicators (eg, ferritin, CRP)

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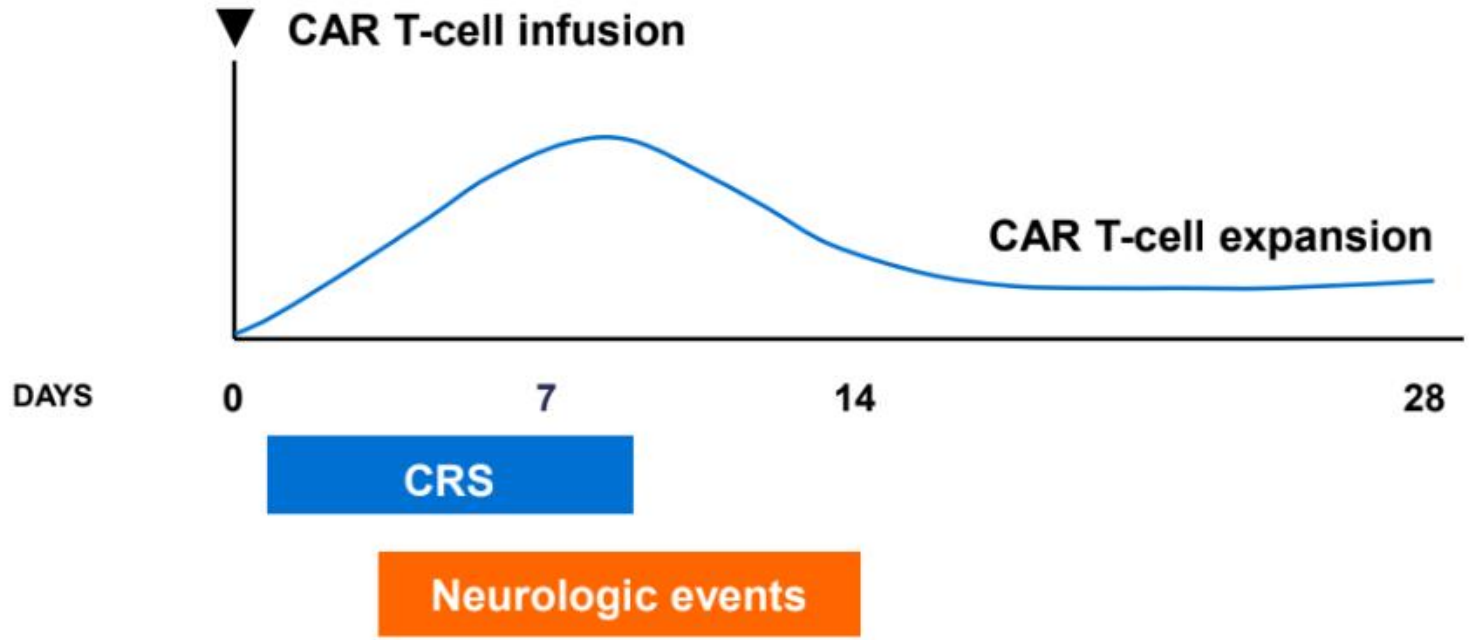

- May occur within minutes or hours but generally appears within days or weeks
- Coincides with maximal T-cell expansion

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CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
With hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or† hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

Grade1	Grade2	Grade3	Grade4

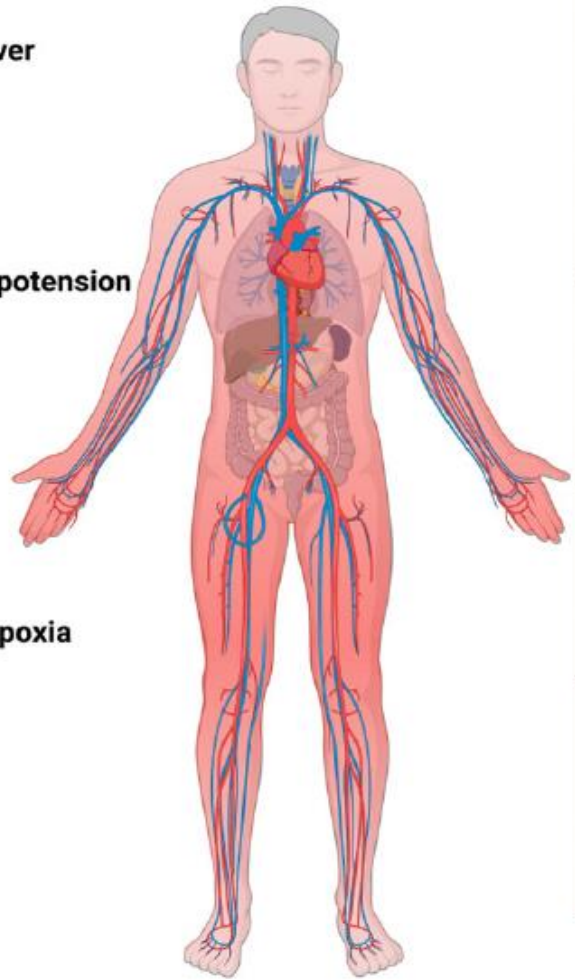
Temperature ≥38°C — **Fever**

with

Hypotension
- No vasopressors
- vasopressor +/- vasopressin
- multiple vasopressors

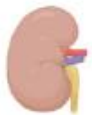
and/or

Hypoxia
- low-flow nasal cannula or blow-by
- high-flow nasal cannula facemask, nonrebreather mask, or Venturi mask
- positive pressure (CPAP, BiPAP)



Cardiovascular:
Tachycardia
Left ventricular systolic dysfunction
QT prolongation
Heart failure

Hepatic and gastrointestinal:
Nausea, vomiting
Diarrhea
Gastrointestinal hemorrhage
Hepatitis
Hepatosplenomegaly
Liver failure



Renal:
Actue kidney injury (AKI)
Renal failure

Hematologic:
Cytopenia
Neutropenia
Thrombocytopenia
Anemia
Coagulopathy
Hypoproteinemia

Musculoskeletal:
Mylagia

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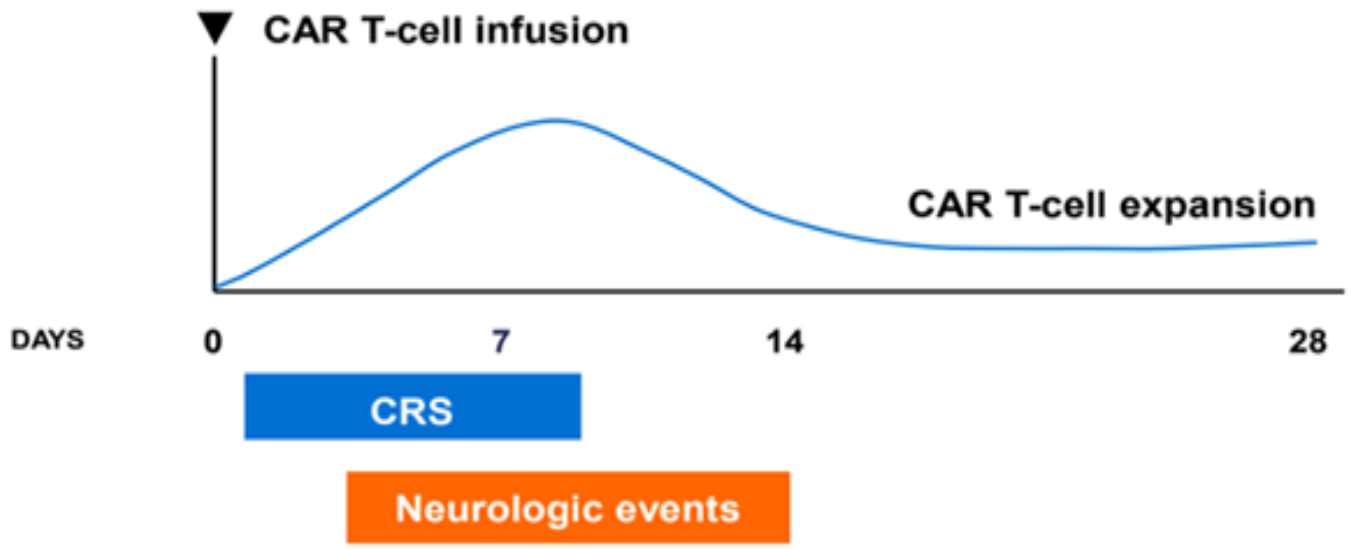
- grade > 2 is reported in 12–30% of cases



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Encephalopathy

Cerebral edema

Headache

Dysphasia

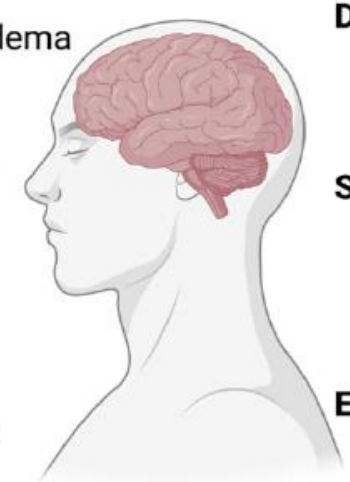
Delirium

Tremor

Ataxia

Myoclonus

Seizures



	Grade1	Grade2	Grade3	Grade4
ICE score	7-9	3-6	0-2	unarousable and unable to perform ICE
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse Stupor or coma
Seizure	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention		Life-threatening prolonged seizure (>5 mins); or Repetitive clinical or electrical seizures without return to baseline in between	
Elevated ICP/cerebral edema	Focal/local edema on neuroimaging		Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad	
Motor findings	Deep focal motor weakness such as hemiparesis or paraparesis			

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Acute

- Concurrent with CRS and high fevers
- Result of elevated cytokines
- Common; some degree of neurotoxicity occurs in nearly all CAR T patients
- Symptoms include decreased attention, confusion, disorientation, delirium, and ataxia
- Effectively resolved with tocilizumab

Delayed

- Occurs within days to weeks following CRS; often on resolution of CRS
- Range of symptoms: confusion, mental status changes, encephalopathy, seizures, hallucinations, aphasia, and coma
- Generally reversible: typical duration ~3 days

Cerebral Edema

- Rare
- Idiosyncratic
- Usually in the acute setting
- Rapid acute onset
- Requires immediate ICU transfer and intervention with mannitol with or without anti-seizure medications
- May be fatal

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Grade1	Grade2	Grade3	Grade4

ICE score

7-9	3-6	0-2	unarousable and unable to perform ICE

ICE		
Orientation:	Orientation to year, month, city, hospital	4 points
Naming:	Ability to name 3 objects (eg, point to clock, pen, button)	3 points
Following Commands:	Ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”)	1 point
Writing:	Ability to write a standard sentence (eg, “Our national bird is the bald eagle”)	1 point
Attention:	Ability to count backwards from 100 by 10	1 point

HLH

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Fulfill 5 of the following clinical/laboratory criteria*:

1. Fever
2. Splenomegaly
   - Cytopenias (at least 2 cell lines) HGB <9; PLT <100,000; ANC <1000
   - Hypertriglyceridemia and/or hypofibrinogenemia
     - Fasting trig >265 mg/dL
     - Fibrinogen <150 mg/L
3. Hemophagocytosis in bone marrow, CSF, or lymph nodes
4. Decreased/absent NK-cell activity*
5. Ferritin >500 µg/L – Diff dx for ferritin >10,000: histiocytic malignancies, adult-onset Still's disease
6. Soluble CD25 >2400 U/mL*

Table 4: Diagnostic criteria of Hemophagocytic lymphohistiocytosis (HLH) / macrophage activation syndrome (MAS) adapted from criteria proposed by the CARTOX Working Group [40].

Diagnostic criteria HLH/MAS
▪ ferritin > 10,000 ng/ml during CRS
AND 2 of the following:
▪ grade ≥ 3 liver toxicity* (increase in levels of bilirubin, aspartate aminotransferase or alanine aminotransferase)
▪ grade ≥ 3 kidney toxicity* (oliguria or increase in serum creatinine)
▪ grade ≥ 3 pulmonary edema*
▪ hemophagocytosis in the bone marrow or other organs

* assessed by Common Terminology Criteria for Adverse Event (CTCAE) version 4.03 [76]

Management Inflammatory Changes

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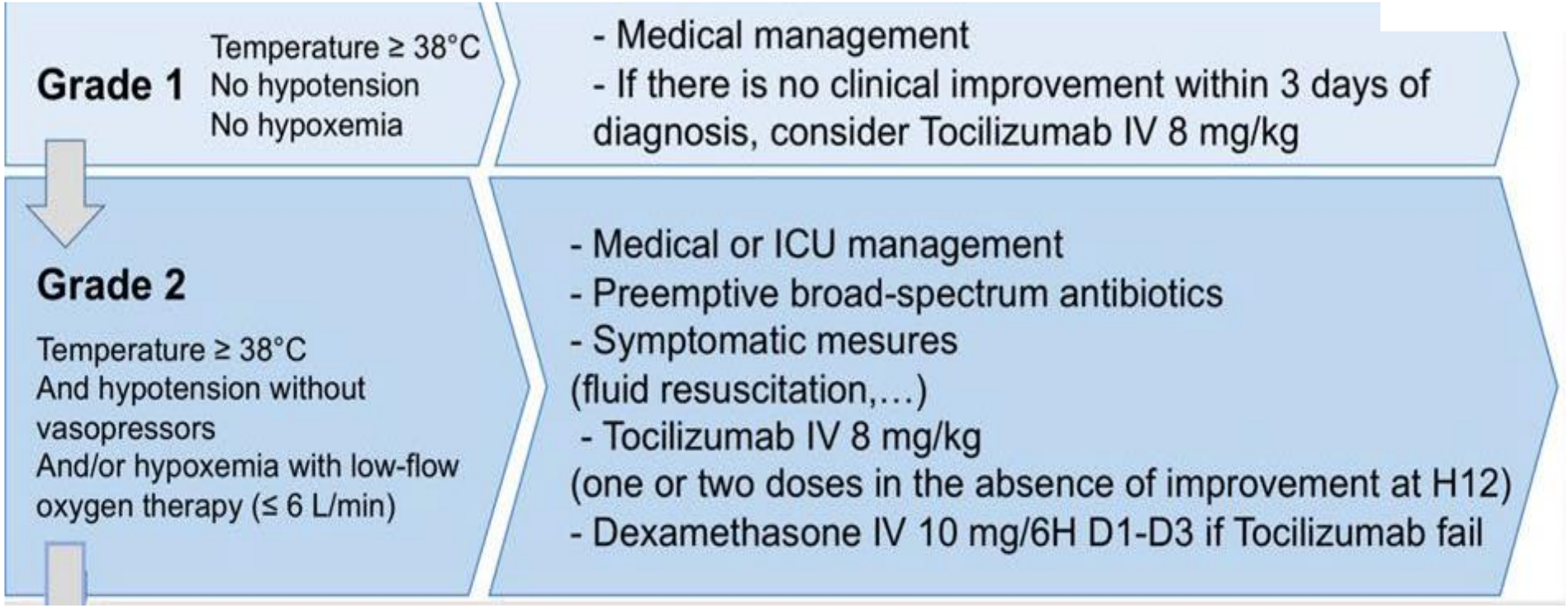
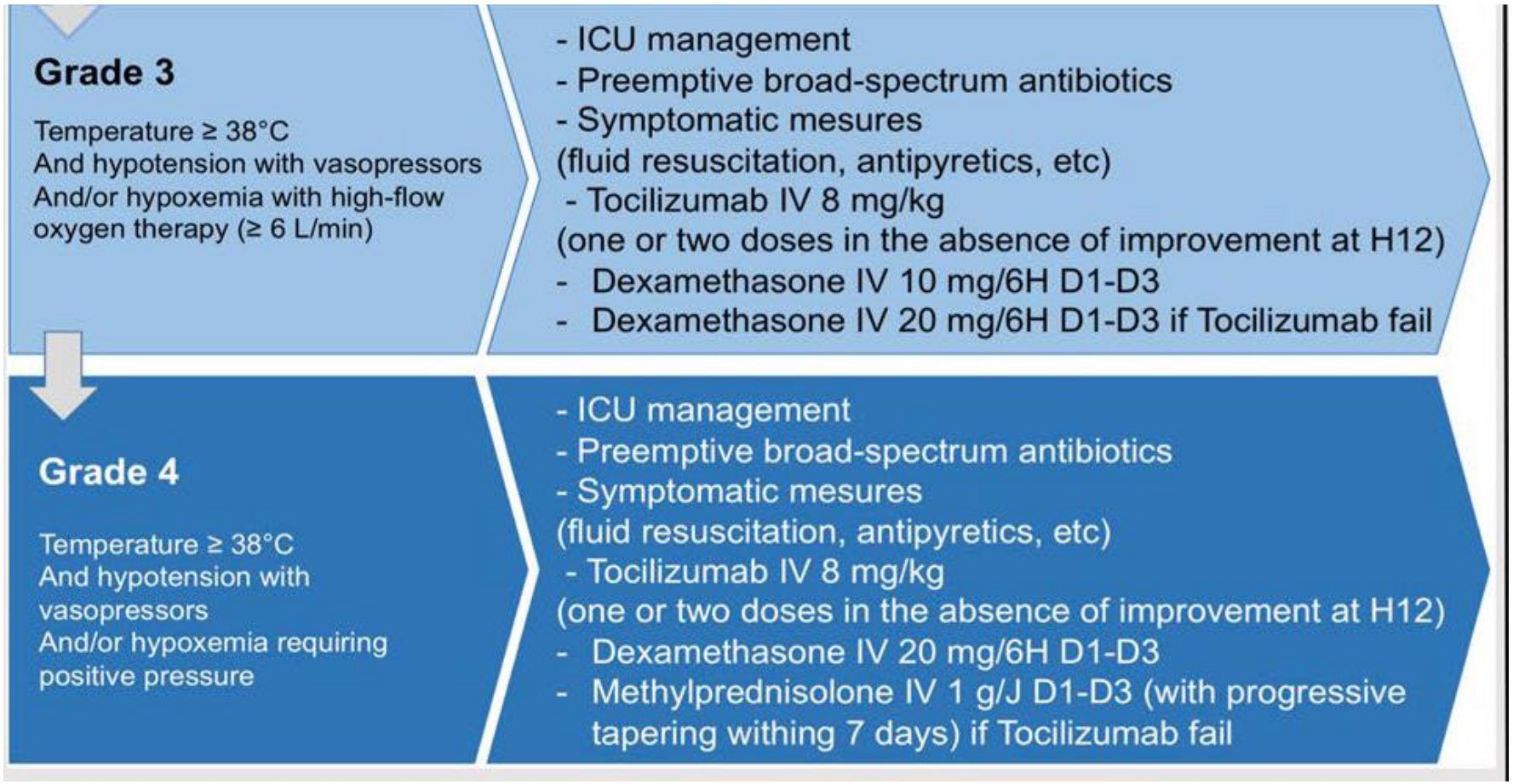
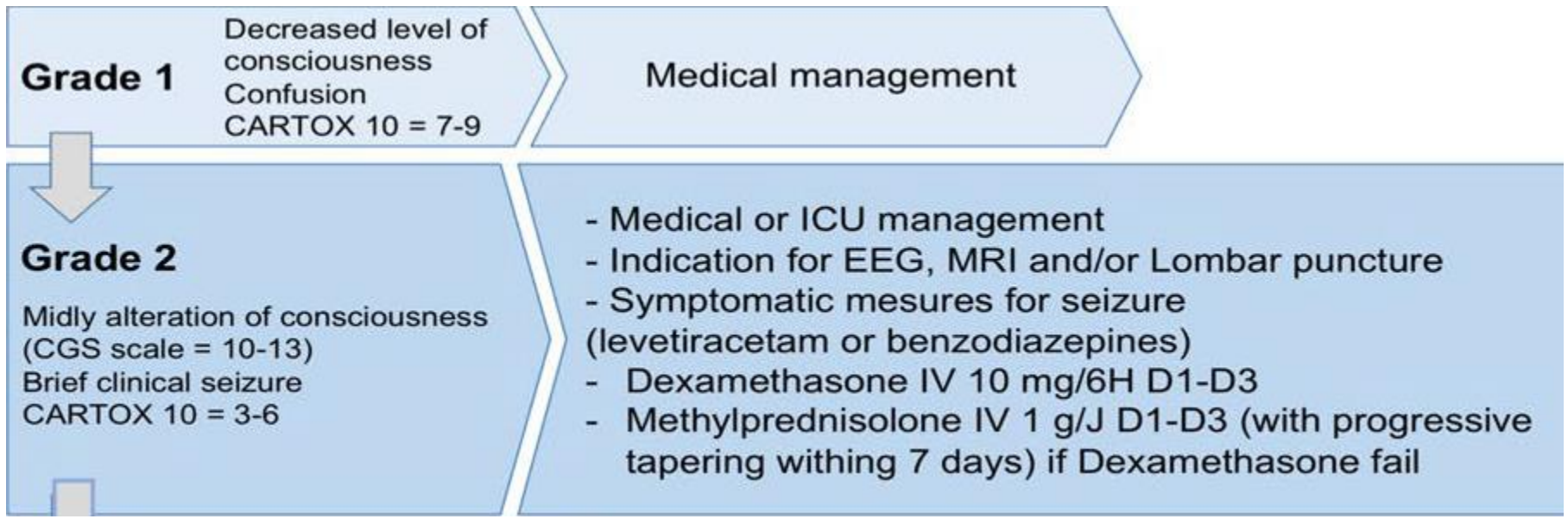
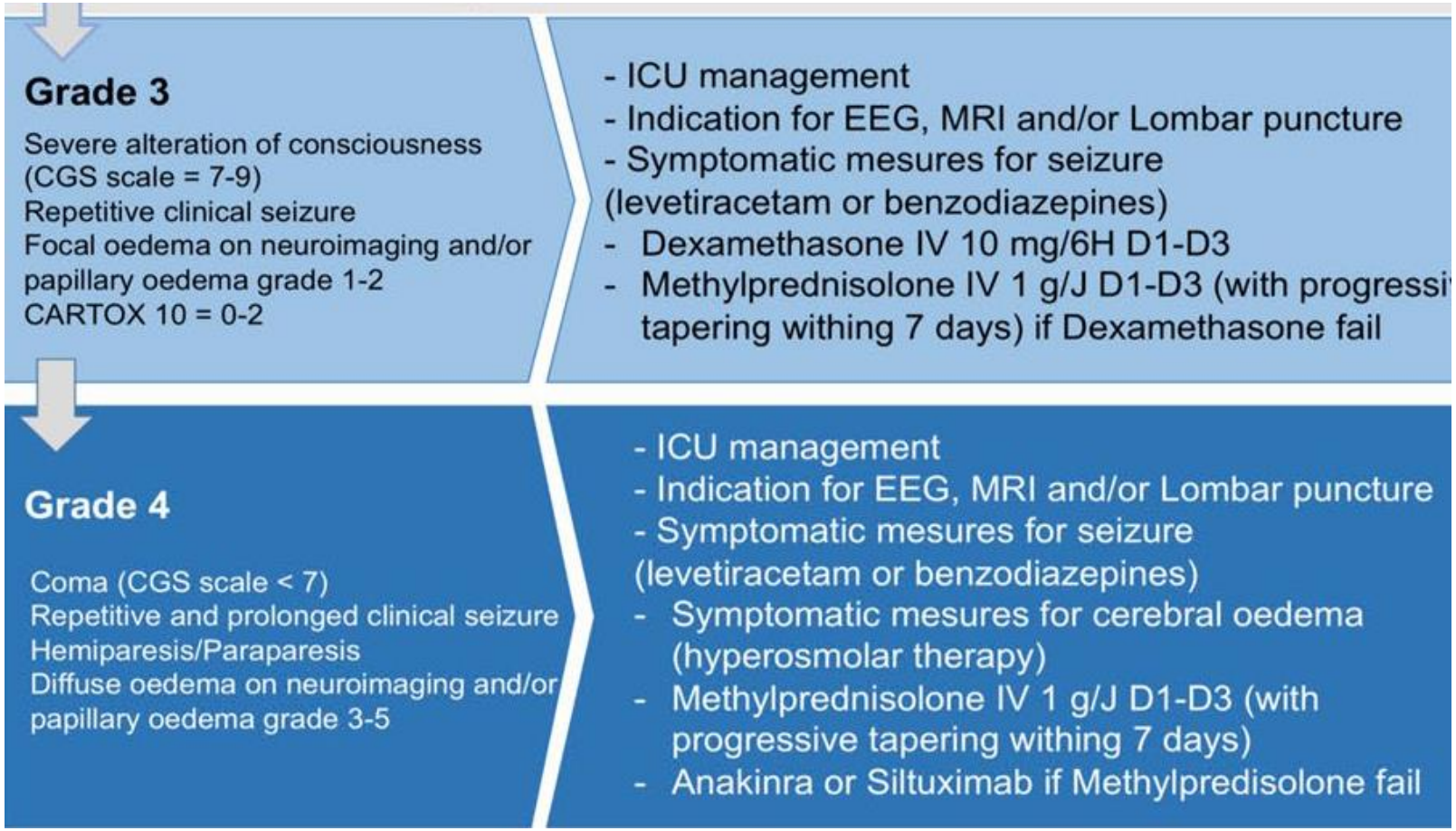
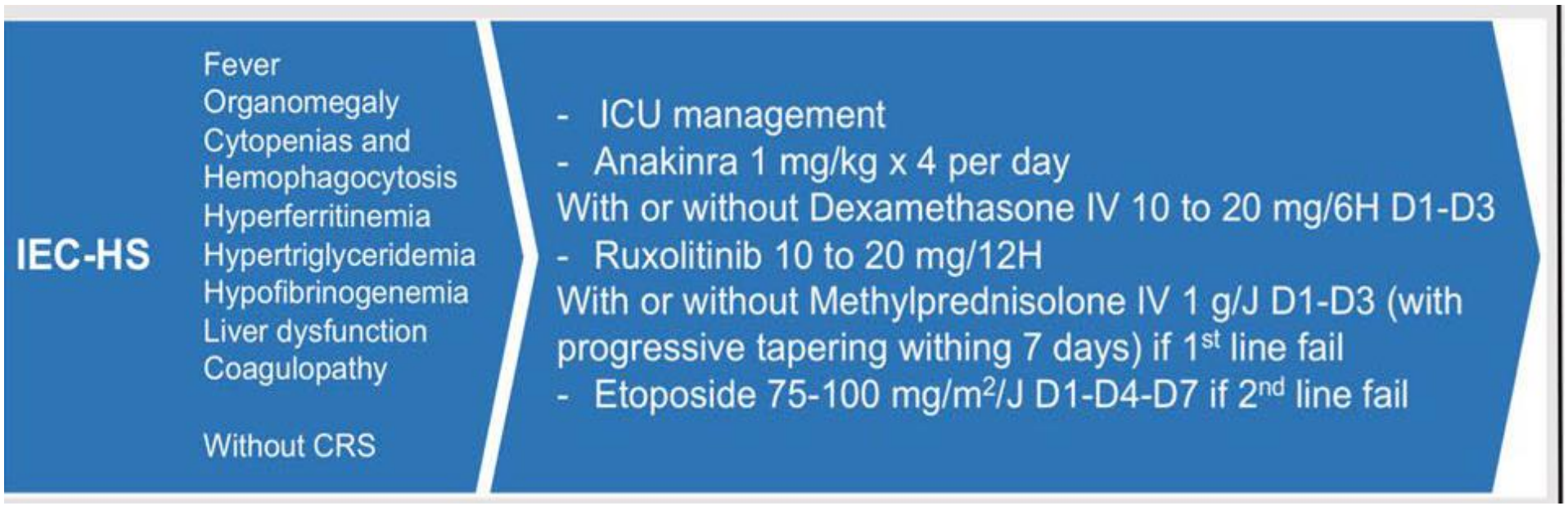



Grade 3
Temperature ≥ 38°C
And hypotension with vasopressors
And/or hypoxemia with high-flow oxygen therapy (≥ 6 L/min)
- ICU management
- Preemptive broad-spectrum antibiotics
- Symptomatic mesures
(fluid resuscitation, antipyretics, etc)
- Tocilizumab IV 8 mg/kg
(one or two doses in the absence of improvement at H12)
- Dexamethasone IV 10 mg/6H D1-D3
- Dexamethasone IV 20 mg/6H D1-D3 if Tocilizumab fail
Grade 4
Temperature ≥ 38°C
And hypotension with vasopressors
And/or hypoxemia requiring positive pressure
- ICU management
- Preemptive broad-spectrum antibiotics
- Symptomatic mesures
(fluid resuscitation, antipyretics, etc)
- Tocilizumab IV 8 mg/kg
(one or two doses in the absence of improvement at H12)
- Dexamethasone IV 20 mg/6H D1-D3
- Methylprednisolone IV 1 g/J D1-D3 (with progressive tapering withing 7 days) if Tocilizumab fail


Grade 1
Decreased level of consciousness
Confusion
CARTOX 10 = 7-9
Medical management
Grade 2
Midly alteration of consciousness (CGS scale = 10-13)
Brief clinical seizure
CARTOX 10 = 3-6
- Medical or ICU management
- Indication for EEG, MRI and/or Lombar puncture
- Symptomatic mesures for seizure (levetiracetam or benzodiazepines)
- Dexamethasone IV 10 mg/6H D1-D3
- Methylprednisolone IV 1 g/J D1-D3 (with progressive tapering withing 7 days) if Dexamethasone fail


Grade 3
Severe alteration of consciousness (CGS scale = 7-9)
Repetitive clinical seizure
Focal oedema on neuroimaging and/or papillary oedema grade 1-2
CARTOX 10 = 0-2
- ICU management
- Indication for EEG, MRI and/or Lombar puncture
- Symptomatic mesures for seizure (levetiracetam or benzodiazepines)
- Dexamethasone IV 10 mg/6H D1-D3
- Methylprednisolone IV 1 g/J D1-D3 (with progressi tapering withing 7 days) if Dexamethasone fail
Grade 4
Coma (CGS scale < 7)
Repetitive and prolonged clinical seizure
Hemiparesis/Paraparesis
Diffuse oedema on neuroimaging and/or papillary oedema grade 3-5
- ICU management
- Indication for EEG, MRI and/or Lombar puncture
- Symptomatic mesures for seizure (levetiracetam or benzodiazepines)
- Symptomatic mesures for cerebral oedema (hyperosmolar therapy)
- Methylprednisolone IV 1 g/J D1-D3 (with progressive tapering withing 7 days)
- Anakinra or Siltuximab if Methylpredisolone fail


IEC-HS
Fever
Organomegaly
Cytopenias and
Hemophagocytosis
Hyperferritinemia
Hypertriglyceridemia
Hypofibrinogenemia
Liver dysfunction
Coagulopathy
Without CRS
- ICU management
- Anakinra 1 mg/kg x 4 per day
With or without Dexamethasone IV 10 to 20 mg/6H D1-D3
- Ruxolitinib 10 to 20 mg/12H
With or without Methylprednisolone IV 1 g/J D1-D3 (with progressive tapering withing 7 days) if 1st line fail
- Etoposide 75-100 mg/m2/J D1-D4-D7 if 2nd line fail

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Grade	CRS	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care (± toci)*	Supportive care (± steroids)*	Supportive care
2	Tocilizumab	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Tocilizumab	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	Tocilizumab + high-dose steroids ICU/critical care	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care

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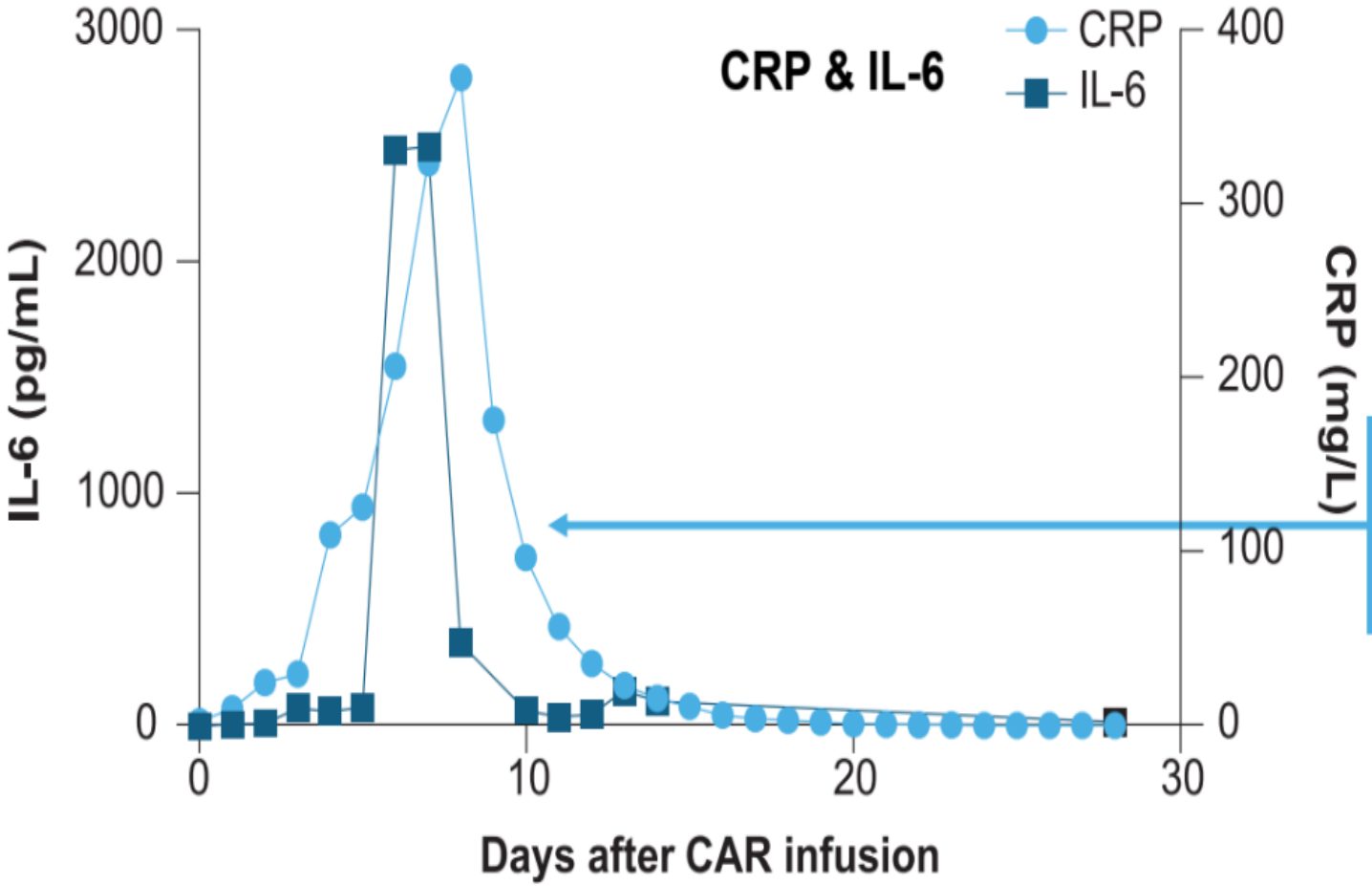

Decreasing serum CRP may be a clinical indicator of improvement

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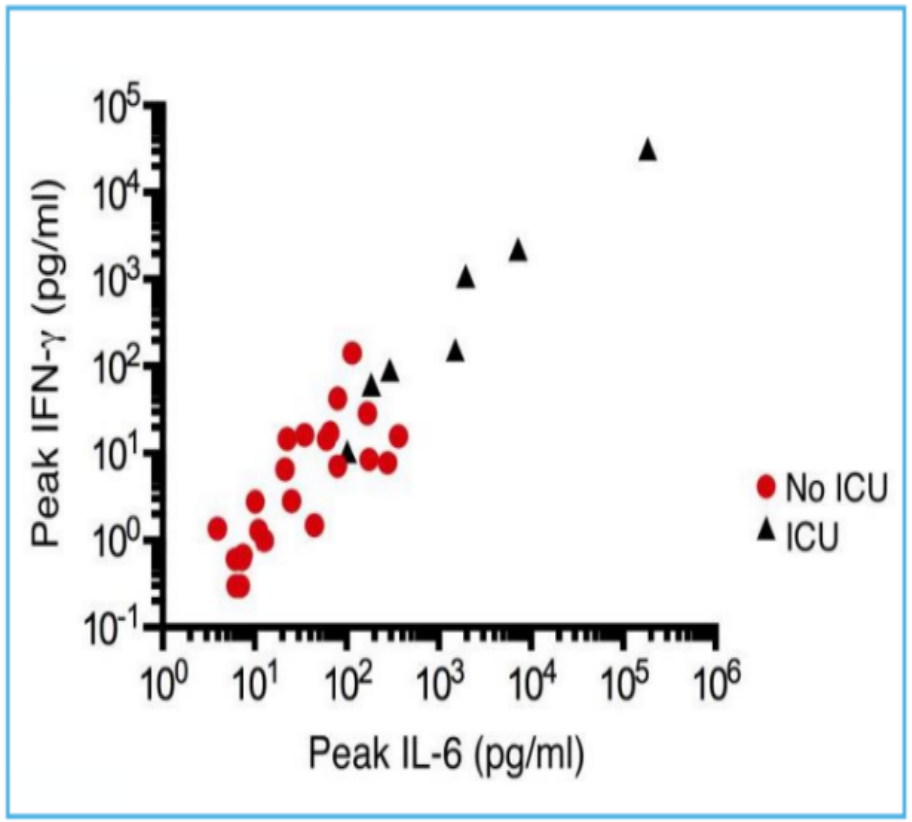
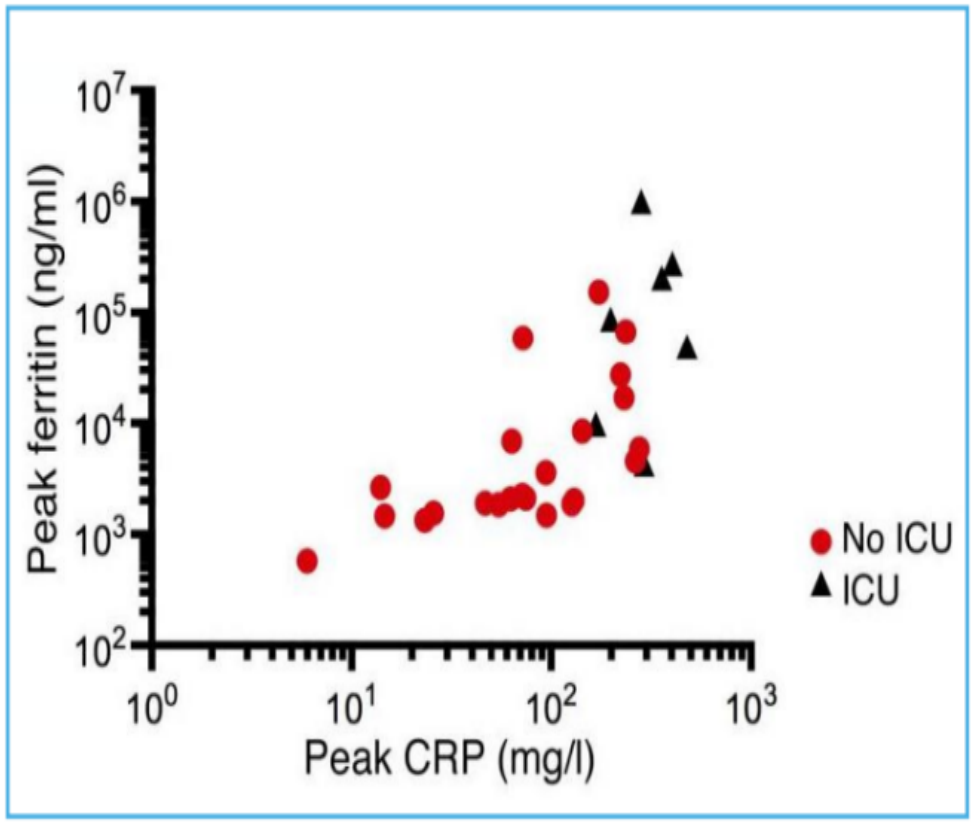
Higher peak IL-6 and IFN-γ levels are observed in patients requiring ICU care



Elevations of serum C-reactive protein (CRP) and ferritin correlate with the occurrence of severe CRS requiring ICU care



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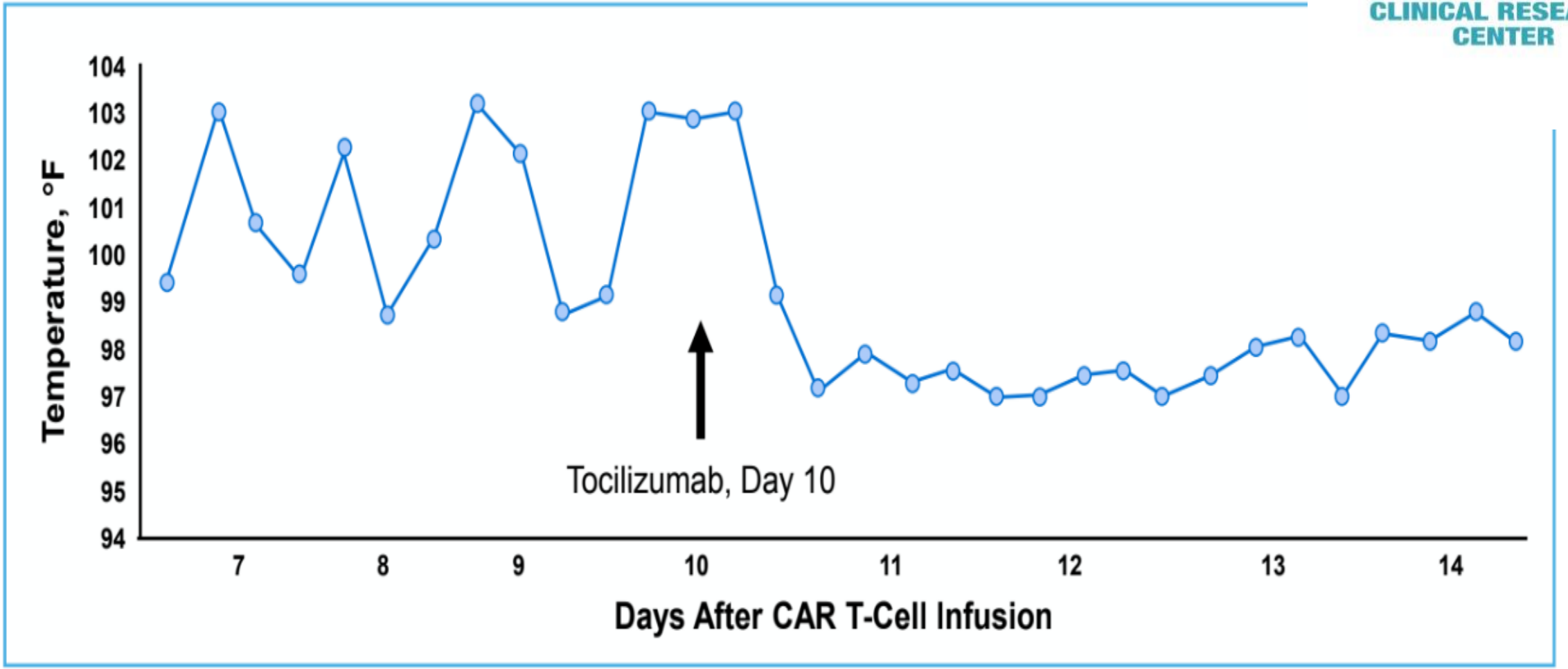

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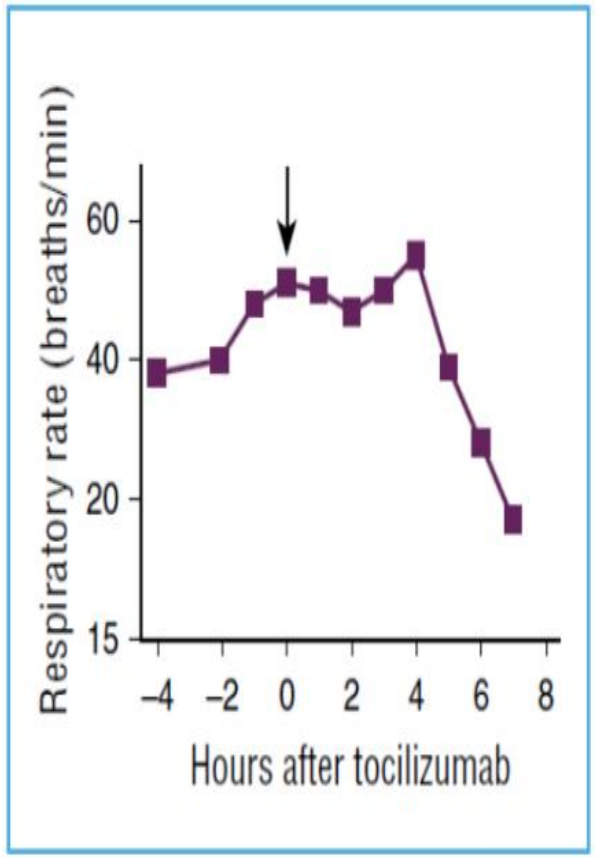

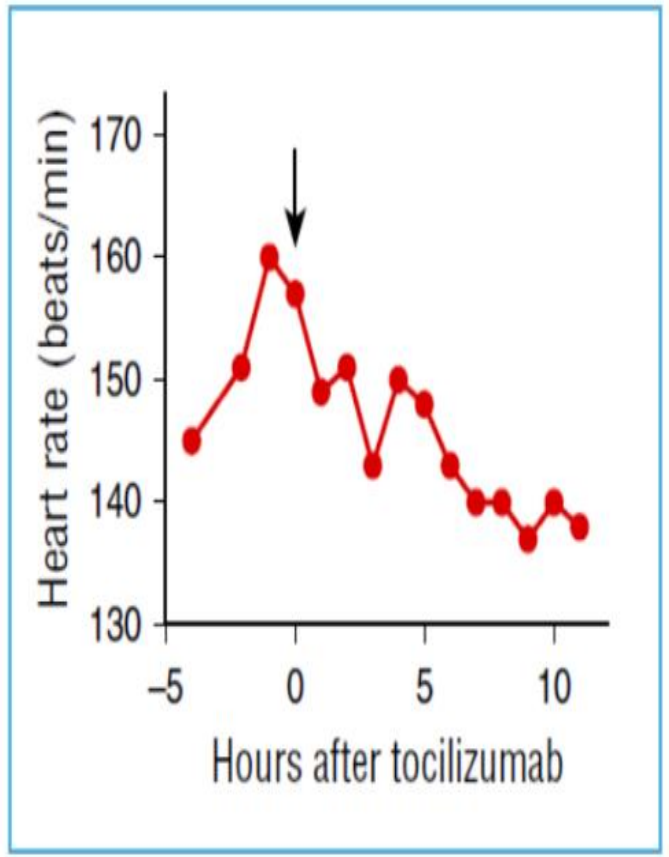

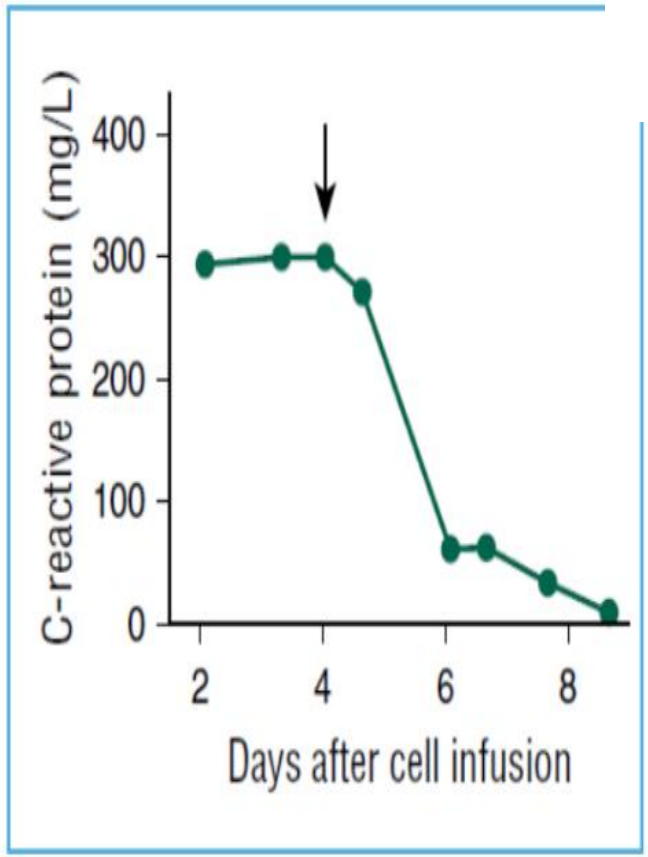

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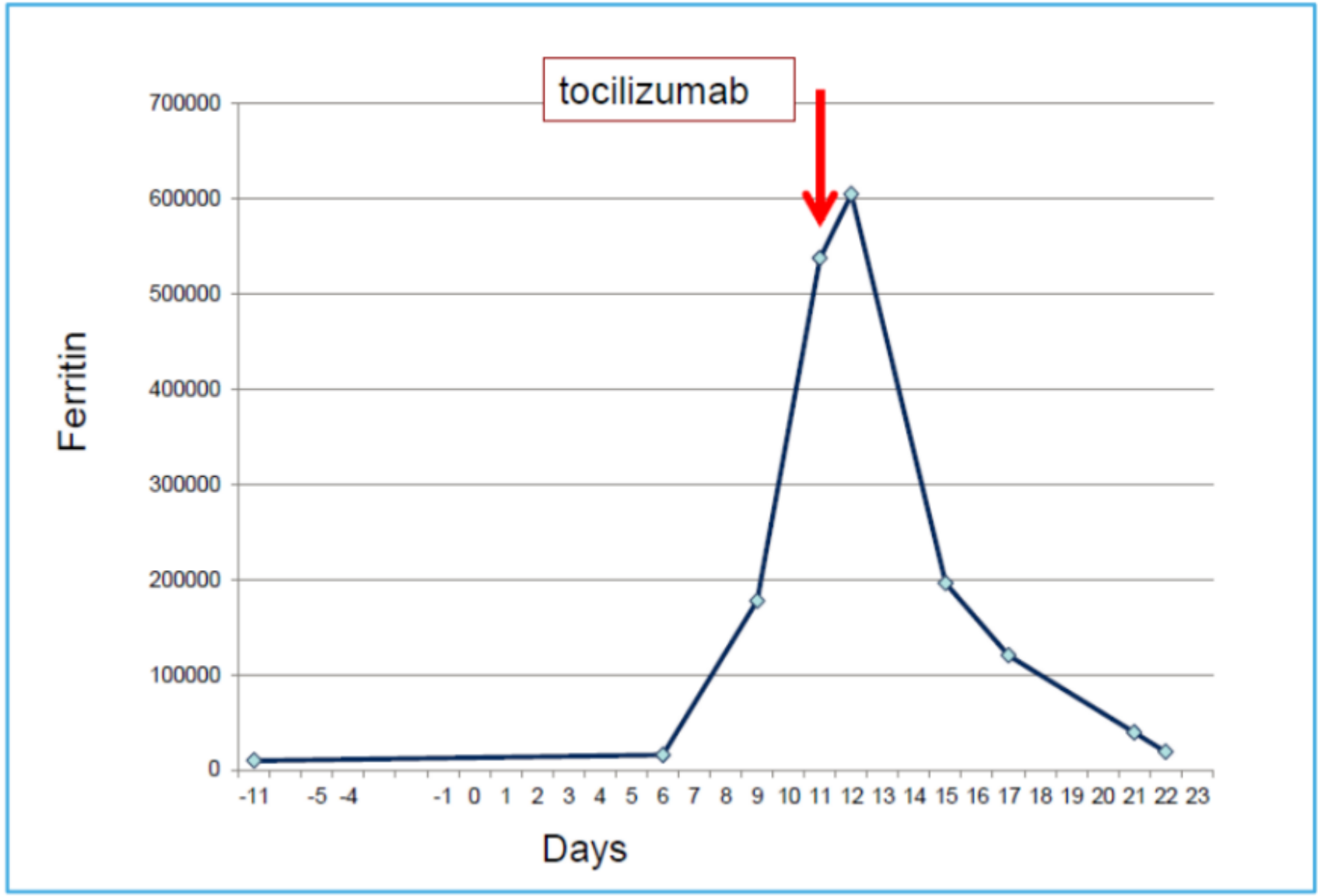

Infections

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- First month: Bacterial (20%), viral (5–10%), and fungal (< 5%)
  - 1st 10 day-lower resp tr

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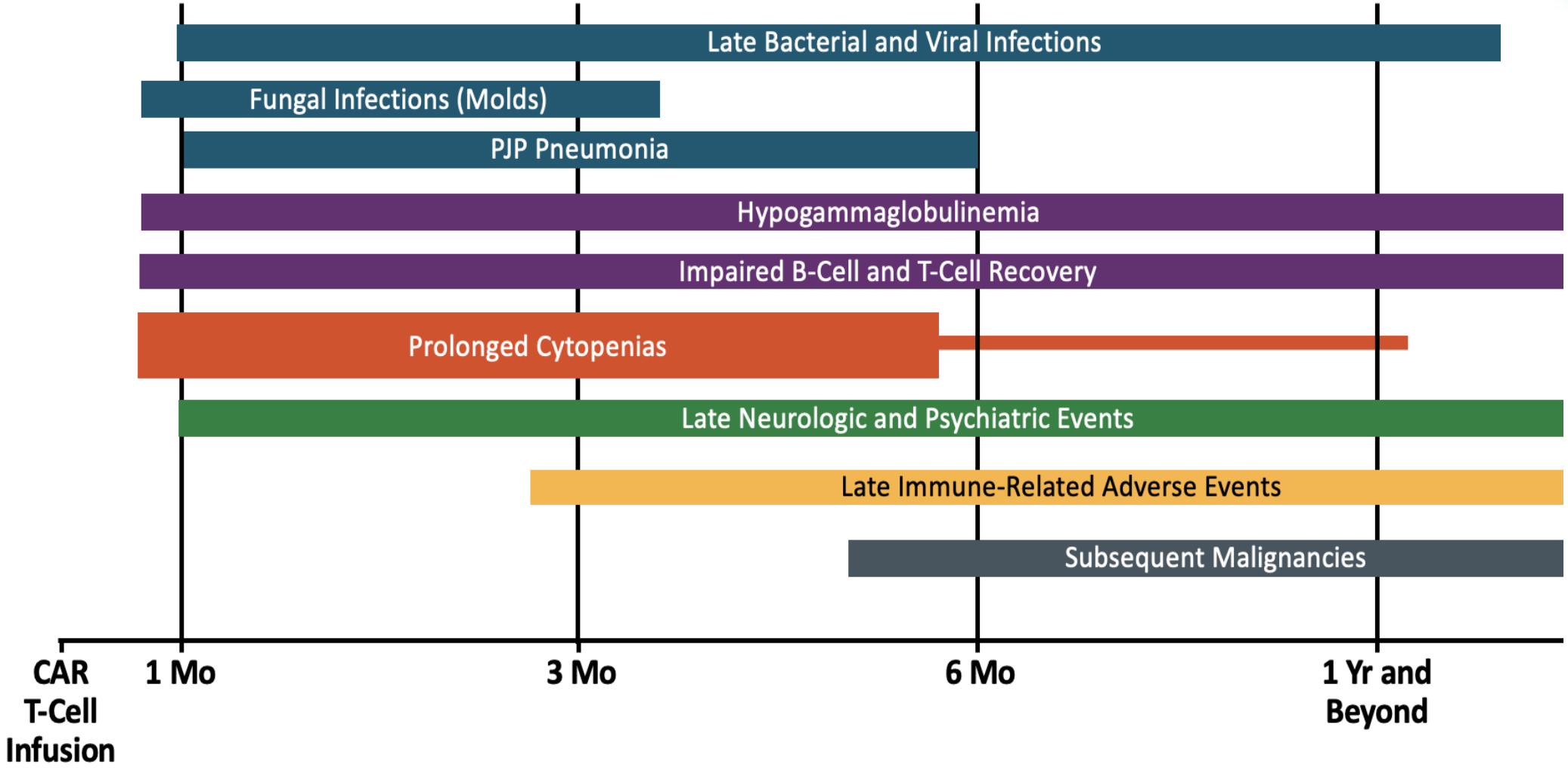

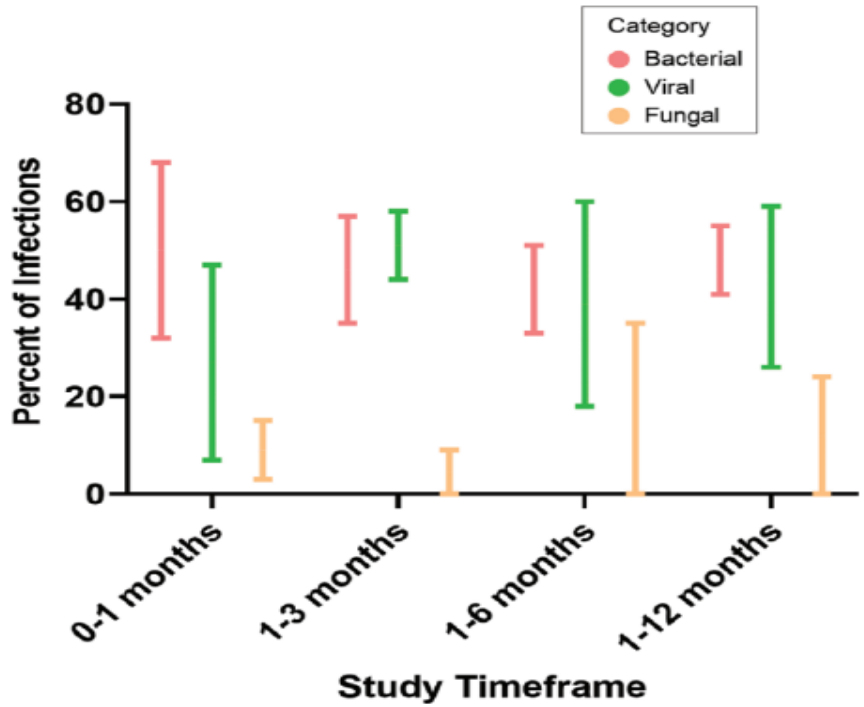

Timeframe	Bacterial cause	Viral cause	Fungal cause	References
0–1 month	32%–68%	7%–47%	3%–15%	35-38,40,49, 50,57,59,79
1–3 months	35%–57%	44%–58%	0%–9%	35,38,59
1–6 months	33%–51%	18%–60%	0%–35%	37,46,49
1–12 months	41%–55%	26%–59%	0%–24%	40,49,59

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CAR-HEMATOTOX Score

Variables	0	1	2
Hemoglobin (g/dL)	> 9.0	< 9.0	
Neutrophil Count (G/L)	> 1.2	< 1.2	
Platelet Count (G/L)	> 175	75 to 175	< 75
C-reactive protein (mg/L)	< 30	> 30	
Ferritin (ng/mL)	< 650	650 to 2000	> 2000
Low Score = 0 to 1 High Score = 2 to 7			

Infectious Prophylaxis

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- No clear standard
  - IVIG: pre-lymphodepletion and continue monthly for the first 6 months
  - GF: Unclear

    GCSF if needed when neutropenic, CRS??

Anti-bacterial	Not routinely recommended Can be considered in case of prolonged neutropenia Intravenous immunoglobulin can be considered with serious and/or recurrent infections with encapsulated organisms and hypogammaglobulinemia < 4 g/L
Anti-viral	Valaciclovir 500 mg x 2 per day or Aciclovir 800 mg x 2 per day
Anti-pneumocystis	Cotrimoxazole 480 mg per day or 960 mg x 3 per week In case of contraindications : Pentamidine inhalation 300 mg per month or Dapsone 100 mg per day or Atovaquone 1500 mg per day
Anti-fungal	Should be considered in case of prolonged neutropenia Posaconazole 300 mg per day or Fluconazole 200 mg per day or Micafungin 50 mg per day

Our experience

“CAR” T Cell Trials

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- Three different clinical studies (Phase I- I/II)
- Autologous (Phase I/II)
  - mRNA is used to transfer genetic material
  - BCMA-targeted second generation CAR T cell
  - Newly diagnosed MM with high risk genetic features
- Allogeneic CAR-T (Phase I/II)
  - BCMA targeted
  - Fifth generation CAR T cell
  - Refractory MM that has received at least three lines of therapy




“CAR” T Cell Trials

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CAR-T treatment side effect experience

- 39 total infusions
- Autologous CAR-T (n1=3, n2=4)
  - Grade 1 CRS (fever, fatigue, muscle and joint pain, headache) was observed and responded to paracetamol
  - Grade 1 Neurotoxicity (tendency to sleep) was observed, spontaneous regression was observed.
- Allogeneic CAR-T (n=3)
  - Grade 2 anemia, grade 2 leukopenia, grade 2 neutropenia and grade 1 thrombocytopenia were observed.
  - No Grade 3-4 adverse events were observed.

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