CAR-T associated Immune effector cell–associated hematotoxicity and infections

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COI disclosure

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CAR-T associated Immune effector cell–associated hematotoxicity - I

- Prolonged cytopenias can predispose patients to significant infectious complications result in extended hospital stays and prevent subsequent salvage therapies at relapse.

- The observed degree and duration of hematotoxicity varies depending on the disease subtype (B-cell precursor acute lymphoblastic leukemia, B-NHL, multiple myeloma), target antigen (CD19, BCMA, others) .

- A recent meta-analysis, higher incidence of post-CAR T cytopenia in BCP-ALL, likely related to extensive bone marrow infiltration or more intensive prior therapy.

Xia Y, et al. Ann Med. 2022;54(1):2951-2965.
Bachy E, et al. Nat Med. 2022;28(10):2145-2154.

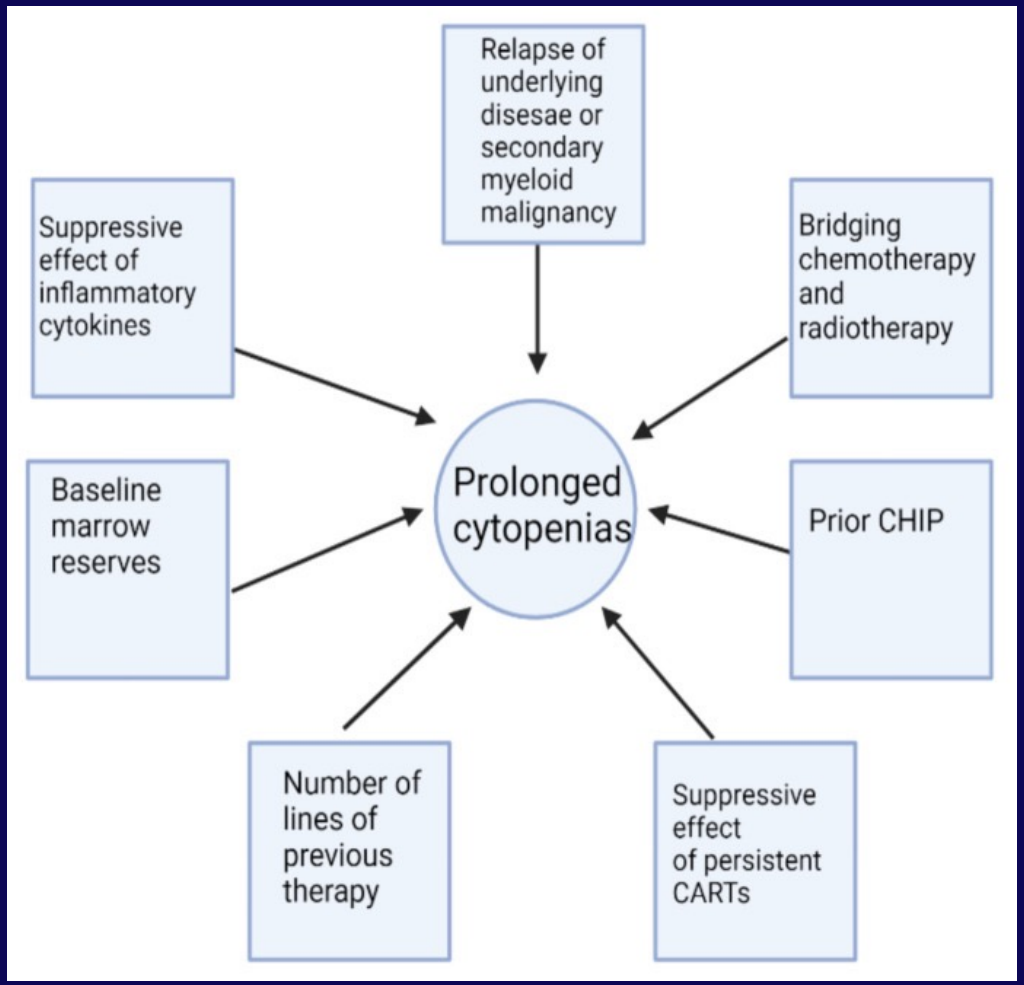
CAR-T associated Immune effector cell–associated hematotoxicity - II

- High rates of cytopenia have also been noted for MCL, in line with the generally high toxicity burden in this disease entity.

- Increased cytopenias in patients receiving CAR products harboring a CD28 as opposed to 4-1BB co-stimulatory domain (Several reports linking high-grade CRS and the associated inflammatory markers to prolonged cytopenias).

Xia Y, et al. Ann Med. 2022;54(1):2951-2965.
Bachy E, et al. Nat Med. 2022;28(10):2145-2154.

Possible Factors Contributing To Cytopenias in CAR-T Therapy



Sharma N, Reagan PM, Liesveld JL. Cancers (Basel). 2022 Mar 15;14(6):1501.

There are 3 distinct phenotypes of post-CAR-T neutropenia (Cytopenia) and neutrophil recovery:

1. Short, related to lymphodepletion.
2. Intermittent, usually responds to G-CSF.Possibly favorable treatment outcomes and higher levels of CAR T-cell expansion and persistence.
3. Aplastic phenotype associated with high morbidity and mortality. Poor response to G-CSF. Observed in minority of patients

The peak of thrombocytopenia is tradionally observed in the second month following CAR T infusion.

Rejeski K, et al. Blood. 2021;138(24):2499-2513.
Rejeski K, et al. Sci Adv. 2023;9(38).

Marked heterogeneity in the reporting and definitions of these long-term hematological side effects across studies.

To address this, a 36 EBMT/EHA expert panel recently developed a consensus grading system.

Early	Day 0-30
Prolonged / Late	After Day 30-90

Clear definitions to ease reporting in trials enable comparative studies of Immune effector cell–associated hematotoxicity – (ICAHT) severity across disease entities and CAR products, and provide a risk adapted management recommendations.

Immune effector cell–associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations

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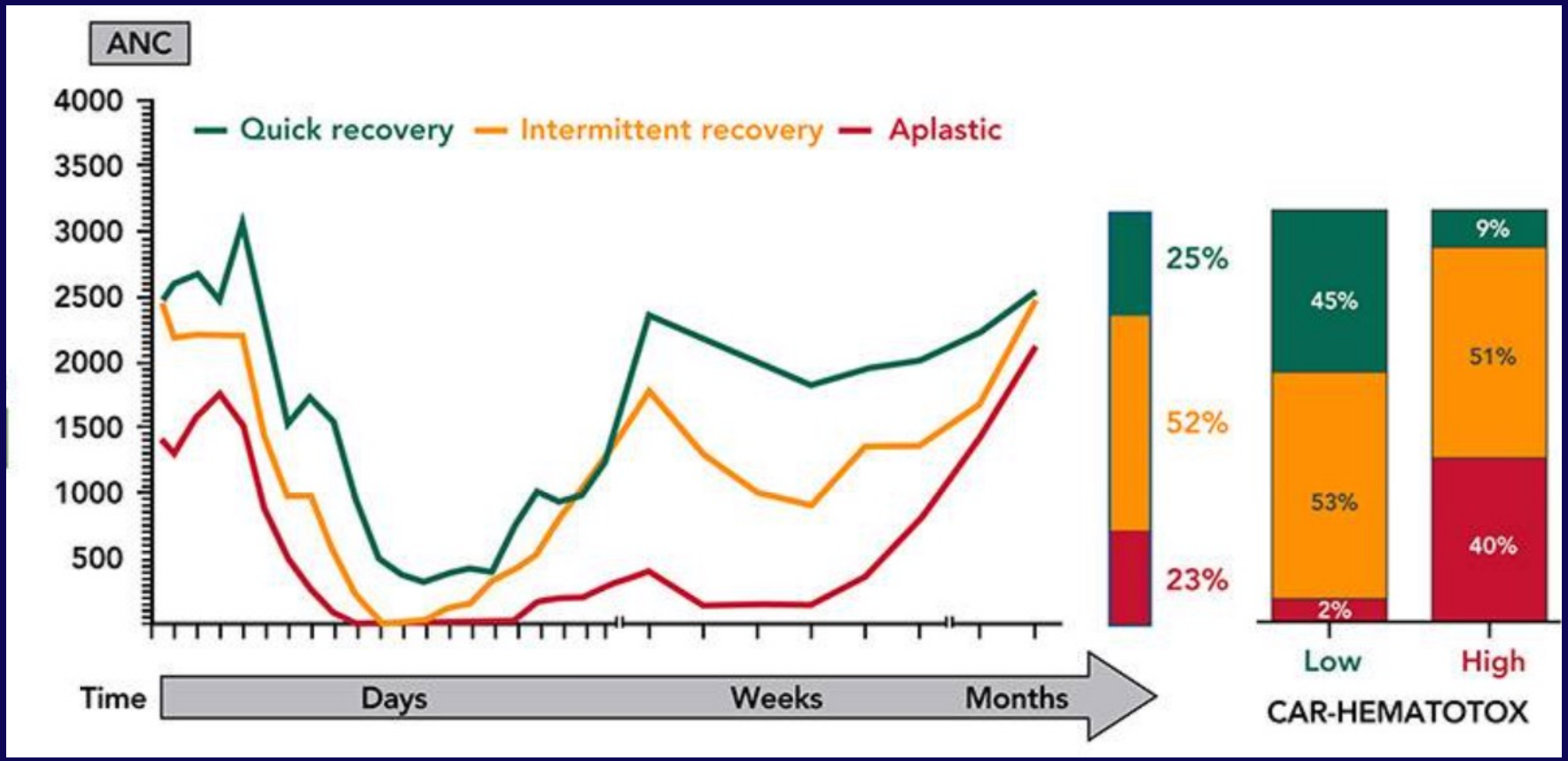
Blood. 2023; 142(10): 865-877.

CAR-HEMATOTOX score

Baseline Features	0 Point	1 Point	2 Points
Platelet Count	> 175,000/µl	75,000 – 175,000/µl	< 75,000/µl
Absolute Neutrophil Count (ANC)	> 1200/µl	< 1200/µl	-
Hemoglobin	> 9.0 g/dl	< 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	> 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650 – 2000 ng/ml	> 2000 ng/ml
Low: 0-1	High: ≥ 2		

Done at Lymphodepeltion

Blood. 2023; 142(10): 865-877.


ANC
4000
3500
3000
2500
2000
1500
1000
500
Quick recovery
Intermittent recovery
Aplastic
Time
Days
Weeks
Months
25%
52%
23%
45%
53%
2%
9%
51%
40%
Low
High
CAR-HEMATOTOX

Workup for Persistent Cytopenia Beyond One Month

- Secondary causes
  (Myelotoxic medications, active infection, others)

- HLH / MAS. Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS)
  (higher rates with CAR T targeting CD22)

- Disease recurrence

- T-MDS

- Safety profile with early G-CSF without increases in the rate of high-grade (e.g. ASTCT grade 3 or higher) CRS or ICANS.

- Data support early G-CSF in high-risk patients to shorten severe neutropenia and prevent infections.

- The optimal day of initiation of G-CSF (prophylactic vs. early; pegylated vs. non-pegylated) in the context of CAR T remains unclear.

- Most CAR T patients (>80%) will adequately respond to growth factor support with count recovery.

- GM-CSF should NOT be used in CAR T and may significantly exacerbate toxicities.

Lievin R, et al. Bone Marrow Transplant. 2022;57(3):431-439. 26.
Miller KC, et al. Blood Cancer J. 2022;12(10):146. 27.
Ma S. Cytotherapy. 2023;25(6):653-658.
Sterner RM, et al. Blood. 2019;133(7):697-709.

Other Therapeutic Interventions for Severe or Persistent ICAHT

- Treat potential secondary causes.
- Cases with an available cryopreserved autologous stem cell product from a prior treatment line hematopoietic cell boosts should be strongly considered (mostly myeloma).
- Other options include thrombopoietin receptor agonists (TPO-RA) such as Eltrombopag or Romiplostim though the data are restricted to a few small case series. The potential improvement of hematopoietic function would mirror the efficacy of TPO-RA in other cases of acquired BM failure.
- Allogeneic HSCT represents the last resort. High risk treatment option. Allo-HSCT will inevitably eradicate CAR T-cells.

Lin Q, et al. Bone Marrow Transpl. 2020;55(6):1203-1205.
Rejeski K, et al. Blood Adv. 2022;6(16):4719-4725.
Drillet G,et al. Blood Adv. 2023;7(4):537-540.
Beyar-Katz O,et al. Ann Hematol. 2022;101(8):1769-1776.

Other Hematologic Complications

- Coagulopathy and hypofibrinogenemia (massive cytokine release and endothelial damage).
- Bleeding and thrombosis after CAR T therapy.
- Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS).
- Tumor lysis syndrome - rare.

Infections after Chimeric Antigen Receptor (CAR) T-cell Therapy

- Infection prevention strategies in CAR T therapy are evolving and are still based on expert opinion consensus and extrapolated from other patient populations, mostly autologous HSCT.

- Bacterial infections predominate early after CD19, while a more equal distribution between bacterial and viral causes is seen after BCMA CAR T-cell therapy.

- Fungal infections are relatively infrequent.

Summary of the Risk Factors For Infection Identified in Literature

Pre-CAR T-Cell Infusion

1. Impaired baseline performance status
2. Number of prior lines of treatment
3. History of recent infections (within 100 days prior to infusion)
4. Adult patients
5. Pre-infusion hypogammaglobinemia
6. History of prior allogeneic transplant
7. ANC <500 cells per mm^3
8. Lymphodepleting chemotherapy

Post-CAR T-Cell Infusion

1. Severe cytopenias (>Grade 3)
2. B-cell aplasia
3. Hypogammaglobinemia
4. Cumulative immunomodulatory exposure
   (Tocilizumab and Corticosteroid after CAR T-cell infusion)

Aljurf. M, et al. HOSCT 2022. 25;15(3):153-158.

CAR-T Therapy Has a Very Heterogeneous Patient Population Accordingly, Pre-CART Treatment Factors are Important

- CD19 risk of infection B-ALL >DLCL >FL
- BCMA CAR T-cell therapy has more viral
- Previous therapies
- Previous allo-HSCT
- Previous infections

“On-target Off-tumor” Effects on Immune Cells

- CD19 is expressed on B-cells at earlier stages (naïve and memory B-cells), and is lacking from the long-lived plasma cells, which are mostly responsible for maintaining stable concentrations of antigen-specific antibodies against previously encountered pathogens. Targeting CD19 thus leads to B-cell depletion and may contribute to hypogammaglobinemia, but pathogen-specific immunoglobulin G (IgG) levels can be maintained.

- BCMA is expressed in all plasma cells, so its targeting may lead to more severe hypogammaglobinemia and a decrease in specific antibody levels.

- Hypogammaglobinemia rates vary greatly between CAR T-cell products and patient populations (pediatric vs. adult).

- Cellular immunity is also durably impaired in CD19 CAR T-cell recipients; CD4+ T-cell counts decrease after infusion and may remain very low, with a median of 155 cells/μL at 1 year and less than 200 cells/μL in half of the patients at 18 months.

Logue JM, et al. Haematologica. 2020;106(4).

Three Risk Groups

- Early Day 0-30
- Late Beyond 30 days after discharge
- Late Still hospitalized beyond day 30

Antibacterial prophylaxis

- Great heterogeneity among institutions
- Should be risk-adapted strategy based on the patient-individual risk profile for infections including the expected incidence rate of protracted, profound neutropenia (ICAHT score)

Immunoglobulin Replacement Therapy (IGRT)

- The benefits of universal prophylaxis with IGRT in the setting of CAR T asymptomatic hypogammaglobulinemia are unclear.

- Important criteria that may be most relevant to prompt IGRT include serious or recurrent bacterial infections in the context of a total serum IgG level less than 400 mg/dL.

- BCMA CAR T-cell therapy recipients and pediatric patients more profound humoral deficits and a theoretically higher benefit from the more liberal use of IGRT.

Kampouri E. Expert Rev Hematol. 2022;15(4):305-320.

Fungal Infections

- Relatively infrequent.
- Rare beyond the first month and after discharge from the hospital.
- Only 8 IF infection out of 280 cases CAR T NHL in one year follow-up, despite the lack of routine antifungal prophylaxis and the high prevalence of severe delayed neutropenia.
- Antifungal prophylaxis practices varies widely across institutions, and the utility remains uncertain given the relatively low incidence after CAR T-cell therapy.

Little JS, et al. Blood Adv. 2022;6(16):4821-4830.

Pneumocystis Jirovecii

- Late PJP pneumonia has been reported in several cases beyond 3 months after CAR T infusion and after cessation of anti-pneumocystis prophylaxis.

- PJP prophylaxis is widely recommended across guidelines and institutions for at least 6 months after cell infusion, although optimal duration remains unknown.

- Late cases of P. Jirovecii pneumonia have been reported in multiple studies after cessation of prophylaxis, suggesting that there may be delayed reconstitution of cellular immunity >6 months after cell infusion.

Baird JH, et al. BloodAdv. 2021;5(1):143-155.

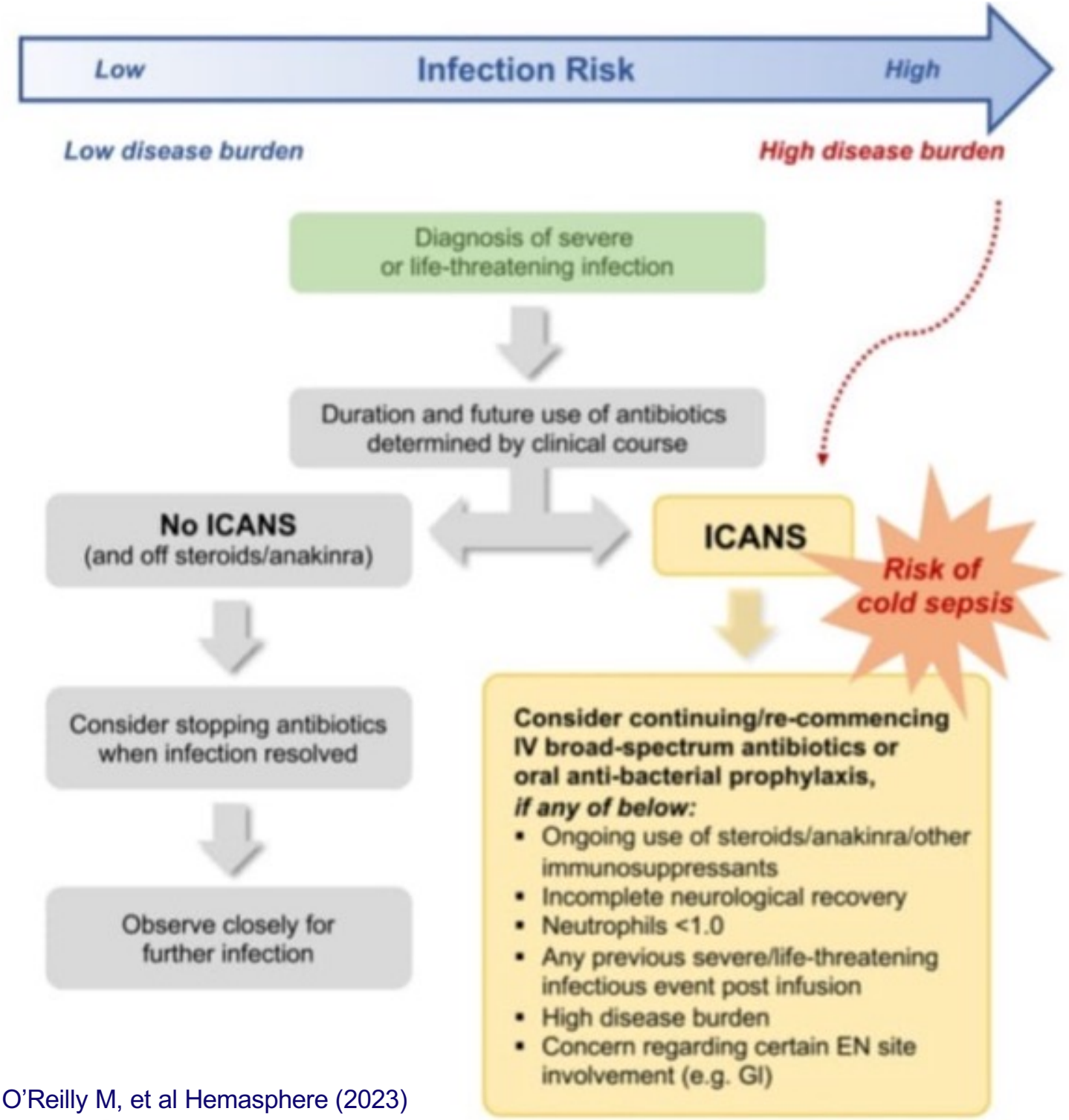
Cytomegalovirus

- Routine CMV monitoring is not recommended in uncomplicated low risk CAR T cases.

- Testing should be considered as clinically appropriate or in potentially high-risk patients, such as those receiving corticosteroids for management of CRS and / or ICANS.

- The clinical relevance of low CMV viremia in low risk patients remains unclear with most patients improving, even without preemptive antiviral therapy.

Chen G, et al. Haematologica. 2023;108(2):615-620.
Wang D, et al. Blood Cancer J. 2021;11(10):5-8.



O'Reilly M, et al Hemasphere (2023)

Other Viruses

- Routine antiviral prophylaxis with Acyclovir or Valacyclovir for human HSV and / or VZV seropositive patients is recommended.
- Duration is less well-defined and ranges from at least 100 days to >1 year after CAR T-cell therapy.
- EBV reactivation - rare.
- HHV-6 reactivation, rare. DDx ICANS.

Hayden PJ, et al. AnnOncol. 2022;33(3):259-275.
Los-Arcos I, et al. Infection. 2021;49(2):215-231.