InternNet CLUB

FÓRUM 2025 • 9ª EDIÇÃO

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As opiniões expressas nestes diapositivos são da responsabilidade dos próprios autores e não refletem necessariamente a posição da Johnson & Johnson Innovative Medicine.

InternNet CLUB

- Aposta da Johnson & Johnson Innovative Medicine na formação contínua dos Internos da especialidade de Hematologia Clínica.

Evento Educacional

- De internos para internos

Objetivos

- *Disseminação e partilha de informação médica e científica, que seja relevante para a prática clínica e para a formação de todos os participantes*
- Revisão de conceitos
- Enriquecer o Curriculum
- *Networking*

Comité científico

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PROGRAMA

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15h00 Mensagem de abertura

Francisca Miranda (ULS de Lisboa Ocidental)
Inês Brito (ULS do Alto Minho)

15h10 Profilaxias, porquê?

Palestrantes:
Filipa Seixas (ULS de Trás-os-montes E Alto Douro)
Inês Damásio (ULS de Viseu Dão-Lafões)
Leonardo Moço (IPO do Porto)

16h20 *Coffee-break*

16h40 Complicações da terapia CAR-T: Uma abordagem prática

Palestrantes:
André Antunes (Hospital Dr. Nélio Mendonça - Funchal)
Cátia Almeida (ULS de Coimbra)
Francys Llanos (IPO de Lisboa)

17h50 *QUIZ*

Moderadoras:
Francisca Miranda (ULS de Lisboa Ocidental)
Inês Brito (ULS do Alto Minho)

18h30 Encerramento

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GRUPO 1

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Profilaxias, porquê?

Palestrantes:

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PROFILAXIAS, PORQUÊ?
Profilaxia Antibiótica

Filipa seixas

PROFILAXIA Antibiótica

Bacteriostático

Impede a proliferação bacteriana mas não as eliminam. Necessitam da adjuvância do sistema imune para eliminação bacteriana.

Ex:

- Macrólidos
- Tetraciclinas
- Clindamicina
- Linezolide

Pouco úteis no Imunodeprimido

Bactericida

Induzem a morte da bactéria, por si só.

Ex:

Beta-lactâmicos

Vancomicina

Fluoroquinolonas

Daptomicina

Metronidazol

PROFILAXIA Antibiótica

Sulfonamidas/ Trimetoprim :

Inibição do metabolismo bacteriano: têm como alvo a síntese do folato, cofator importante na síntese de aminoácidos, enzimas e ácidos nucleicos.

Bactericidas

Quinolonas:

Inibição da síntese de DNA por inibição da girase nas bactérias Gram negativas e da topoisomerase IV nas gram positivas.

PROFILAXIA Antibiótica

Fatores que aumentam a predisposição infeciosa:

NEUTROPENIA

1. 1-3.4 milhões de casos/ ano de agranulocitose
2. Predomínio de agentes gram positivos neste doente

Neutropenia
Doença de base
Tratamento imunossupressor
Gravidade da Neutropenia G4
Duração da Neutropenia >7 dias

PROFILAXIA Antibiótica

Fatores que aumentam a predisposição infeciosa:

Corticoterapia

1. Diminuição da capacidade de fagocitose pelos macrófagos alveolares;
2. Diminuição da apresentação antigénica e mobilização dos linfócitos;

Aumento do risco é dose dependente!

Supressão de células T e depleção de linfócitos

PROFILAXIA Antibiótica

Principais Agentes Infeciosos:

Causa direta	Patologia/ condição	Agentes
Neutropenia	• Quimioterapia • Leucemia aguda	Bacilos Gram Negativo (entéricas e não entéricas) *Staphylococcus aureus* *Staphylococcus* coagulase negativos *Streptococcus*
Deficiência Linfócitos T	• Linfomas Não Hodgkin • Transplantação • Corticoterapia • Quimioterapia • Imunoterapia	Bactérias intracelulares *(Legionella spp, mycobactéria)* *Nocardia*
Deficiência Linfócitos B	• Mieloma Múltiplo • Leucemia Aguda • Corticoterapia • Quimioterapia • Plasmaférese • Imunodeficiências congénitas	Bactérias capsuladas *(Pneumococcus, Haemophylus influenza, neisseria Meningitidies)* *Salmonella spp,* *Campylobacter*
Deficiência esplénica	• Esplenectomizados • Hipoesplenismo / asplenismo	Bactérias capsuladas *(Pneumococcus, Haemophylus influenza, neisseria Meningitidies)*

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Organisms associated with infection in individuals with various immune deficits – UpToDate

PROFILAXIA Antibiótica

Pneumocystis Jirovecii

- Recomendação da profilaxia com TMP/SMX
- Foi demonstrada redução do risco de Pneumocistose
- Em caso de intolerância/ alergia
  - Atavaquona 1.5g/dia
  - Dapsona
  - Pentamidina

Quando?

- LMA e LLA – durante tratamento ;
- Linfoma – não é recomendado por rotina, mas se CD4<200 cel./mm3 ou durante o tratamento, se justificado;
- Mieloma múltiplo – durante o tratamento;
- Alta dose de corticóide (>20mg/dia, 4 semanas);
- Análogos das purinas (Fludarabina, cladribina);
- Alemtuzumab;
- iBTK

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D. Gilbert, H. Chambers, G. Eliopoulos, M. Saag, A. Pavia. H.W. Boucher, Guía Sanford de Terapéutica Antimicrobiana 2021

PROFILAXIA Antibiótica

Recomendações na doença Hematológica:

Globalmente – Neutrófilos < 500 / mm3 num período superior a 7 dias.

Utilidade: Minimizar o risco de bacteriémia e Neutropenia febril potencialmente fatal.

Agente: Levofloxacina

PROFILAXIA Antibiótica

Leucemia Mielóide Aguda - Indução: - Consolidação e Manutenção	 - Considerar na Neutropenia - Sem indicação
Leucemia Linfoblástica Aguda - Indução - Novas terapêuticas: Blinatumumab	 - Considerar na Neutropenia - Sem indicação
Linfomas Hodgkin/ Não Hodgkin - Terapêuticas standard - Quimioterapia Intensiva como HyperCVAD	 - Sem indicação - Considerar na Neutropenia
Mieloma Múltiplo - Inibidores proteossoma/ Daratumumab /Biespecificos - Quimioterapia intensiva VTD-PACE	 - Não estão indicados por rotina - Considerar na Neutropenia

D. Gilbert, H. Chambers, G. Eliopoulos, M. Saag, A. Pavia. H.W. Boucher, Guía Sanford de Terapéutica Antimicrobiana 2021

- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections. Version 2.2023. http://www.nccn.org (Accessed on April 17, 2024).

PROFILAXIA Antibiótica

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Transplante de progenitores Hematopoiéticos

- Profilaxia antimicrobiana com uma fluoroquinolona no período de neutropenia não demonstrou impacto direto na mortalidade e nem menor incidência de bacteriémias por microorganismos multirresistentes .
- A sua utilização deverá ser adequada a cada centro/doente
- Levofloxacina 500 mg por dia, durante a neutropenia

PROFILAXIA Antibiótica

Transplante de progenitores Hematopoiéticos

Fator de risco	Tipo Infeção	Agentes
D0-D30 Neutropenia Mucosite Rotura de Barreira Cutânea Catéter	Bacteriémia por foco endógeno oral/ intestinal Bacteriémia Catéter Infeção pele Neutropenia febril	Cocos gram positivos: *Staphylococcus epidermidids, Staphylococcus aureus, Streptococcus viridans* Bacilos Gram negativos: enterobactérias: *E.coli, Klebsiella, Enterobacter, Serratia. Pseudomonas aeruginosa, Acinetobacter.*
D31-D100 Imunossupressor	Bacteriémia Pneumonia Cistite Hemorrágica (ALO-TPH)	Predomínio de bacilos Gram Negativos: *E.coli e Pseudomonas aeruginosa.*
>101 dias Hipogamaglobulinémia Imunodeficiência/ CD4/ linfócitos B	Bacteriémia e Pneumonia	Bactérias capsuladas: *Pneumococcus, Haemophylus influenza, neisseria Meningitidies* Bactérias intracelulares: *Listeria, Legionella, Nocardia e Mycobacterium*.

Young JAH, Weisdorf DJ. Infections in Recipients of Hematopoietic Stem Cell Transplants. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 2015;3425-39.e5.

PROFILAXIA Antibiótica

Esplenectomia, hipoesplenismo e asplenismo

- Deficiência na opsonização, fagocitose e resposta imune adaptativa mediada por células B.

Doenças associadas a asplenismo/ hipoesplenismo como hemoglobinopatias/ drepanocitose
Esplenectomizados por doença hematológica

Bactérias capsuladas:
Pneumococcus, Haemophylus influenza, Neisseria meningitidies

PROFILAXIA Antibiótica

Esplenectomia, hipoesplenismo e asplenismo

Esquema recomendado: Amoxicilina 250 mg 12/12h

Se intolerância/ alergia medicamentosa: Azitromicina 250 mg /dia
ou claritromicina 250 mg 12/12h

Esplenectomia cirúrgica:
- Durante 2 anos, após procedimento.

Esplenectomia por causa hematológica:
- Vitalícia

Bibliografia

- D. Gilbert, H. Chambers, G. Eliopoulos, M. Saag, A. Pavia. H.W. Boucher, Guía Sanford de Terapéutica Antimicrobiana 2021
- John R Wingard, MD, Eric Bow, MD, Prophylaxis of infection during chemotherapy-induced neutropenia in high-risk adults - Dec 2024. UpTodate
- Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. J Clin Oncol 2018; 36:3043.
- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections. Version 2.2023. http://www.nccn.org (Accessed on April 17, 2024).
- Young JAH, Weisdorf DJ. Infections in Recipients of Hematopoietic Stem Cell Transplants. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 2015;3425-39.e5.

PROFILAXIAS, PORQUÊ?
Profilaxia anti-fúngica

Inês Damásio

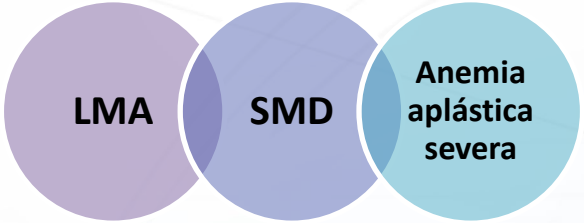
PROFILAXIA ANTI-FÚNGICA

Os doentes hematológicos são um grupo de doentes de risco para doença fúngica invasiva com elevada morbilidade e mortalidade relacionada

Fatores de risco para infeção fúngica invasiva:

- Duração da neutropenia
- Severidade da neutropenia
- Uso prolongado de antibióticos
- Relacionados com o tratamento (nº ciclos de quimioterapia, intensidade do tratamento)

Recomendação forte: Neutropenia prolongada (neutrófilos<500/µL por mais de 7 dias)



PROFILAXIA ANTI-FÚNGICA

CLASSIFICAÇÃO DOS FUNGOS

Leveduras
(um só núcleo)

Candida, Cryptococcus, Rhodotorula

Filamentosos (hifas) ou bolores
(multinucleados)

Aspergillus, Zygomycetes, Scedosporidium, Fusarium

Dimórficos
Levedura (forma parasitária ou patogénica); micélio (forma saprófita)

Micoses endémicas – *Coccidioides, Histoplasma, Blastomycosis Paracoccidiodes, Sporothrix*

Table 3. WHO fungal priority pathogens list

Critical group	High group	Medium group
Cryptococcus neoformans	*Nakaseomyces glabrata (Candida glabrata)*	*Scedosporium* spp.
Candida auris	*Histoplasma* spp.	*Lomentospora prolificans*
Aspergillus fumigatus	Eumycetoma causative agents	*Coccidioides* spp.
Candida albicans	Mucorales	*Pichia kudriavzeveii (Candida krusei)*
	Fusarium spp.	*Cryptococcus gattii*
	Candida tropicalis	*Talaromyces marneffei*
	Candida parapsilosis	*Pneumocystis jirovecii*
		Paracoccidioides spp.

WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

PROFILAXIA ANTI-FÚNGICA

O diagnóstico de doença fúngica invasiva implica um elevado grau de suspeição

Necessidade de culturas e/ou histopatologia→ diagnóstico e tratamento tardios

Ainda se associa nos dias de hoje a elevada mortalidade!

Problema emergente:
Pressão seletiva com a utilização de antifúngicos em profilaxia e tratamento empírico e na agricultura

↑ resistências: ↑*Candida não-albicans; Aspergillus* resistente a voriconazol; novas espécies *Aspergillus (terreus, lentulus, ustus*) e Mucorales (*Rhizopus* e *Mucor*)

Fungos emergentes: *Fusarium, Lomentospora, Scedosporium spp; Candida auris* (R aos antifúngicos clássicos)

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Selecionar os doentes de risco!

PROFILAXIA ANTI-FÚNGICA

Doente em risco de infeção por:

Candida spp

8-24%

Colonizam a pele e mucosas→ Mucosite!!!

- **Fluconazol***
- **Equinocandinas (espetro mais largo, apenas EV)**
  - **-- Caspofungina**
  - **-- Micafungina**
  - **-- Anidulofungina**
- **Restantes azois**

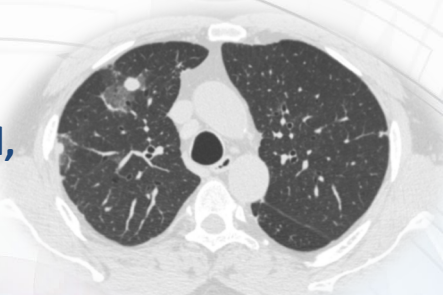
Aspergillus spp

2 a 28% (maioria 5-10%)

- ++ pneumonia

- Achados: ≥1 nódulo com ou sem opacidades em vidro despolido ao redor (sinal do halo), cavidades ou consolidação focal

- **Posaconazol**
- **Voriconazol**
- **Itraconazol, Isavuconazol, AnfoB**



**C. krusei* e *C. glabrata* são habitualmente R.

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Mucormicose: rino-orbitária, pulmonar, cerebral e/ou disseminada

PROFILAXIA ANTI-FÚNGICA

POSOLOGIA

Table 2. Strength of recommendation and QoE for antifungal prophylaxis in patients with high-risk neutropenia (<500 cells/μL ≥ 7 d

Intention	Intervention	SoR
Prevent IFD in patients with neutropenia (<500 cells/μL >7 days), excluding allogeneic HSCT	Posaconazole	A
		B
	Amphotericin B, liposomal, inhalation	B
	Isavuconazole	B
	Voriconazole	B
	Micafungin	B
	Amphotericin B, liposomal, i.v.	C
	Caspofungin	C
	Fluconazole	C
	Itraconazole, p.o. and i.v.	C
	SUBA-Itraconazole	C
	Amphotericin B deoxycholate	D

[a]Strong recommendation in AML/MDS RIC only.
[b]Other settings, e.g. VSAA and palliative treatment of MDS.
HSCT, haematopoietic stem cell transplantation; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; SUBA, SuperBioAv

Table 3. Dosage of recommended drugs (also refer to Table 2)

Drug	Dosage
Posaconazole, oral suspension	200 mg q8h p.o.
Posaconazole, tablet	300 mg q24h p.o. (q12h on day 1)
Posaconazole, i.v.	300 mg q24h i.v. (q12h on day 1)
Amphotericin B, liposomal, inhalation	12.5 mg twice weekly
Amphotericin B, liposomal, i.v.	Dosage not defined; variable dosages and dosing intervals
Caspofungin	50 mg q24h i.v. (70 mg on day 1, 70 mg q24h if patient weighs >80 kg)
Micafungin	50 mg q24h i.v.
Anidulafungin	100 mg q24h i.v. (200 mg on day 1)
Fluconazole	400 mg q24h p.o.
Itraconazole, capsules or i.v. formulation	200 mg q24h p.o./i.v.
Itraconazole, oral solution	2.5–7.5 mg/kg/d or 200 mg q24h
SUBA-itraconazole	200 mg q24h p.o.
Voriconazole **6mg/kg q12h D1**	4 mg/kg q12h i.v./p.o. **200mg q12h p.o.**
Isavuconazole	200 mg q24h i.v. (q8h on days 1–2)

i.v., intravenous; p.o., per os; SUBA, SuperBioAvailability.

Stemler J et al. Primary prophylaxis of invasive fungal diseases in patients with haematological malignancies: 2022 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). J Antimicrob Chemother. 2023 Aug 2;78(8):1813-1826. doi: 10.1093/jac/dkad143. PMID: 37311136; PMCID: PMC10393896.

PROFILAXIA ANTI-FÚNGICA

MONITORIZAÇÃO

Recomendado:
- Na suspeita de uma bIFD
- Condições que altere o metabolismo (obesidade, terapia substitutiva de órgão, GVHD intestinal ou UCI)

Table 4. Recommendations on TDM

Drug	Rationale	Target	SoR	QoE	Comment	Reference
Any triazole: in case of suspected breakthrough IFD	To clarify treatment options	Variable (see below)	A	III		
Oral itraconazole	To monitor for efficacy and toxicity	>0.5 mg/L	B	IIt		104–107
Isavuconazole	To monitor in case of toxicity	2–5 mg/L	C	IIt	Higher concentrations have been associated with an increased risk of adverse events	33,68,108–113
Posaconazole oral suspension	To support efficacy; in case of suspected impaired resorption	>0.7 mg/L (prophylaxis) >1 mg/L (treatment)	B	IIt	Reduced plasma levels have been demonstrated e.g. in case of GI-GvHD, diarrhoea, concomitant PPI	19,114–125
Posaconazole oral or i.v.	To support efficacy		B	III		
Voriconazole	To support efficacy	>1 mg/L	B	IIt		126,127
Voriconazole	To avoid toxicity	<4.5 mg/L	A	II	Recommendation in case of clinically attributed toxicity	

Comment: recommendations are not generally applicable for a prophylactic setting and refer to specific situation, see section 'Therapeutic drug monitoring and metabolism'.
GI-GvHD, gastrointestinal graft-versus-host-disease; IFD, invasive fungal infection; PPI, proton pump inhibitors

Voriconazol ou posaconazol: 3 dias após inicio ou ajuste de dose
Itraconazol:7 dias após inicio ou ajuste de dose

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Stemler J et al. Primary prophylaxis of invasive fungal diseases in patients with haematological malignancies: 2022 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). J Antimicrob Chemother. 2023 Aug 2;78(8):1813-1826. doi: 10.1093/jac/dkad143. PMID: 37311136; PMCID: PMC10393896.

PROFILAXIA ANTI-FÚNGICA

RECOMENDAÇÕES

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	Molecular target	Licensed indication or approval status (in the EU) in adults	Antifungal prophylaxis—recommendation	Antifungal prophylaxis—comment
Azacitidine	Inhibition of DNA methyltransferases that aberrantly hypermethylate tumour suppressor gene promoters	Acute myeloid leukaemia (>30% BM blasts); secondary acute myeloid leukaemia from myelodysplastic syndrome (20–30% BM blasts); myelodysplastic syndrome (intermediate to high risk on the IPSS-R); chronic myelomonocytic leukaemia (10–29% abnormal BM cells)	Conditional for antifungal prophylaxis; low certainty of evidence	Not generally recommended, but should be considered in patients pretreated with chemotherapy, in those with neutropenia at treatment initiation, or those with previous invasive fungal disease
Decitabine	Inhibition of DNA methyltransferases aberrantly hypermethylating tumour suppressor gene promoters	De-novo or secondary acute myeloid leukaemia	Conditional for antifungal prophylaxis; low certainty of evidence	Extrapolated from azacitidine
Venetoclax	Selective inhibitor of BCL2 (ie, antiapoptotic protein)	Chronic lymphocytic leukaemia; acute myeloid leukaemia (combination with HMA)	Conditional for antifungal prophylaxis; low certainty of evidence	Preferably with a triazole; adapt dose when using posaconazole or voriconazole concomitantly
Midostaurin	FLT3 inhibitor	Acute myeloid leukaemia with *FLT3* mutation	Conditional for antifungal prophylaxis; low certainty of evidence	Strong recommendation for triazoles during remission-induction treatment; individual decision for or against antifungal prophylaxis during maintenance treatment Monitor closely for potential DDI
Gilteritinib	Highly selective second-generation FLT3 inhibitor	Relapsed or refractory acute myeloid leukaemia with *FLT3* mutation	Either for or against antifungal prophylaxis (ie, context dependent); low certainty of evidence	In gilteritinib monotherapy, no benefit of antifungal prophylaxis; triazole prophylaxis should be considered in patients pretreated with chemotherapy or patients with long lasting neutropenia (ie, context-dependent)

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Stemler J et al. Antifungal prophylaxis in adult patients with acute myeloid leukaemia treated with novel targeted therapies: a systematic review and expert consensus recommendation from the European Hematology Association. Lancet Haematol. 2022 May;9(5):e361-e373. doi: 10.1016/S2352-3026(22)00073-4. Erratum in: Lancet Haematol. 2022 Jun;9(6):e398. doi: 10.1016/S2352-3026(22)00143-0. PMID: 35483397.

PROFILAXIA ANTI-FÚNGICA

RECOMENDAÇÕES

Quizartinib	FLT3-internal tandem duplication inhibitor	Acute myeloid leukaemia, currently not licensed[2]	Conditional for antifungal prophylaxis; low certainty of evidence	Strong recommendation for triazoles during remission-induction treatment, with a dose reduction of quizartinib; in quizartinib monotherapy, no recommendation for antifungal prophylaxis
Sorafenib	Multikinase inhibitor (endothelial growth factor receptors, SCFR, and FLT3)	Hepatocellular carcinoma, advanced renal cell carcinoma, thyroid carcinoma; off-label use for acute myeloid leukaemia	Conditional for antifungal prophylaxis; very low certainty of evidence	Strong recommendation for triazoles during remission-induction treatment
Ivosidenib	Isocitrate dehydrogenase-1 enzyme inhibitor	Acute myeloid leukaemia with *IDH1* mutation*	Either for or against antifungal prophylaxis (ie, context dependent); very low certainty of evidence	Consensus statement†; concomitant to CYP43A4 inhibitors, reduce ivosidenib dose to 250 mg/day
Enasidenib§¶	Isocitrate dehydrogenase-2 enzyme inhibitor	Acute myeloid leukaemia with *IDH2* mutation*‡	No recommendation	No comment
Gemtuzumab ozogamicin	Humanised CD33-directed monoclonal antibody–drug conjugate	Acute myeloid leukaemia with CD33 expression, in combination with chemotherapy during induction and consolidation treatment	Conditional for antifungal prophylaxis; very low certainty of evidence	Strong recommendation for triazoles during remission-induction treatment

- Quimioterapia de indução
- Caso a caso nas consolidações e manutenções

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Stemler J et al. Antifungal prophylaxis in adult patients with acute myeloid leukaemia treated with novel targeted therapies: a systematic review and expert consensus recommendation from the European Hematology Association. Lancet Haematol. 2022 May;9(5):e361-e373. doi: 10.1016/S2352-3026(22)00073-4. Erratum in: Lancet Haematol. 2022 Jun;9(6):e398. doi: 10.1016/S2352-3026(22)00143-0. PMID: 35483397.

PROFILAXIA ANTI-FÚNGICA

RECOMENDAÇÕES

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Transplante de progenitores hematopoiéticos

3 fases de maior risco de infeção fúngica invasiva

> Após condicionamento (fase de pré-enxerto)

> Pós enxerto inicial (GVHD aguda com necessidade de corticoterapia de alta dose, intestinal com disfunção de barreira)

> Pós enxerto tardio (GVHD crónica com necessidade de corticoterapia)

Alogénicos > Autólogos

PROFILAXIA ANTI-FÚNGICA

RECOMENDAÇÕES

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Outras indicações

(continued from above)	Antibacterial	Antifungal	Antiviral	PJP
High-dose Steroids		Mold-active prophylaxis if ≥ 1 mg/kg/day prednisone equivalents for 2 weeks (threshold not well defined, consider patient-specific risk factors)		
Purine Analogs *(fludarabine, cladribine, clofarabine, pentostatin)*		Consider mold-active prophylaxis if ANC <500 cells/mm^3 for >7 days		
Lymphoma *Most regimens*		No routine prophylaxis		
Intensive chemotherapy (e.g. R-CODOX-M/R-IVAC, HyperCVAD)		Consider fluconazole during neutropenia		
MT-R for PCNSL		No routine prophylaxis		
Multiple Myeloma *Proteasome inhibitors*		No routine prophylaxis		
Daratumumab				
Intensive chemotherapy (e.g. VTE-PACE)		Consider fluconazole during neutropenia		

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Edna Cheung, William Alegria, Gabriel Mannis, Stanford Antimicrobial Safety and Sustainability Program. Antimicrobial Prophylaxis in Hematology/Oncology Patients Admitted to Stanford Health Care.2020. disponível em https://med.stanford.edu/content/dam/sm/bugsanddrugs/documents/clinicalpathways/SHC-heme-onc-antimicrobial-prophylaxis.pdf

PROFILAXIA ANTI-FÚNGICA

INTERAÇÕES

Table 5. Targeted tumour therapies and potential drug–drug interactions

Population	Intention	Intervention	SoR	QoE	Reference
AML/MDS patients treated with					
Venetoclax	Prevent IFD	use triazole antifungal prophylaxis	A[a]	IIu,t	33, 72, 74, 75, 78
	Prevent toxicity	Reduce dose of venetoclax by at least 75% in combination with posaconazole or voriconazole and by 50% in combination with fluconazole or isavuconazole	A	IIu,t	
Gilteritinib	Prevent IFD	Use triazole antifungal prophylaxis without dose adjustment	A[a]	IIu	77
Midostaurin	Prevent IFD	If indicated, use triazole antifungal prophylaxis without dose adjustment	A	IIu	76
Quizartinib	Prevent IFD	If indicated, use triazole antifungal prophylaxis without dose adjustment	A[a]	IIu,t	79
	Prevent toxicity	Reduce quizartinib dose (60 to 30 mg *or* 30 to 20 mg) in combination with posaconazole or voriconazole	B	III	
Ivosidenib	Prevent IFD	If indicated, use triazole antifungal prophylaxis without dose adjustment	A[a]	III	80
	Prevent toxicity	Reduce ivosidenib dose to 250 mg/day in combination with posaconazole or voriconazole	B	III	

100mg→70mg

AML, acute myeloid leukaemia; IFD, invasive fungal disease; MDS, myelodysplastic syndrome.
[a]Strong recommendation for antifungal prophylaxis, if neutropenia ≥7 days is expected or present.

Stemler J et al. Primary prophylaxis of invasive fungal diseases in patients with haematological malignancies: 2022 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). J Antimicrob Chemother. 2023 Aug 2;78(8):1813-1826. doi: 10.1093/jac/dkad143. PMID: 37311136; PMCID: PMC10393896.

PROFILAXIA ANTI-FÚNGICA

Table 7. Recommendations for non-pharmaceutical interventions for prophylaxis of invasive fungal infections

Intention	Intervention	SoR	QoE	Reference
To prevent IFD	Neutropenic diet	D	IIr,u	84–86
To prevent invasive aspergillosis	Wearing well-fitting (FFP2) masks	C	IIt	87
To prevent IFD	HEPA filters	A	IIu	88–91
	LAF systems	B	IIu	
To prevent CVC-related fungal bloodstream infections	Chlorhexidine-coated CVC dressings	C	I	92
To prevent IFD	romyelocel-L*	B	I	93–95
	granulocyte transfusions	B	IIr	
	G-CSF	B	IIu	
To prevent IFD	Quit smoking	A	IIu	96–98

CVC, central venous catheter; FFP2, filtering face piece 2; G-CSF, granulocyte-colony-stimulating factor; HEPA, high efficiency particulate air; IFD, invasive fungal disease; LAF, laminar air flow.
*Cryopreserved human allogeneic myeloid progenitor cells.

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Stemler J et al. Primary prophylaxis of invasive fungal diseases in patients with haematological malignancies: 2022 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). J Antimicrob Chemother. 2023 Aug 2;78(8):1813-1826. doi: 10.1093/jac/dkad143. PMID: 37311136; PMCID: PMC10393896.

PROFILAXIA ANTI-FÚNGICA

PROFILAXIA SECUNDÁRIA

História prévia de infeção fúngica invasiva (++ *Aspergillus)* têm elevado risco de recorrência da infeção com quimioterapia

A profilaxia secundária pode prevenir a reativação da infeção na maioria dos doentes

VORICONAZOL

1ª linha para tratamento de infeção por *Aspergillus* spp e foi o melhor estudado como profilaxia secundária

PROFILAXIA ANTI-FÚNGICA

BIBLIOGRAFIA

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- Stemler J. et al. Antifungal prophylaxis in adult patients with acute myeloid leukaemia treated with novel targeted therapies: a systematic review and expert consensus recommendation from the European Hematology Association. Lancet Haematol. 2022 May;9(5):e361-e373. doi: 10.1016/S2352-3026(22)00073-4. Erratum in: Lancet Haematol. 2022 Jun;9(6):e398. doi: 10.1016/S2352-3026(22)00143-0. PMID: 35483397.

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- WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

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Profilaxias, porquê?

Leonardo Maia Moço

PROFILAXIAS, PORQUÊ?

PROFILAXIA ANTI-VÍRICA

	Antiviral
General Considerations	• HSV or VZV seropositive • Prior HSV or VZV episode • T-cell suppression • Prolonged neutropenia • Mucositis
Utility	Reduce risk of viral reactivation
Agents	Acyclovir
Preferred	
Alternative	If patient preference: famciclovir, valacyclovir

Antiviral Prophylaxis

Agent	Spectrum	Dosing	Dose Adjustment	CYP Drug Interactions	Adverse Effects
Acyclovir	Herpes simplex, Varicella zoster	400 mg PO BID* 2 mg/kg IV q12h (adjusted body weight in obese)	Renal	None	Increased SCr or BUN, AKI, phlebitis (with IV), headache, neurotoxicity, rash
Famciclovir	Similar to acyclovir	250 mg PO BID	Renal	None	Similar to acyclovir
Valacyclovir	Similar to acyclovir	500 mg PO BID	Renal	None	Similar to acyclovir

*Acyclovir 800 mg PO BID after hematopoietic cell transplant

200mg PO BID in fragile patients, with kidney disease

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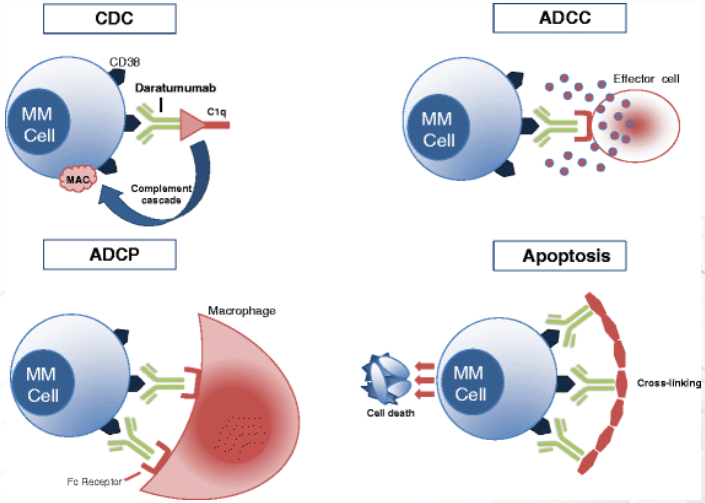
PROFILAXIAS, PORQUÊ?

PROFILAXIA ANTI-VÍRICA

AML *Induction*	During treatment course
Consolidation or low-intensity treatment	
ALL *Induction through maintenance*	During treatment course
Blinatumomab (for relapsed/refractory ALL)	Consider during treatment course
Lymphoma *Most regimens*	Consider during treatment course
Intensive chemotherapy (e.g. R-CODOX-M/R-IVAC, HyperCVAD)	
MT-R for PCNSL	
Multiple Myeloma *Proteasome inhibitors*	During treatment course
Daratumumab	During treatment course and 3 months after
Intensive chemotherapy (e.g. VTE-PACE)	Consider during treatment course

Daratumumab



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PROFILAXIAS, PORQUÊ?

PROFILAXIA ANTI-VÍRICA

AML *Induction*	During treatment course
Consolidation or low-intensity treatment	
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Blinatumomab (for relapsed/refractory ALL)	Consider during treatment course
Lymphoma *Most regimens*	Consider during treatment course
Intensive chemotherapy (e.g. R-CODOX-M/R-IVAC, HyperCVAD)	
MT-R for PCNSL	
Multiple Myeloma *Proteasome inhibitors*	During treatment course
Daratumumab	During treatment course and 3 months after
Intensive chemotherapy (e.g. VTE-PACE)	Consider during treatment course

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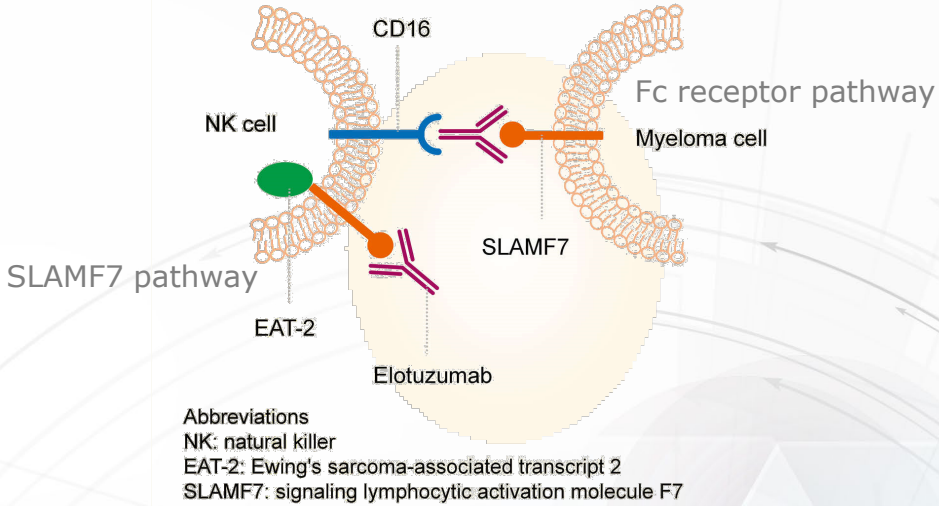
Elotuzumab



PROFILAXIAS, PORQUÊ?

PROFILAXIA ANTI-VÍRICA

High-dose Steroids	Consider during treatment course (threshold not well defined, increased risk with ≥ 10 mg/day prednisone equivalents)
Purine Analogs *(fludarabine, cladribine, clofarabine, pentostatin)*	Consider during treatment course

Considerations for specific treatments

Treatment Agent	Prophylaxis	Additional Monitoring
Alemtuzumab	HSV and PJP prophylaxis until minimum of 2 months after treatment and CD4 > 200 cells/mm^3	CMV surveillance
BTK inhibitors (e.g. ibrutinib)	No routine prophylaxis, generally higher infection risk in first 6 months Consider VZV and PJP prophylaxis (assess patient-specific risk factors)	Consider differential diagnoses (viral, bacterial, fungal, PJP) if clinical suspicion for infection
PI3K inhibitors (e.g. idelalisib)	Consider PJP prophylaxis	CMV surveillance

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PROFILAXIAS, PORQUÊ?

PROFILAXIA ANTI-VÍRICA

	Fred Hutchinson Cancer Center	City of Hope National Medical Center	Memorial Sloan Kettering Cancer Center	Published guidelines and references
HSV 1, 2	Acyclovir (initially IV, then 800 mg) or valacyclovir (500 mg) twice daily for 1 y or 6 mo after discontinuation of systemic immunosuppression; at least 3 y after UBC transplantation†	Acyclovir (initially IV, then 400 mg twice daily) or valacyclovir (500 mg) twice daily for 1 y or 6 mo after discontinuation`n of systemic immunosuppression†	Acyclovir (initially IV, then 400 mg twice daily for 1 y or 6 mo after discontinuation of systemic immunosuppression; at least 3 y after UBC transplantation	Tomblyn et al 2009[34]
VZV				
Antivirals	Acyclovir (initially IV, then 800 mg) or valacyclovir (500 mg) twice daily for 1 y or 6 mo after discontinuation of systemic immunosuppression; at least 3 y after UBC transplantation	Acyclovir (initially IV, then 400 mg twice daily) or valacyclovir (500 mg) twice daily for 1 y or 6 mo after discontinuation of systemic immunosuppression	Acyclovir (initially IV, then 400 mg twice daily for 1 y or 6 mo after discontinuation of systemic immunosuppression; at least 3 y after UBC transplantation	Tomblyn et al 2009[34]

Transplante de precursores hematopoiéticos

Duração recomendada:
>6m após descontinuação de IST
e CD4+ > 200/mL

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Sanjeet S. Dadwal, Genovefa A. Papanicolaou, Michael Boeckh; How I prevent viral reactivation in high-risk patients. Blood 2023; 141 (17): 2062–2074.
doi: https://doi.org/10.1182/blood.2021014676

PROFILAXIAS, PORQUÊ?

PROFILAXIA ANTI-VÍRICA

CMV

R+

D+/R−

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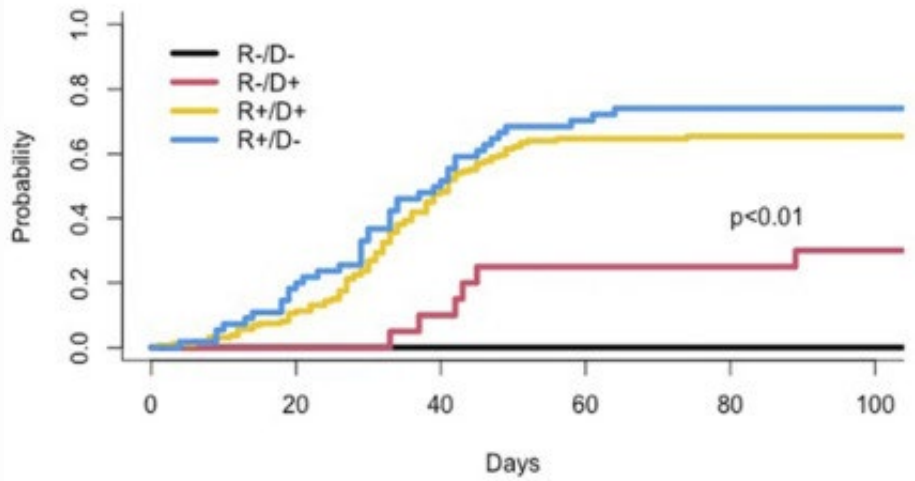
Figure 1 CMV Reactivation - Serology pre HCST



Transplante de precursores hematopoiéticos

RISK FACTOR	CMV REACTIVATION	CMV DISEASE
D-/R+		
GVHD		
UD/MMD		
AGE (↑)		

Vinicius Campos Molla, Roberta Azevedo, Jessica Fernandes Ramos, Danilo Belchior Ponciano, Pedro Henrique Arruda de Moraes, Ana Rita Da Fonseca, Maria Cristina Nunez Seiwald, Mariana Serpa, Aliana Meneses Ferreira, Roberta Shcolnik Szor, Rayana Bomfim Leonel, Erick Menezes Xavier, Vanderson Rocha, Luciana Tucunduva, Yana Novis, Marcio Nucci, Esper Kallas, Celso Arrais; Increased Risk of for Cytomegalovirus Reactivation after Allogeneic HSCT in T-Cell Depleted Patients. Blood 2020; 136 (Supplement 1): 36–37.

PROFILAXIAS, PORQUÊ?

PROFILAXIA ANTI-VÍRICA

	Fred Hutchinson Cancer Center	City of Hope National Medical Center	Memorial Sloan Kettering Cancer Center	Published guidelines and references
CMV				
R⁺	Before day 100: letermovir	Before day 100: letermovir	Before day 100: letermovir	Ljungman et al 2019[33] Hakki et al 2021[41]
	Highest risk (UBCT): start at day 2	Regardless of risk stratification, start at day 7	High risk: start at day 7, treat preemptively if viral load reaches 300 IU/mL Low risk: with start of other oral medications (before day 28), treat preemptively if viral load reaches 1000 IU/mL	
	High risk: start at day 7, treat preemptively if viral load reaches 150 IU/mL Low risk: with start of other oral medications (before day 28), treat preemptively if viral load reaches 500 IU/mL	High risk: treat preemptively if viral load reaches >470 IU/mL Low risk: treat preemptively if viral load reaches 1410 IU/mL		
	After day 100: preemptive therapy in high-risk patients (threshold ≥500 IU/mL)	After day 100: preemptive therapy in high-risk patients (threshold ≥470 IU/mL)	After day 100: High-risk patients: letermovir through day 180 or cessation of immunosuppressants. Preemptive therapy (threshold >300 IU/mL ×2)	
	Low risk patients: preemptive therapy (threshold 1000 IU/mL)	Low risk patients: preemptive therapy (threshold 1000 IU/mL)	Low risk patients: preemptive therapy (threshold 1000 IU/mL)	
D⁺/R⁻	PCR-guided preemptive therapy at Low Risk ≥500 IU/mL High Risk ≥150 IU/mL After day 100: ≥500 IU/mL	PCR-guided preemptive therapy at ≥470 IU/mL ×2 (same threshold after day 100)	PCR-guided preemptive therapy at Low Risk >500 IU/mL; High Risk >137 IU/mL After day 100: >500 IU/mL	Ljungman et al 2019[33] Hakki et al 2021[41]

Transplante de precursores hematopoiéticos

TCD or alemtuzumab
Mismatch
Haploidêntico
CCT >1mg/kg/d

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Sanjeet S. Dadwal, Genovefa A. Papanicolaou, Michael Boeckh; How I prevent viral reactivation in high-risk patients. Blood 2023; 141 (17): 2062–2074. doi: https://doi.org/10.1182/blood.2021014676

PROFILAXIAS, PORQUÊ?

PROFILAXIA ANTI-VÍRICA

	Fred Hutchinson Cancer Center	City of Hope National Medical Center	Memorial Sloan Kettering Cancer Center	Published guidelines and references
CMV				
R⁺	Before day 100: letermovir	Before day 100: letermovir	Before day 100: letermovir	Ljungman et al 2019[33] Hakki et al 2021[41]
	Highest risk (UBCT): start at day 2 High risk: start at day 7, treat preemptively if viral load reaches 150 IU/mL Low risk: with start of other oral medications (before day 28), treat preemptively if viral load reaches 500 IU/mL	Regardless of risk stratification, start at day 7 High risk: treat preemptively if viral load reaches >470 IU/mL Low risk: treat preemptively if viral load reaches 1410 IU/mL	High risk: start at day 7, treat preemptively if viral load reaches 300 IU/mL Low risk: with start of other oral medications (before day 28), treat preemptively if viral load reaches 1000 IU/mL	
	After day 100: preemptive therapy in high-risk patients (threshold ≥500 IU/mL)	After day 100: preemptive therapy in high-risk patients (threshold ≥470 IU/mL)	After day 100: High-risk patients: letermovir through day 180 or cessation of immunosuppressants. Preemptive therapy (threshold >300 IU/mL ×2)	
	Low risk patients: preemptive therapy (threshold 1000 IU/mL)	Low risk patients: preemptive therapy (threshold 1000 IU/mL)	Low risk patients: preemptive therapy (threshold 1000 IU/mL)	
D⁺/R⁻	PCR-guided preemptive therapy at Low Risk ≥500 IU/mL High Risk ≥150 IU/mL After day 100: ≥500 IU/mL	PCR-guided preemptive therapy at ≥470 IU/mL ×2 (same threshold after day 100)	PCR-guided preemptive therapy at Low Risk >500 IU/mL; High Risk >137 IU/mL After day 100: >500 IU/mL	Ljungman et al 2019[33] Hakki et al 2021[41]

Transplante de precursores hematopoiéticos

ATENÇÃO !

Se indicação para letermovir: manter (val)aciclovir

Se indicação para tx pre-emptivo com (val)ganciclovir suspender (val)aciclovir

Se indicação para tx pre-emptivo de 2ªL com foscarnet ou maribavir: retomar (val)aciclovir

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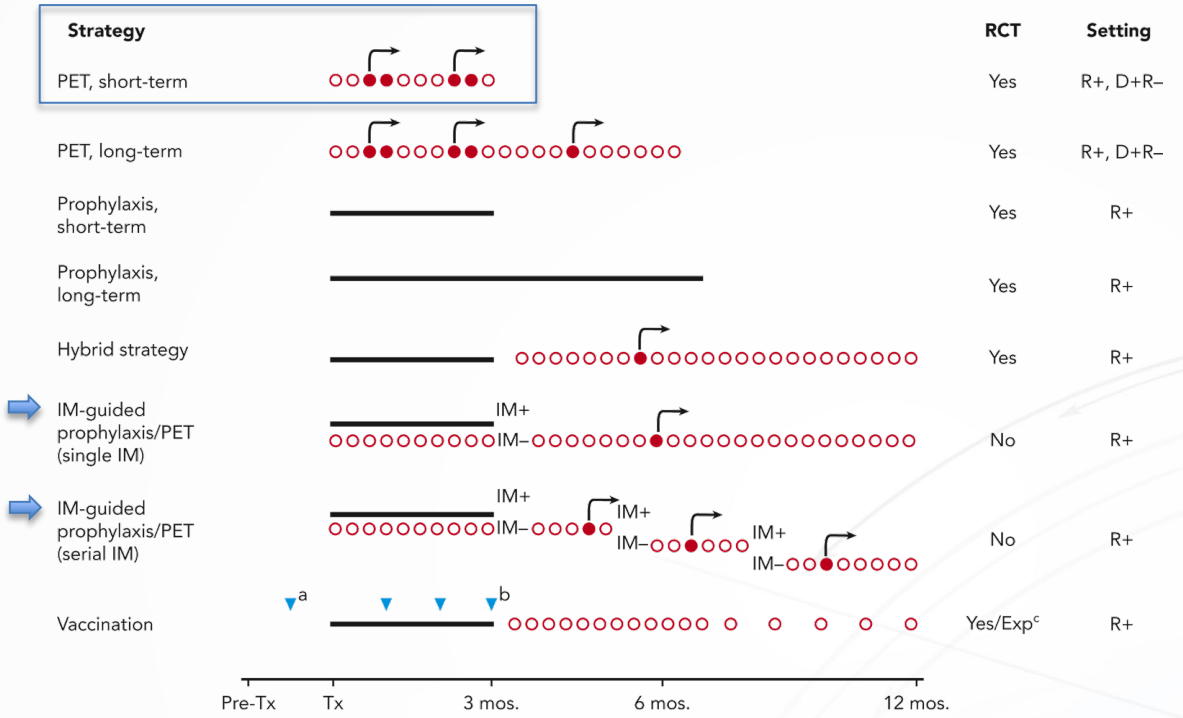
Sanjeet S. Dadwal, Genovefa A. Papanicolaou, Michael Boeckh; How I prevent viral reactivation in high-risk patients. Blood 2023; 141 (17): 2062–2074. doi: https://doi.org/10.1182/blood.2021014676

PROFILAXIAS, PORQUÊ?

PROFILAXIA ANTI-VÍRICA



Transplante de precursores hematopoiéticos

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Sanjeet S. Dadwal, Genovefa A. Papanicolaou, Michael Boeckh; How I prevent viral reactivation in high-risk patients. Blood 2023; 141 (17): 2062–2074. doi: https://doi.org/10.1182/blood.2021014676

PROFILAXIAS, PORQUÊ?

PROFILAXIA ANTI-VÍRICA

	Fred Hutchinson Cancer Center	City of Hope National Medical Center	Memorial Sloan Kettering Cancer Center	Published guidelines and references
EBV	No routine prophylaxis T-cell depletion: PCR surveillance and preemptive rituximab at ≥1000 copies/mL	No routine prophylaxis T-cell depletion: PCR surveillance and preemptive rituximab at >2000 copies/mL	No routine prophylaxis T-cell depletion, UCB, ATG: PCR surveillance and preemptive rituximab or donor-derived EBV CTL infusion (or third party EBV CTL for UCB)§	Tomblyn et al 2009[34]
HHV-6	Symptom-based surveillance with PCR work-up in suspected cases	Symptom-based surveillance with PCR work-up in suspected cases	Symptom-based surveillance with PCR work-up in suspected cases	Ward et al 2019[43]
			UCB: PCR surveillance until day 60, treatment based on clinical suspicion for disease	
Adenovirus	Targeted PCR surveillance and preemptive treatment (threshold ≥1000 copies/mL) in high-risk settings (TCD, ATG)	Targeted PCR surveillance and preemptive treatment (no fixed viral load threshold) in high-risk settings (TCD, ATG)	Targeted PCR surveillance and preemptive treatment in high-risk settings (TCD, ATG, UCB, Haploidentical, mismatched) Thresholds dependent on time from transplant, donor and graft type‖	Tomblyn et al 2009[34]
	Low risk setting: symptom-based testing and treatment of disease	Low risk setting: symptom-baesd testing and treatment of disease	Low risk setting: symptom-based testing and treatment of disease	
BK virus	No specific antiviral prophylaxis	No specific antiviral prophylaxis	No specific antiviral prophylaxis	Cesaro et al 2018[44]

‖High risk setting: ADV viral load: <day 30, >200 copies/mL; day 30 to 100, >1000 copies/mL; >day 100, >10 000 copies/mL.

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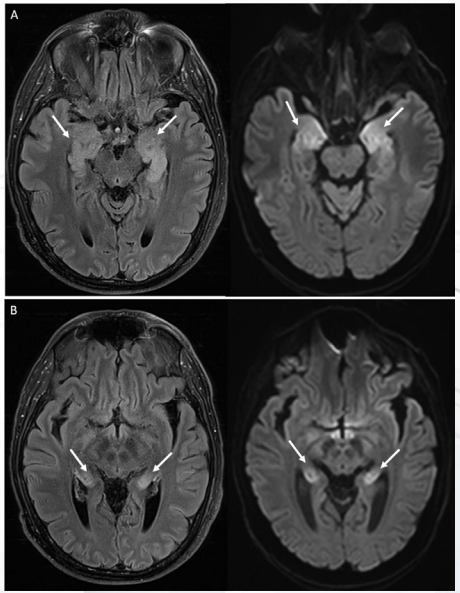
Sanjeet S. Dadwal, Genovefa A. Papanicolaou, Michael Boeckh; How I prevent viral reactivation in high-risk patients. Blood 2023; 141 (17): 2062–2074. doi: https://doi.org/10.1182/blood.2021014676

Transplante de precursores hematopoiéticos



Encefalite Límbica a HHV6

PROFILAXIAS, PORQUÊ?

VACINAÇÃO

Sob tratamento

ANTES: > **2-4 semanas**

APÓS: > **3 meses**
OU
> 6 meses se terapêutica anti-célula B

ATENÇÃO

Se for necessário vacinar em tratamento ativo, a toma deve ser feita imediatamente antes do ciclo seguinte

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Einarsson J, Wilkinson AN. Vaccination considerations for patients receiving cancer therapy. Can Fam Physician. 2022 Oct;68(10):751-752. doi: 10.46747/cfp.6810751. PMID: 36241417; PMCID: PMC9833152.

PROFILAXIAS, PORQUÊ?

VACINAÇÃO

ATENÇÃO
Considerar sempre como vacina-*naive*

Transplante de precursores hematopoiéticos

Vaccine	Recommendation level[a]	Time post-SCT to initiate vaccination	Number of doses
Pneumococcal conjugate	II	3–6 mon	3-4[b]
Inactivated influenza	II	4–6 mon	Annually
Tetanus-diphtheria-acelluar pertussis[c]	Tetanus-diphtheria (II) Pertussis (III)	6–12 mon	3[d]
Haemophilus influenzae type b	II	6–12 mon	3
Hepatitis B	II	6–12 mon	3
Hepatitis A	III	6–12 mon	2
Measles-Mumps-Rubella	II Contraindicated if < 24 mon post-SCT, active GVHD, on immune suppression	24 mon	1-2
Meningococcus	II	6-12 mon	1
Inactivated poliovirus	III	6-12 mon	3
Chickenpox	III Contraindicated if < 24 mon post-SCT, active GVHD, on immune suppression	24 mon	1

Pneumococcus
H. influenza
Vírus influenza
SARS-CoV-3
após **3M**

Vacinas vivas
(VASPR, VZV)
após **24M**

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Lee DG. Vaccination of Hematopoietic Stem Cell Transplantation Recipients: Perspective in Korea. Infect Chemother. 2013 Sep;45(3):272-282. https://doi.org/10.3947/ic.2013.45.3.272

PROFILAXIAS, PORQUÊ?

VACINAÇÃO

Transplante de precursores hematopoiéticos

Table 29.1 ECIL recommendations for allogeneic-HCT recipients (Cordonnier et al. 2019)

Vaccine	No. of doses[a]	Time post-HCT to initiate vaccine	Grading
Influenza (inactivated)	1 (or 2, special cases)[b]	• >6 months • As long as patient is judged to be IS • Yearly, lifelong • From 3 months in case of a community outbreak	AIIr BIIr BIIr
Measles–mumps–rubella • Measles In sero(−) patients, with no GVHD, no IS, no REL of underlying disease, and no IGIV during the previous months, at least 3 months, ideally between 8 and 11 months • Rubella In sero(−) women and of childbearing potential, with same precautions as for measles vaccine	1 (2 in children) MMR 1 MMR	• ≥24 months ≥12 months in case of measles outbreak in patients with low-grade IS • ≥24 months	BIIu CIII CIIu
Virus hepatitis B[c] • Sero(−) patients before HCT and patients vaccinated pre-HCT but lost their immunity at 6 months) • Previously infected and anti-HBs <10 IU/L • Sero(−) patients with a donor with positive anti-HBc	3[d]	6–12 months 6–12 months Vaccine before transplant	BIIt BIII BIII

Ponderar 2ª toma se 1ª toma + precoce

Carreras E, Dufour C, Mohty M, Kröger N, eds. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies. 7th ed. Cham (CH): Springer; 2019.

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PROFILAXIAS, PORQUÊ?

VACINAÇÃO

Transplante de precursores hematopoiéticos

P13
P23

Table 29.1 ECIL recommendations for allogeneic-HCT recipients (Cordonnier et al. 2019)

Vaccine	No. of doses[a]	Time post-HCT to initiate vaccine	Grading
Pneumococcal conjugate (PCV) **Polysaccharidic vaccine** In case of GVHD, use PCV instead of PPS for this fourth dose (BIIr)	3 1	3 months 12 months (no earlier than 8 weeks after last PCV)	AI BI
Meningococcal conjugate (in accordance with country recommendations and local prevalence)	2	From 6 months • For men-C or tetravalent vaccine • For men-B vaccine	BIIu BIII
Haemophilus influenzae conjugate	3	3 months or 6 months	BIIr
Diphtheria-tetanus (DT is preferred to Td CIII)	3[e]	From 6 months	BIu
Pertussis (acellular) (DTaP is preferred over Tdap CIII)	3[e]	From 6 to 12 months	CIII
SARS-CoV-2		Three doses of COVID-19 (preferably mRNA) vaccine starting 3–6 months post-HCT as primary course Further booster vaccine doses recommended as per local guidelines, and at least 3–6 months after the last dose of vaccine[36,75,79,146]	

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Carreras E, Dufour C, Mohty M, Kröger N, eds. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies. 7th ed. Cham (CH): Springer; 2019.

PROFILAXIAS, PORQUÊ?

VACINAÇÃO

Transplante de precursores hematopoiéticos

Table 29.1 ECIL recommendations for allogeneic-HCT recipients (Cordonnier et al. 2019)

Vaccine	No. of doses[a]	Time post-HCT to initiate vaccine	Grading
Human papilloma virus (HPV) Follow recommendations for general population in each country	According to official label	From 6 to 12 months	BIIu
Inactivated polio	3[e]	6–12 months	BIIu
Live-attenuated varicella vaccine	1	Can be considered in sero(−) patients, with ALL the following: >24 m from HCT, no GVHD, no IS, no REL of the underlying disease, and no IGIV in the previous months, at least 3 months, ideally between 8 and 11 months	BIIr
	2	The addition of a second dose in adults may be considered in patients who were sero(−) before HCT or had no history of VZ infect	
Live-attenuated zoster vaccine	Not recommended		DIII

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Carreras E, Dufour C, Mohty M, Kröger N, eds. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies. 7th ed. Cham (CH): Springer; 2019.

PROFILAXIAS, PORQUÊ?

VACINAÇÃO

CART

Vacinas inativadas: >3-**6m**
Vacinas vivas atenuadas: >**12m**

Vaccines	Pre-CAR-T	≥6 months	≥8 months	≥10 months	≥12 months	≥18 months
IIV	Influenza	Influenza				
PCV	(se endémico)	PCV13	PCV13	PCV13		
PPSV23						PPSV23
DTaP		DTaP	Td	Td		
HAV		HAV			HAV	
HBV	(se endémico)	HBV	HBV		HBV	
Varicella zoster[b]					aRZV	aRZV
SARS-CoV-2	Pelo menos **2 sem** antes da linfodepleção	≥ **3-6 months**				

Revaccination with a primary course of three mRNA COVID-19 vaccines is now recommended for patients following CAR-T therapy

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Reynolds G, Hall VG, Teh BW. Vaccine schedule recommendations and updates for patients with hematologic malignancy post-hematopoietic cell transplant or CAR T-cell therapy. Transpl Infect Dis. 2023;25 Suppl 1(Suppl 1):e14109. doi:10.1111/tid.14109

PROFILAXIAS, PORQUÊ?

VACINAÇÃO

Monitorização da reconstituição imune 

- CD4+ > 200/uL
- CD19+ ou CD20+ > 20/uL
- IgG > 400 mg/dL
- (IgA > 6 mg/dL)

Imunoterapias que **não** interferem com resposta B/T a imunizações:

- iBTK
- TKI
- Inibidores de checkpoint
- IMiD

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Reynolds G, Hall VG, Teh BW. Vaccine schedule recommendations and updates for patients with hematologic malignancy post-hematopoietic cell transplant or CAR T-cell therapy. Transpl Infect Dis. 2023;25 Suppl 1(Suppl 1):e14109. doi:10.1111/tid.14109

PROFILAXIAS, PORQUÊ?

VACINAÇÃO

Conviventes de doentes imunodeprimidos

- Influenza: anual
- SARS-CoV-2: anual
- (VZV se seronegativos)

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Direção-Geral da Saúde. Programa Nacional de Vacinação 2020. Lisboa: DGS, 2020
Centers for Disease Control and Prevention, Immunization Schedules;
https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html; consultado a 02/01/2025.

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Coffee-Break

16h20 às 16h40

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GRUPO 2

Complicações da terapia CAR-T: Uma abordagem prática

Palestrantes:

André Antunes (Hospital Dr. Nélio Mendonça - Funchal)

Cátia Almeida (ULS de Coimbra)

Francys Llanos (IPO de Lisboa)

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FÓRUM 2025 • 9ª EDIÇÃO

Complicações da terapia CAR-T: Uma abordagem prática

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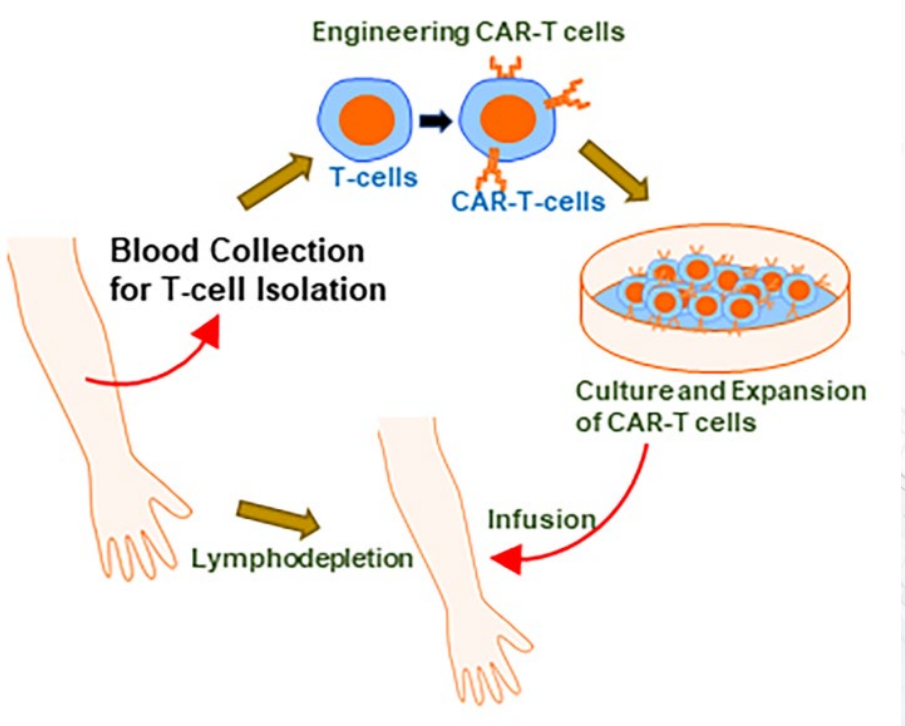
Introdução e Fundamento

Cátia Almeida

Complicações da terapia CAR-T

INTRODUÇÃO

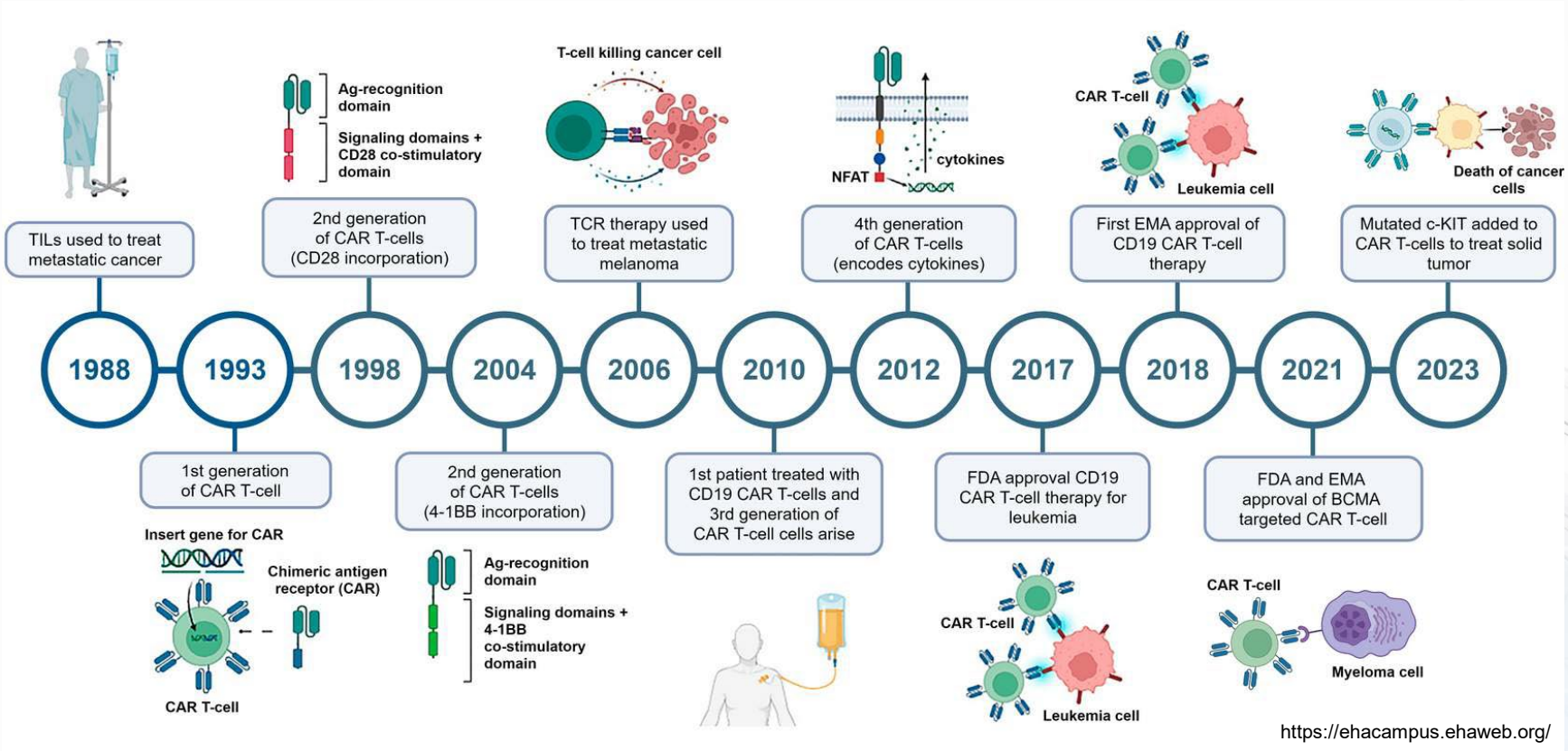
- Representa um grande avanço no tratamento de patologias hematológicas;
- Imunoterapia que modifica as células T do doente para expressarem a proteína CAR na sua superfície;
- Têm sido observadas elevadas taxas de resposta com esta terapêutica



Ahmar Aamid et al, 2020

Complicações da terapia CAR-T

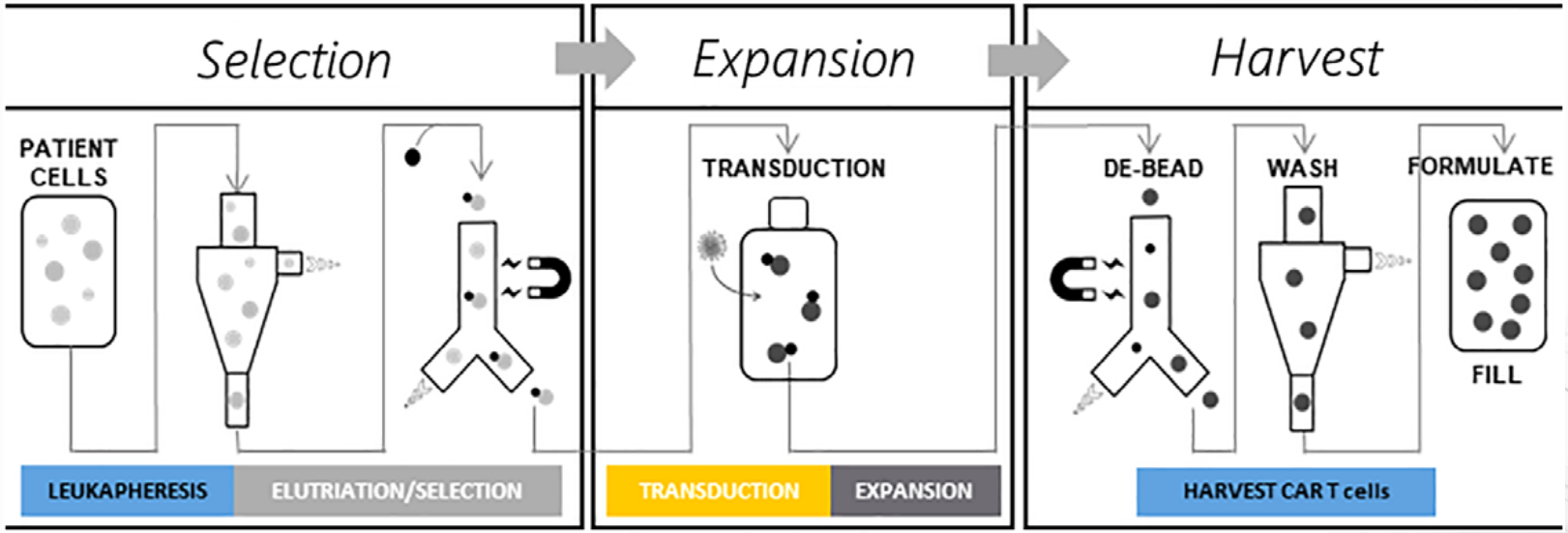
TERAPIA CART: EVOLUÇÃO HISTÓRICA



https://ehacampus.ehaweb.org/

Complicações da terapia CAR-T

TERAPIA CART: PROCESSO DE PRODUÇÃO



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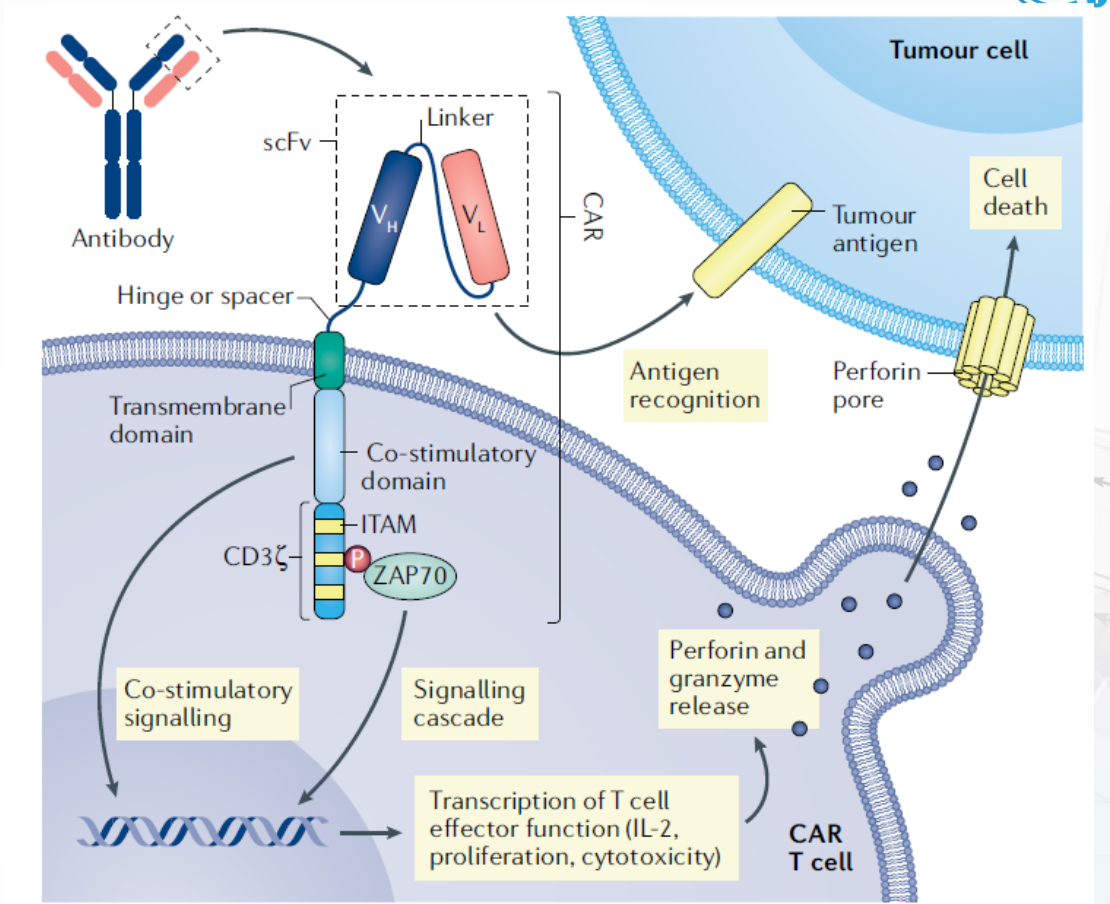
Feins, A. Et al, An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer, 2019

Complicações da terapia CAR-T

TERAPIA CART:
MECANISMO DE AÇÃO



Larson et al, 2021

Complicações da terapia CAR-T

TERAPIA CART: TERAPÊUTICAS APROVADAS

Commercial CAR T-cell therapy	Target	Indication	Date of EMA marketing authorization	Date of FDA marketing authorization
tisagenlecleucel/Kymriah®	CD19	Paediatric 3L+ ALL	September 2018 (EMA, 2021b)	August 2017 (FDA, 2021c)
		3L+ DLBCL	September 2018 (EMA, 2021b)	May 2018 (FDA, 2021c)
		3L+ HGBL	—	May 2018 (FDA, 2021c)
		3L+ DLBCL from FL	—	May 2018 (FDA, 2021c)
		3L+ FL	March 2022/positive CHMP opinion received (EMA, 2022c)	—
axicabtagene ciloleucel/Yescarta®	CD19	3L+ DLBCL	September 2018 (EMA, 2021d)	October 2017 (FDA, 2022c)
		2L+ DLBCL	—	April 2022 (FDA, 2022b)
		3L+ PMBCL	September 2018 (EMA, 2021d)	October 2017 (FDA, 2022c)
		3L+ HGBL	—	October 2017 (FDA, 2022c)
		3L+ DLBCL from FL	—	October 2017 (FDA, 2022c)
		4L+ FL (EMA)	April 2022/positive CHMP opinion received (EMA, 2022d)	April 2021 (FDA, 2022c)
		3L+ FL (FDA)		
brexucabtagene autoleucel/Tecartus®	CD19	3L+ MCL (EMA)	December 2020 (EMA, 2021c)	July 2020 (FDA, 2021d)
		2L+ MCL (FDA)		
		Adult 2L+ ALL	—	October 2021 (FDA, 2021d)
isocabtagene maraleucel/Breyanzi®	CD19	3L+ DLBCL	April 2022 (EMA, 2022a)	February 2021 (FDA, 2021b)
		3L+ PMBCL	April 2022 (EMA, 2022a)	February 2021 (FDA, 2021b)
		3L+ HGBL	—	February 2021 (FDA, 2021b)
		3L+ DLBCL from FL	—	February 2021 (FDA, 2021b)
		3L+ FL (grade 3B)	April 2022 (EMA, 2022a)	February 2021 (FDA, 2021b)
idecabtagene vicleucel/Abecma®	BCMA	4L+ MM (EMA)	August 2021 (EMA, 2021a)	March 2021 (FDA, 2021a)
		5L+ MM (FDA)		
ciltacabtagene autoleucel/Carvykti®	BCMA	4L+ MM (EMA)	March 2022/positive CHMP opinion received (EMA, 2022b)	February 2022 (FDA, 2022a)
		5L+ MM (FDA)		

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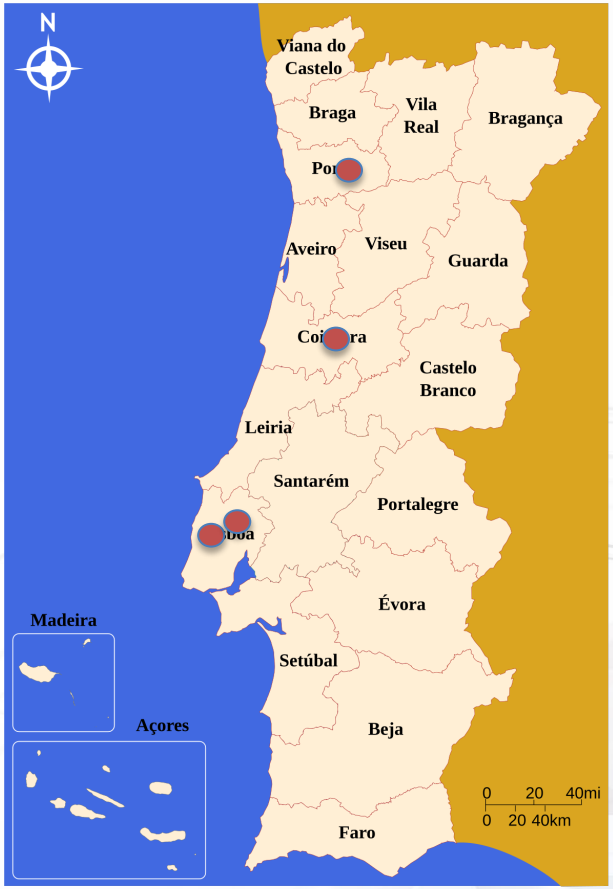
Jommi et al, 2022

Complicações da terapia CAR-T

TERAPIA CART: E EM PORTUGAL?

- IPO Porto
- ULS Coimbra
- ULS Santa Maria
- IPO Lisboa



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Complicações Imunológicas Precoces

André Antunes

Complicações Imunológicas Precoces

Síndrome de Libertação de Citocinas

Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas (CRS)

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➢ Prevalência e Factores de Risco

- Tipo de CAR-T
- Dose de CAR-T
- Idade
- Carga Tumoral
- Infeção concomitante
- Hipofosfatémia

	Grau 1-2	Grau ≥3
Axi-cel	90% (76 – 100%)	7% (6 – 11%)
Tisa-cel	57% (49 – 61%)	6% (0 – 23%)
Liso-cel	43% (36 – 60%)	1% (1– 2%)
Brexu-cel	91%	15%
Cilta-cel	95%	5%
Ide-cel	88%	5%

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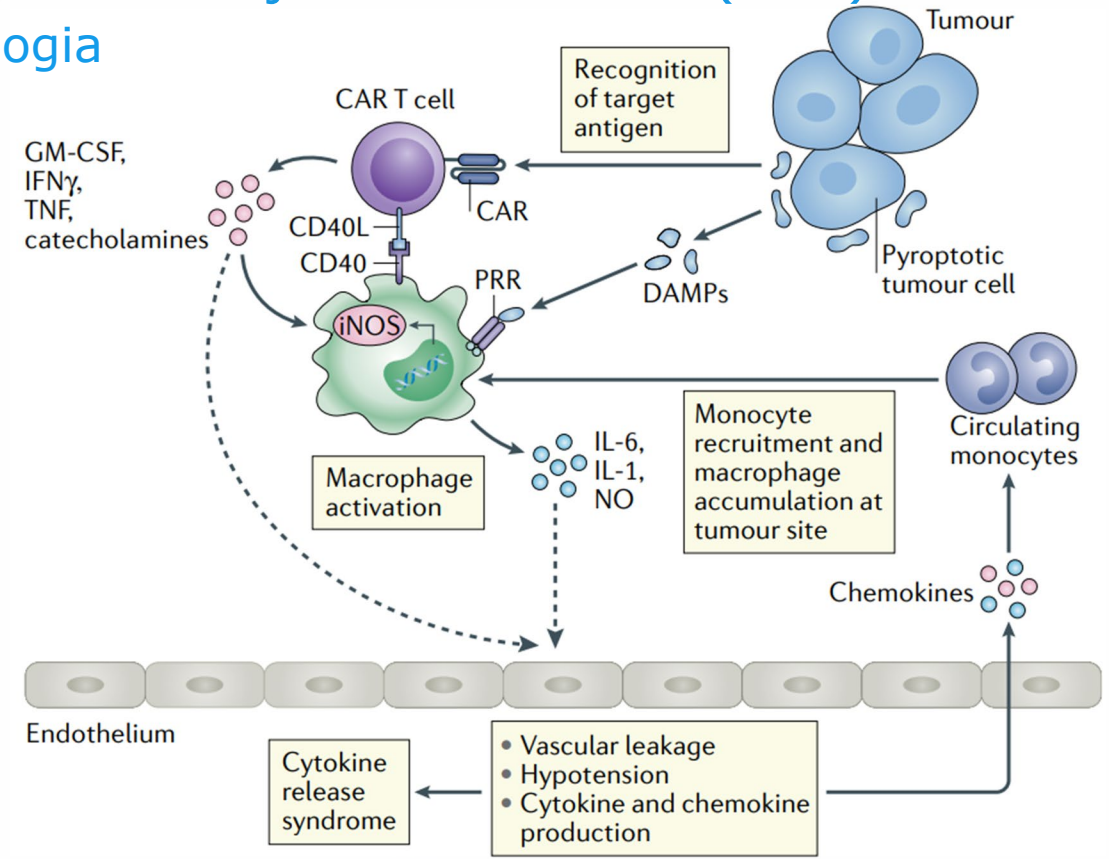
Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas (CRS)

- Fisiopatologia



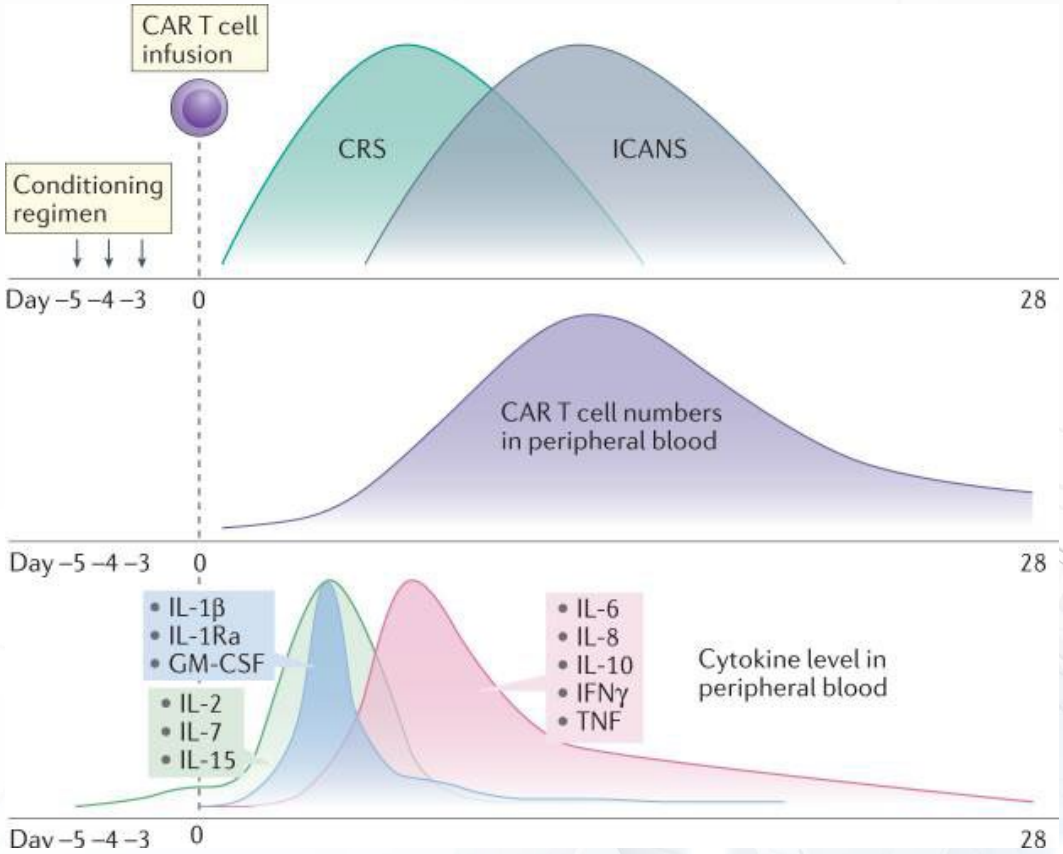
Morris, Emma C et al. "Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy." *Nature reviews. Immunology* vol. 22,2 (2022)

Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas (CRS)

➢ Abordagem Diagnóstica

- Início: D+1 a D+14 (Mediana D+3)
- Duração: 1 – 10 dias (Mediana 4 dias)



Morris, Emma C et al. "Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy." *Nature reviews. Immunology* vol. 22,2 (2022)

Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas (CRS)

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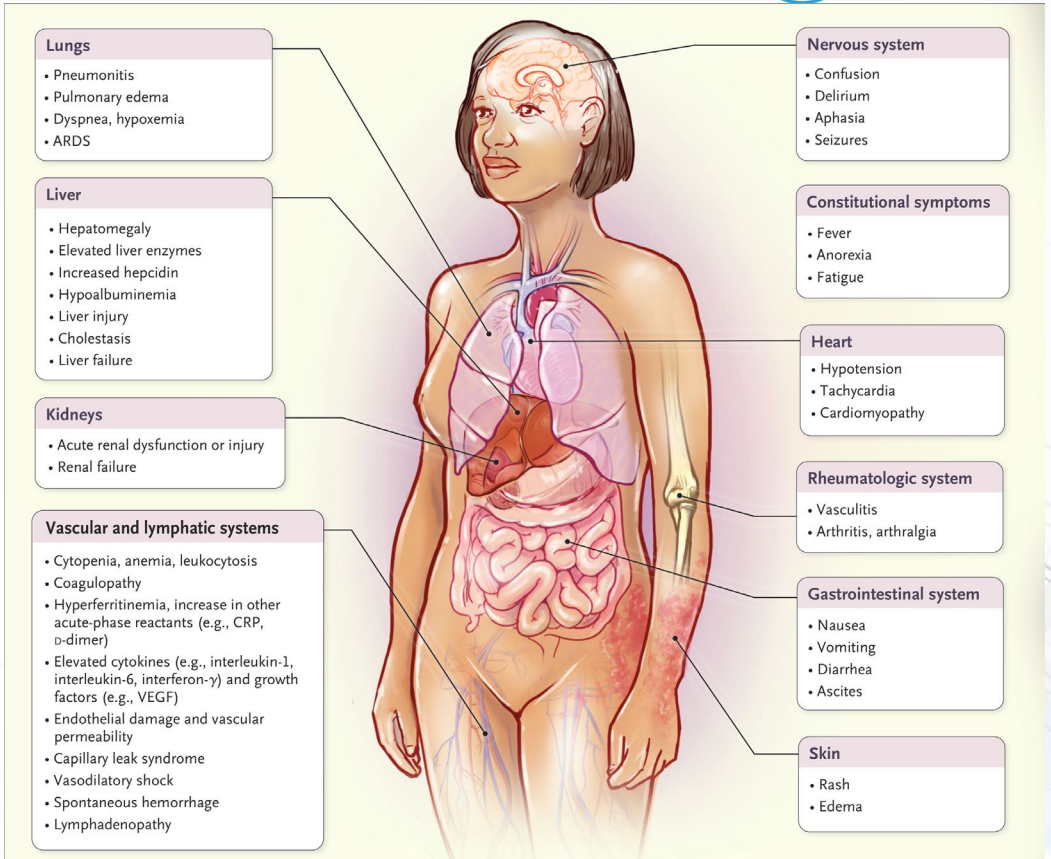
➢ Abordagem Diagnóstica

- Febre
- Sintomas constitucionais
- Instabilidade hemodinâmica
- Hipóxia

⚠ Diagnóstico de exclusão



Fajgenbaum, David C, and Carl H June. "Cytokine Storm." *The New England journal of medicine* vol. 383,23 (2020)

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Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas

- Abordagem Diagnóstica

Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas

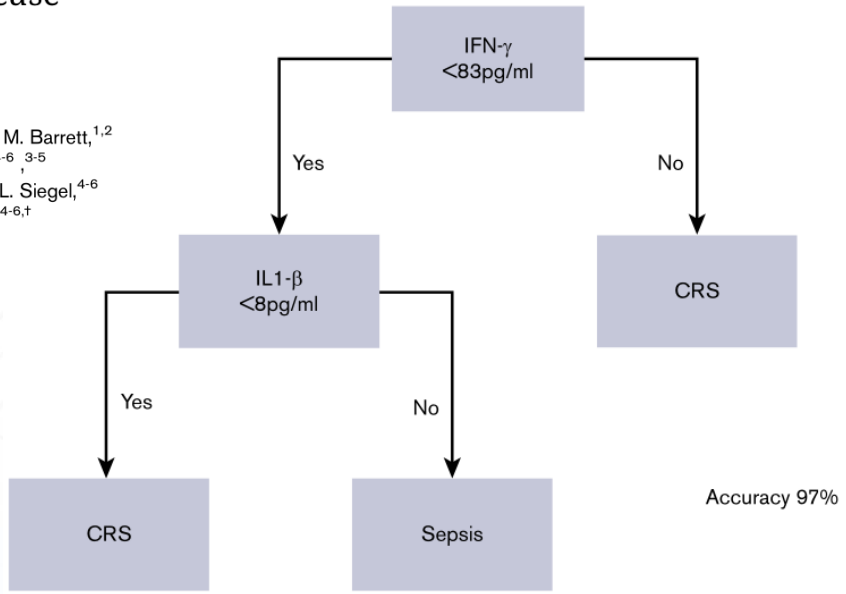
➢ Abordagem Diagnóstica

REGULAR ARTICLE

blood advances

Diagnostic biomarkers to differentiate sepsis from cytokine release syndrome in critically ill children

Caroline Diorio,[1,2,*] Pamela A. Shaw,[3,*] Edward Pequignot,[4] Alena Orlenko,[3] Fang Chen,[4-6] Richard Aplenc,[1,2,5] David M. Barrett,[1,2] Hamid Bassiri,[7] Edward Behrens,[2,8] Amanda M. DiNofia,[1,2] Vanessa Gonzalez,[4-6] Natalka Koterba,[4-6] Bruce L. Levine,[4-6,3-5] Shannon L. Maude,[1,2] Nuala J. Meyer,[9] Jason H. Moore,[3] Michele Paessler,[6] David L. Porter,[5,10] Jenny L. Bush,[11] Don L. Siegel,[4-6] Megan M. Davis,[4] Donglan Zhang,[11] Carl H. June,[4-6] Stephan A. Grupp,[1,2,5] J. Joseph Melenhorst,[4-6,†] Simon F. Lacey,[4-6,†] Scott L. Weiss,[11-14,†] and David T. Teachey[1,2,5,†]



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Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas

➢ Graduação (ASTCT)

Grau 1

Febre
+
Sem Hipotensão
+
Sem Hipoxemia

Grau 2

Febre
+
Hipotensão sem necessidade de vasopressores
±
Hipoxemia com necessidade de O2 por óculos nasais ≤6L/min

Grau 3

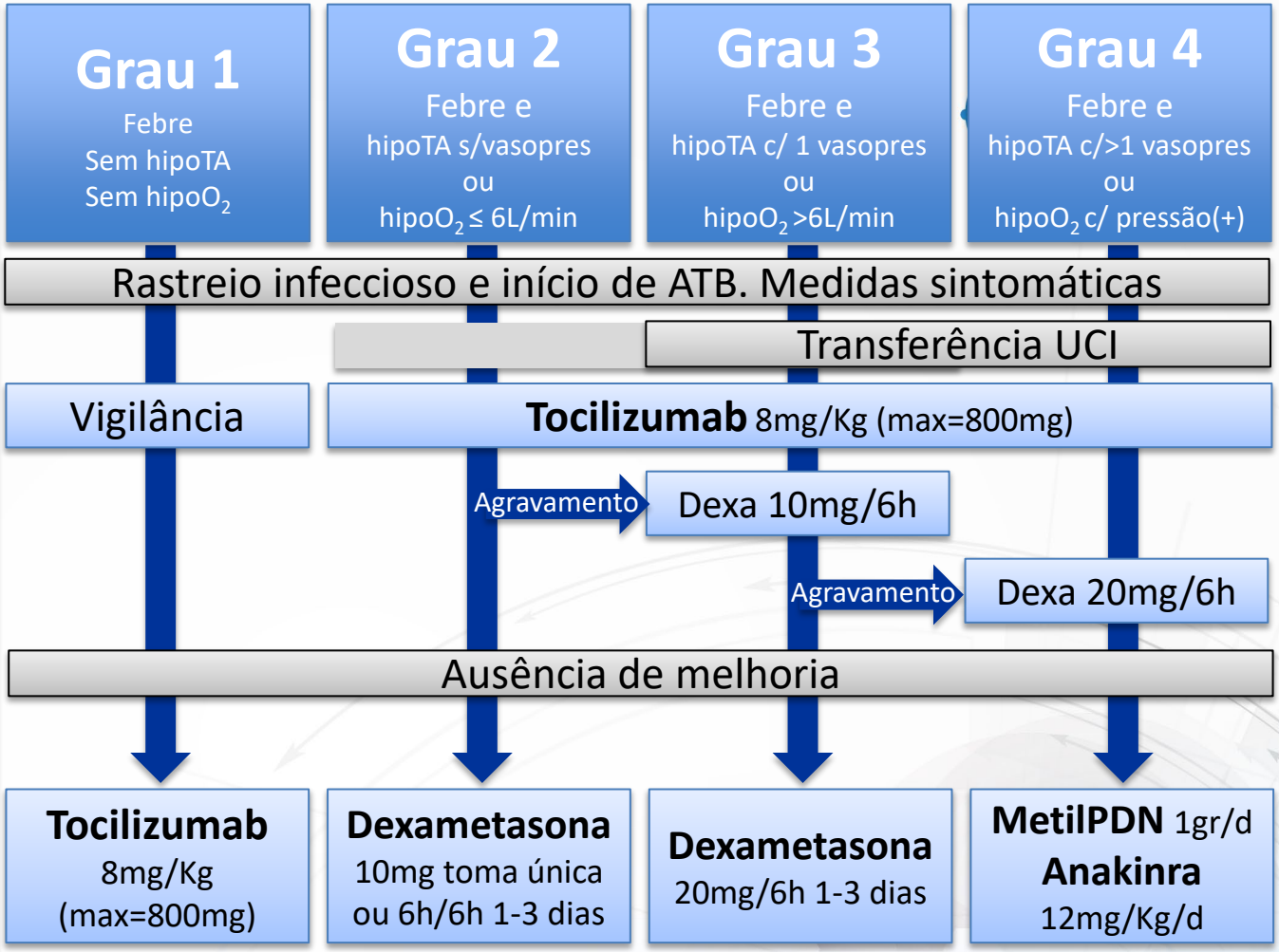
Febre
+
Hipotensão com necessidade de 1 vasopressor
±
Hipoxemia com necessidade de O2 por masc. facial, Venturi, *High-Flow*

Grau 4

Febre
+
Hipotensão com necessidade de ≥1 vasopressor (exclui vasipressina)
±
Hipoxemia com necessidade de O2 com pressão positiva (CPAP, BiPAP, VMI)

Complicações da terapia CAR-T
CRS

- Abordagem Terapêutica



Adaptado de Hayden, P J et al. "Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)." *Annals of oncology : official journal of the European Society for Medical Oncology* vol. 33,3 (2022)

Complicações da terapia CAR-T
CRS

- Abordagem Terapêutica

Complicações Imunológicas Precoces

Síndrome de Ativação Macrofágica

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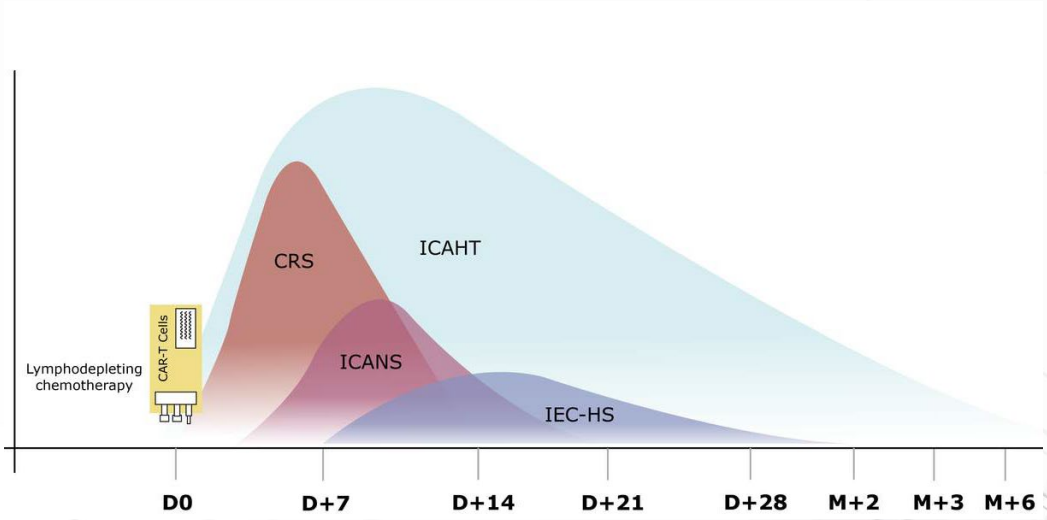
Complicações da terapia CAR-T

Síndrome de Ativação Macrofágica (IEC-HS)

- Complicação rara mas grave
- Inicio variável

- Síndrome hiperinflamatório sistémico
- Ativação de macrófagos e linfócitos, hemofagocitose e lesão multiorgânica



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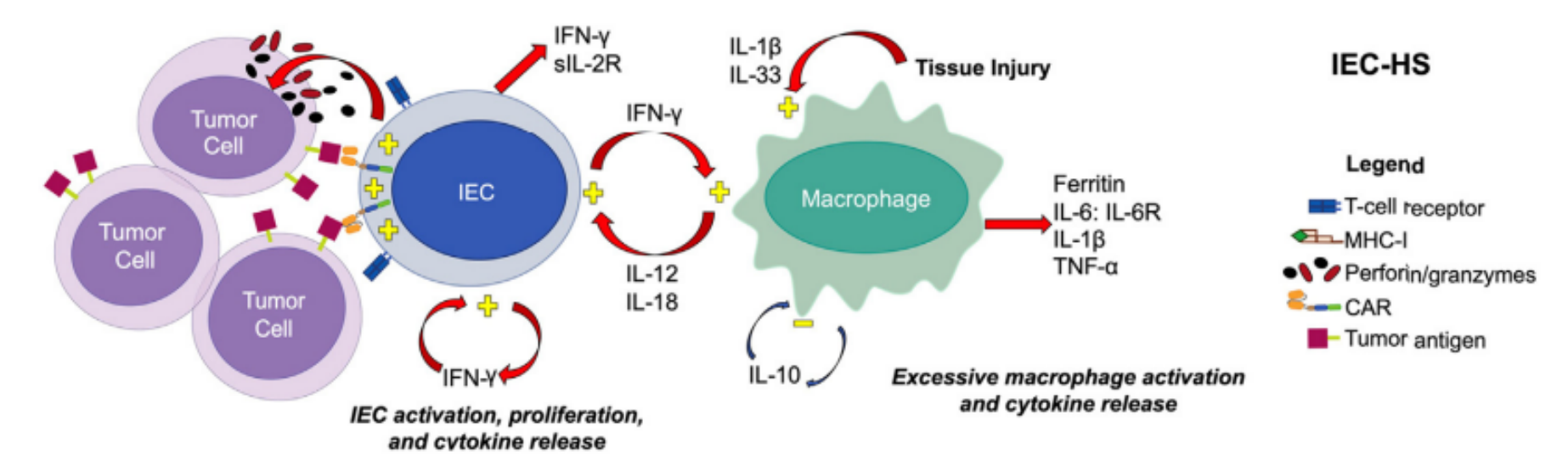
Hines, Melissa R et al. "Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome." *Transplantation and cellular therapy* vol. 29,7 (2023)

Complicações da terapia CAR-T

Síndrome de Ativação Macrofágica (IEC-HS)

➢ Fisiopatologia



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Hines, Melissa R et al. "Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome." *Transplantation and cellular therapy* vol. 29,7 (2023)

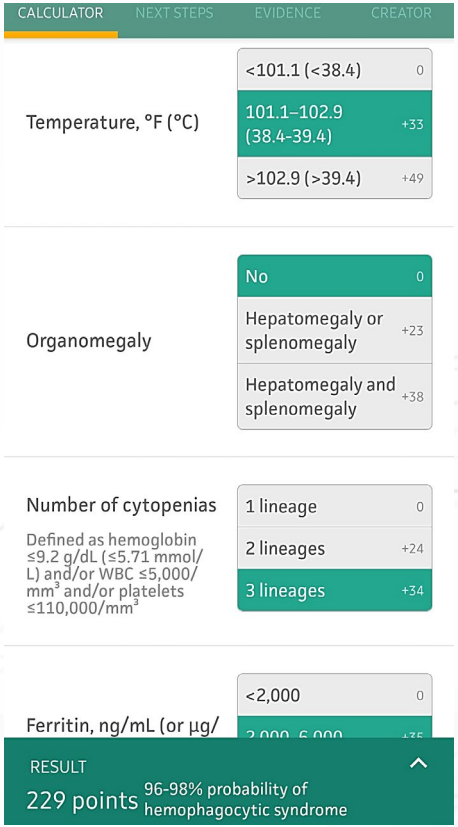
Complicações da terapia CAR-T

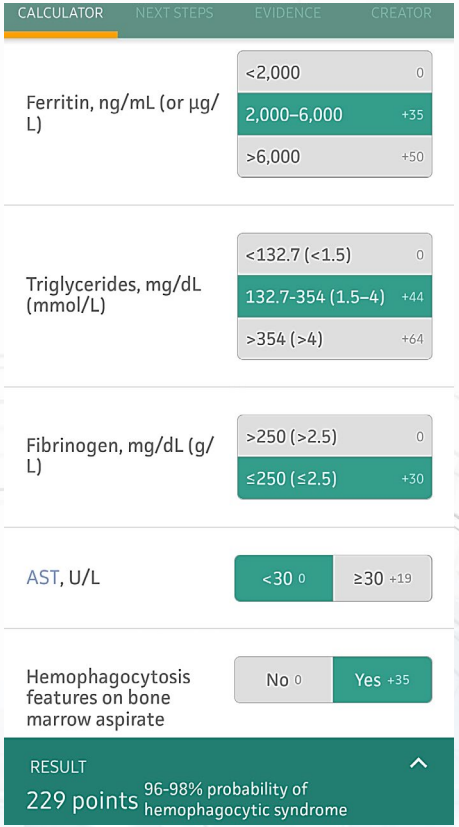
Síndrome de Ativação Macrofágica

➢ Abordagem Diagnóstica

Pelo menos 5 de:

- Febre
- Esplenomegalia
- Citopénia ≥2
- Hipertrigliceridémia (≥3 mmol/L) ou Hipofibrinogenémia (<1.5 g/L)
- ↑ Ferritina (≥500 µg/L)
- ↑ sCD25 (≥2.400 U/ml
- ↓ Actividade linf NK
- Hemafagocitose





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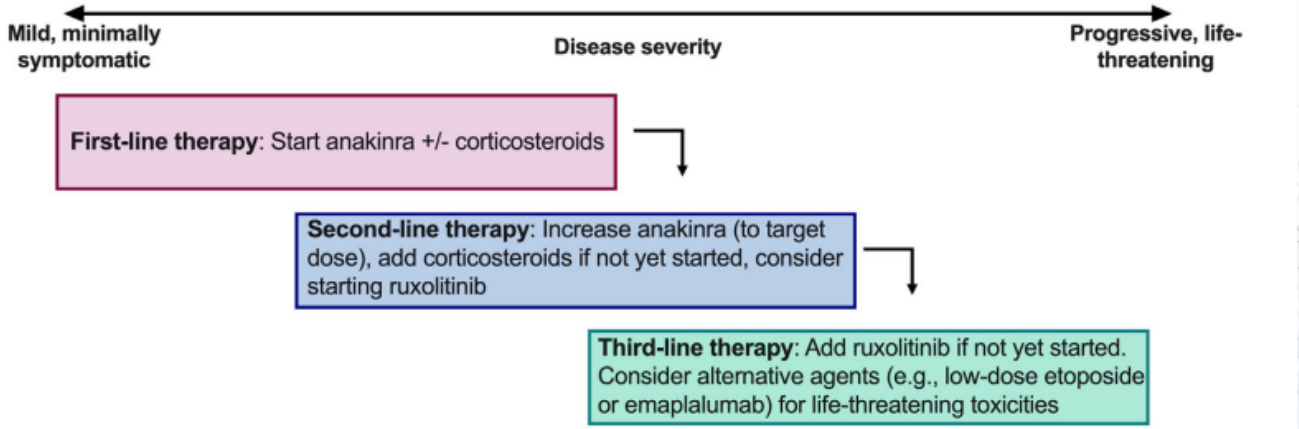
Complicações da terapia CAR-T
MAS

- Abordagem Terapêutica

Monitoring	
• Daily monitoring of complete blood cell count with differential and coagulation parameters (PT/PTT) and fibrinogen • Frequent (eg, daily) evaluation for renal and hepatic dysfunction • Assessment for bacterial, viral reactivation or new infection, and fungal disease, in blood, urine, and sputum cultures, with or without sampling of other possible infectious sources (eg, bronchoscopy, cerebrospinal fluid), • Consider testing for HLH diagnostic parameters, including soluble CD25, NK cell function, triglycerides, IFN-γ, CXCL9 ratio, CXCL10, IL-10, and IL-18	
Cytopenias and coagulopathy	
Cytopenias	• Maintain hemoglobin $\geq$7 g/dL [147,148]. • Platelet count $\geq$50 cells $\times$ 10^9/L is recommended in those with active bleeding or coagulopathy. • Use of romiplostim or eltrombopag is unknown. • Use of G-CSF to maintain an absolute neutrophil count $\geq$500 cells/mm^3 remains controversial during periods of active inflammation [132–135]. • Consult gynecology in female patients with menorrhagia
Coagulopathy	• Aggressive management with cryoprecipitate or fibrinogen concentrate is recommended to keep fibrinogen level >100 if no bleeding and >150 if bleeding is present [140]. • If INR is >1.5, then vitamin K supplementation should be considered. If INR is >2, then administration of fresh frozen plasma in addition to cryoprecipitate should be considered. • Use of agents for prevention of venous thromboembolism should be used with caution with preference for agents that are easily reversed (ie, heparin). • Consult hematology for patients with refractory or difficult to manage coagulopathy.



Hines, Melissa R et al. "Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome." *Transplantation and cellular therapy* vol. 29,7 (2023)

Complicações Imunológicas Precoces

Immune effector cell-associated neurotoxicity syndrome

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Complicações da terapia CAR-T
ICANS

➢ Prevalência e Factores de Risco

- Tipo de CAR-T
- Idade
- Doença neurológica prévia
- Carga tumoral
- CRS precoce e severo
- Trombocitopénia
- Estado inflamatório pré-infusão
- Neurofilament Light Chain

	Grau 1-2	Grau ≥3
Axi-cel	51% (59 – 72%)	19% (19 – 32%)
Tisa-cel	28% (10 – 37%)	6% (2 – 11%)
Liso-cel	22% (12 – 31%)	6% (4 – 10%)
Brexu-cel	63%	19%
Cilta-cel	22%	12%
Ide-cel	15%	3%

Complicações da terapia CAR-T
ICANS

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➢ Prevalência e Factores de Risco

- Tipo de CAR-T
- Idade
- Doença neurológica prévia
- Carga tumoral
- CRS precoce e severo
- Trombocitopénia
- Estado inflamatório pré-infus
- Neurofilament Light Chain

JAMA Oncology | Brief Report

Assessment of Pretreatment and Posttreatment Evolution of Neurofilament Light Chain Levels in Patients Who Develop Immune Effector Cell–Associated Neurotoxicity Syndrome

Omar H. Butt, MD, PhD; Alice Y. Zhou, MD, PhD; Paolo F. Caimi, MD; Patrick H. Luckett, PhD; Julie K. Wisch, PhD; Paul-Robert Derenoncourt, MD; Kenneth Lee, BS; Gregory F. Wu, MD, PhD; Marcos J. G. de Lima, MD; Jian L. Campian, MD, PhD; Matthew J. Frank, MD, PhD; John F. DiPersio, MD, PhD; Armin Ghobadi, MD; Beau M. Ances, MD, PhD

Supplemental content

IMPORTANCE Determining whether neurofilament light chain (NfL) elevations in patients who develop immune effector cell–associated neurotoxicity syndrome (ICANS) occur before or after infusion of cellular product is important to identify high-risk patients and inform whether neuroaxonal injury is latent or a consequence of treatment.

OBJECTIVE To quantify serial NfL levels in patients undergoing cellular therapy.

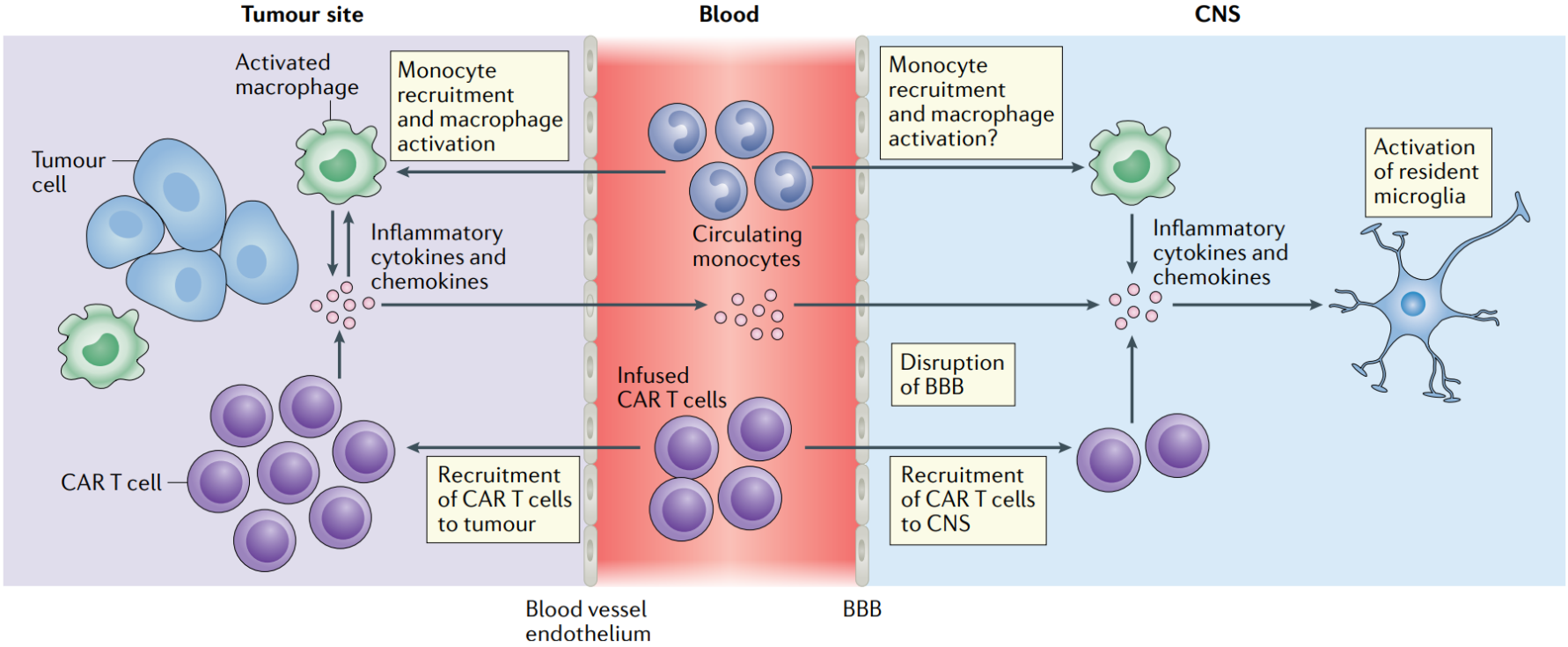
DESIGN, SETTING, AND PARTICIPANTS This retrospective 2-center study examined plasma NfL levels in 30 patients with detailed medical and treatment history, including all major pretreatment and posttreatment risk factors. Exclusion criteria included dementia and severe, symptomatic central nervous system (CNS) involvement.

MAIN OUTCOMES AND MEASURES Patients' NfL levels were measured at 7 time points: baseline (prelymphodepletion), during lymphodepletion, postinfusion day (D) 1, D3, D7, D14, and D30. Prediction accuracy for the development of ICANS was next modeled using receiver operating characteristic (ROC) classification. Finally, univariate and multivariate modeling examined the association between NfL levels, ICANS, and potential risk factors including demographic (age, sex), oncologic (tumor burden, history of CNS involvement), neurologic (history of nononcologic CNS disease or neuropathy), and neurotoxic exposure histories (vincristine, cytarabine, methotrexate, or CNS radiotherapy).

Complicações da terapia CAR-T

ICANS

➢ Fisiopatologia



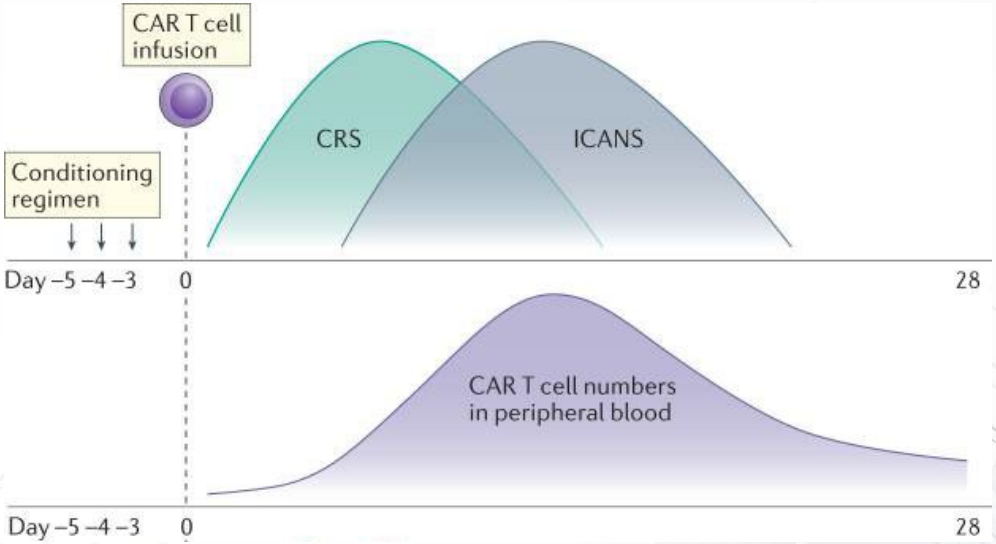
Innovative Medicine

Morris, E.C., Neelapu, S.S., Giavridis, T. *et al.* Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat Rev Immunol* **22**, 85–96 (2022).

Complicações da terapia CAR-T
ICANS

➢ Abordagem Diagnóstica

- Mediana inicio: D+6
  - Até 10% de ICANS tardio
- Mediana duração: 8 dias



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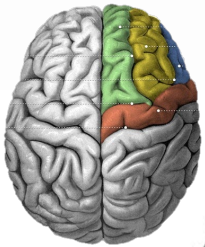
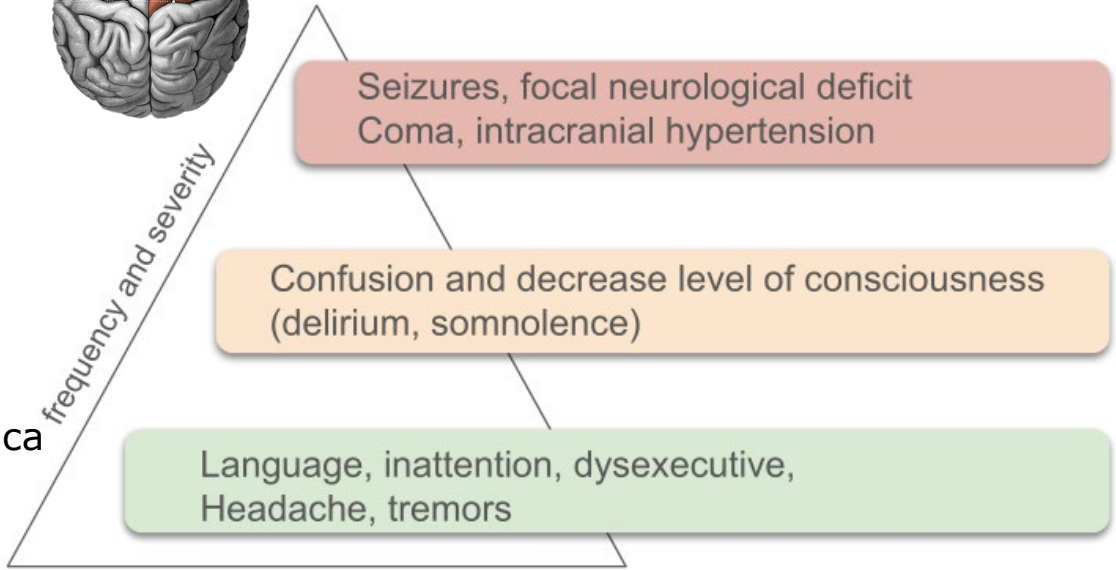
Morris, E.C., Neelapu, S.S., Giavridis, T. *et al.* Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat Rev Immunol* **22**, 85–96 (2022).

Complicações da terapia CAR-T
ICANS

➢ Abordagem Diagnóstica

- Clínica
  - **Encefalopatia frontal**
- Eletroencefalograma
  - Atividade de base lenta
  - Atividade paroxística
- RMN
  - Edema focal/generalizado
  - Hemorragias punctiformes
  - ↑ Realce leptomeníngeo
  - ↑ Intensidade FLAIR s. branca
- Punção Lombar





Complicações da terapia CAR-T

ICANS

➢ Abordagem Diagnóstica

- Clínica
  - **Encefalopatia frontal**
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  - Atividade de base lenta
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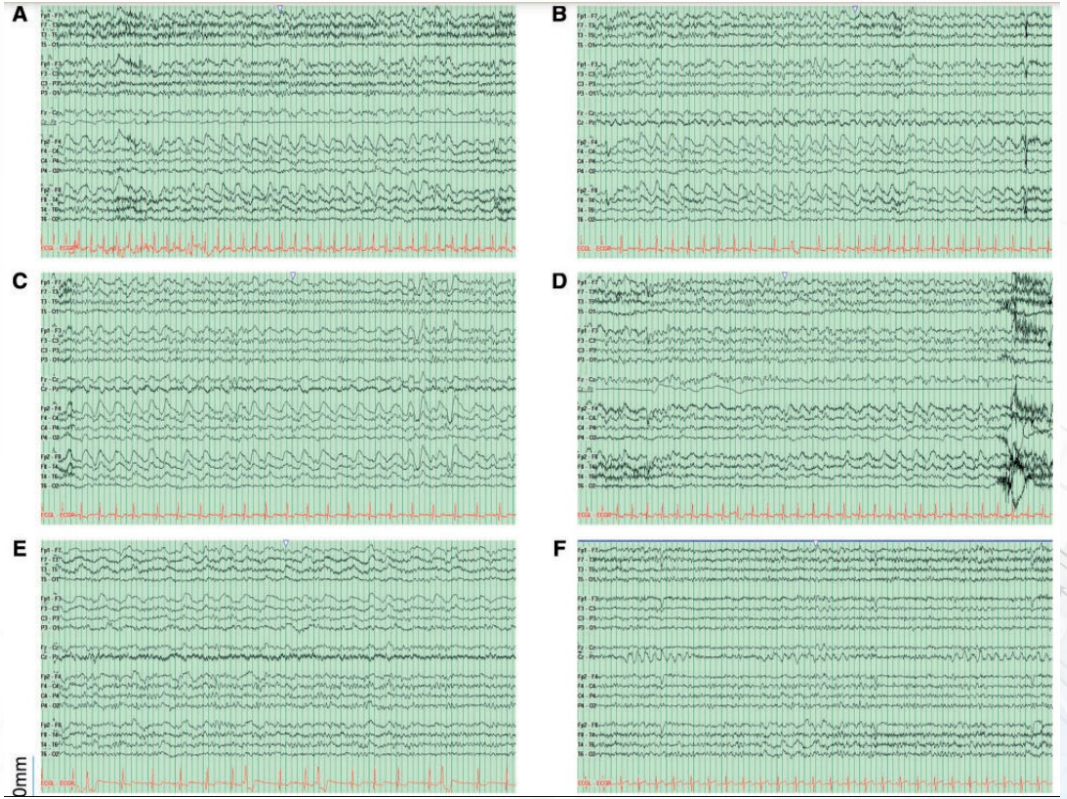
- Punção Lombar



Daniel B Rubin et all, Neurological toxicities associated with chimeric antigen receptor T-cell therapy, *Brain*, May 2019

Complicações da terapia CAR-T
ICANS

InternNet CLUB
FÓRUM 2025 • 9ª EDIÇÃO

➢ Abordagem Diagnóstica

- Clínica
  - **Encefalopatia frontal**
- Eletroencefalograma
  - Atividade de base lenta
  - Atividade paroxística
- RMN
  - Edema focal/generalizado
  - Hemorragias punctiformes
  - ↑ Realce leptomeníngeo
  - ↑ Intensidade FLAIR s. branca
- Punção Lombar

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REGULAR ARTICLE

blood advances

Check for upda

Impact of diagnostic investigations in the management of CAR T-cell–associated neurotoxicity

Matteo Mauget,[1,2] Sophie Lemercier,[3] Quentin Quelven,[2] Adel Maamar,[2] Faustine Lhomme,[1] Sophie De Guibert,[1] Roch Houot,[1,4] and Guillaume Manson[1]

[1]Department of Hematology, [2]Department of Infectious Diseases and Intensive Care Unit, and [3]Department of Neurology, University Hospital of Rennes, Rennes, France; and [4]INSERM, U1236, Rennes, France

Key Points

- Data from a large cohort of CAR T-cell–treated patients question guidelines regarding diagnostic investigations in ICANS management.
- Our results emphazise for the first time the role of EEG in the current guidelines but questions the need for systematic MRI and LP.

International guidelines regarding the management of immune effector cell–associated neurotoxicity syndrome (ICANS) recommend several diagnostic investigations, including magnetic resonance imaging (MRI), lumbar puncture (LP), and electroencephalogram (EEG) based on ICANS grade. However, the impact of these investigations has not yet been evaluated. Here, we aimed to describe the role of MRI, LP, and EEG in the management of ICANS in a cohort of real-life patients treated with chimeric antigen receptor (CAR) T cells at the University Hospital of Rennes, France. Between August 2018 and January 2023, a total of 190 consecutive patients were treated with CAR T cells. Among those, 91 (48%) developed ICANS. MRI was performed in 71 patients (78%) with ICANS, with a therapeutic impact in 4% of patients, despite frequent abnormal findings. LP was performed in 43 patients (47%), which led to preemptive antimicrobial agents in 7% of patients, although no infection was eventually detected. Systematic EEG was performed in 51 patients (56%), which led to therapeutic modifications in 16% of patients. Our study shows that EEG is the diagnostic investigation with the greatest therapeutic impact, whereas MRI and LP appear to have a limited therapeutic impact. Our results emphasize the role of EEG in the current guidelines but question the need for systematic MRI and LP, which might be left to the discretion of the treating physician.

Complicações da terapia CAR-T
ICANS

➢ Abordagem Diagnóstica

- Clínica
  - **Encefalopatia frontal**
- Eletroencefalograma
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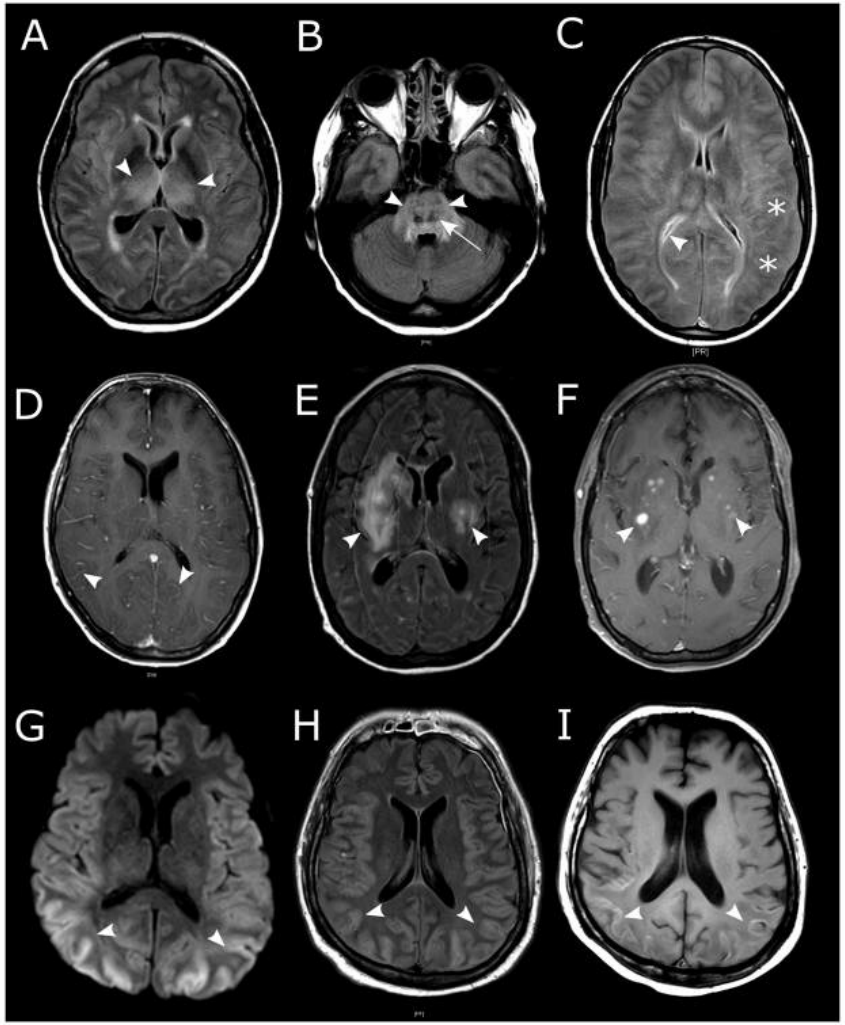


Johnson&Johnson
Innovative Medicine

Gust, Juliane et al. "Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR-T Cells." *Cancer discovery* vol. 7,12 (2017)

Complicações da terapia CAR-T

ICANS

➢ Graduação

***Score* ICE** (Immune Effector Cell Encephalopathy)

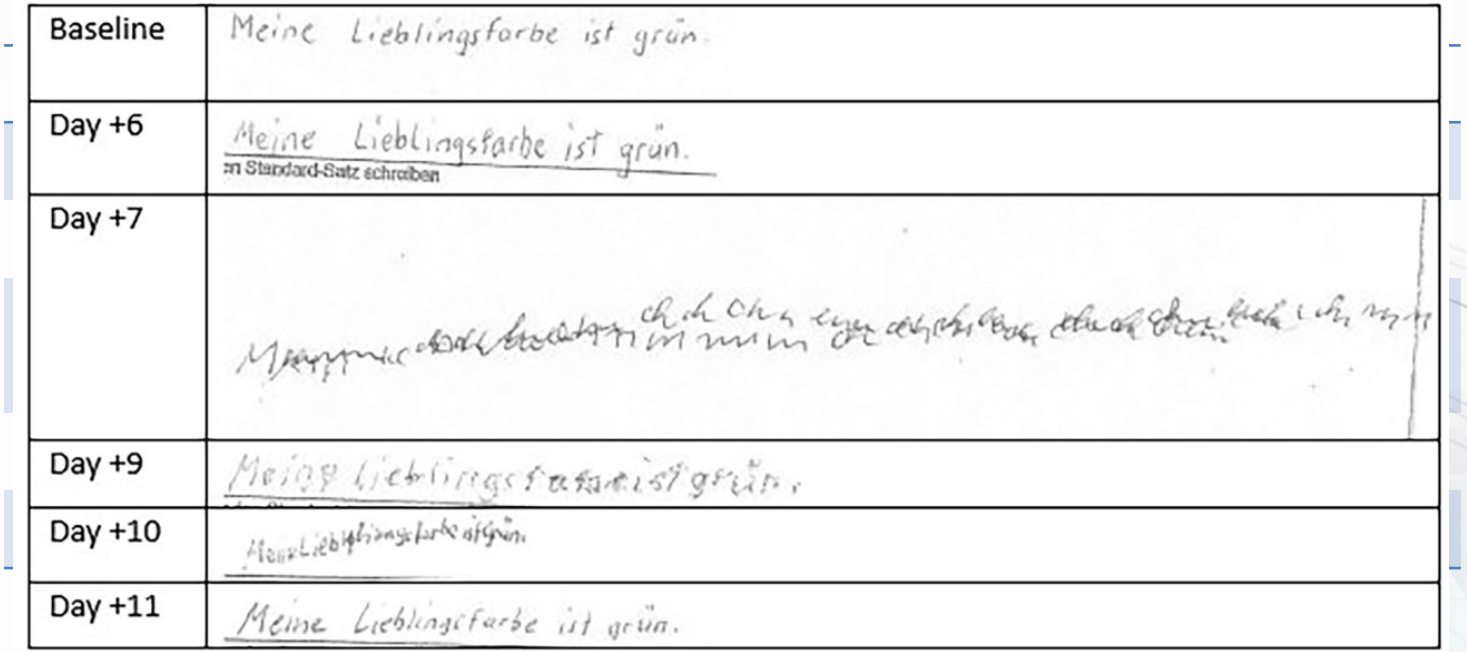
Teste	Pontuação
Orientação: Orientação no ano, mês, cidade, hospital	4
Nomeação: Capacidade de nomear 3 objetos	3
Cumprimento de ordens: Capacidade de seguir ordens simples (“sorrir”, “tocar com 3 dedos na testa”)	1
Escrita: Capacidade de escrever uma frase *standart*	1
Atenção: Capacidade de contar de 100 até 0, de 10 em 10	1

Complicações da terapia CAR-T

ICANS

- Graduação

***Score* ICE** (Immune Effector Cell Encephalopathy)



Baseline	Meine Lieblingsfarbe ist grün.
Day +6	Meine Lieblingsfarbe ist grün. (in Standard-Satz schreiben)
Day +7	
Day +9	
Day +10	
Day +11	Meine Lieblingsfarbe ist grün.

Johnson&Johnson Innovative Medicine

Schroeder, Torsten et al. "Management of chimeric antigen receptor T (CAR-T) cell-associated toxicities." *Intensive care medicine* vol. 50,9 (2024)

Complicações da terapia CAR-T

ICANS

➢ Graduação

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Complicações da terapia CAR-T

ICANS

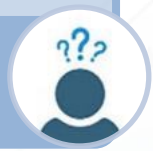
➢ Graduação

Grau 1

- ICE 7-9
- Diminuição do nível de consciência: Despertar espontâneo

Grau 2

- ICE 3-6
- Diminuição do nível de consciência: Despertar à voz

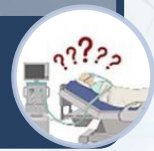


Grau 3

- ICE 0-2
- Diminuição do nível de consciência: Despertar a estimulo táctil
- Edema focal em exame de imagem
- Convulsão/Actividade epilética com resolução rápida

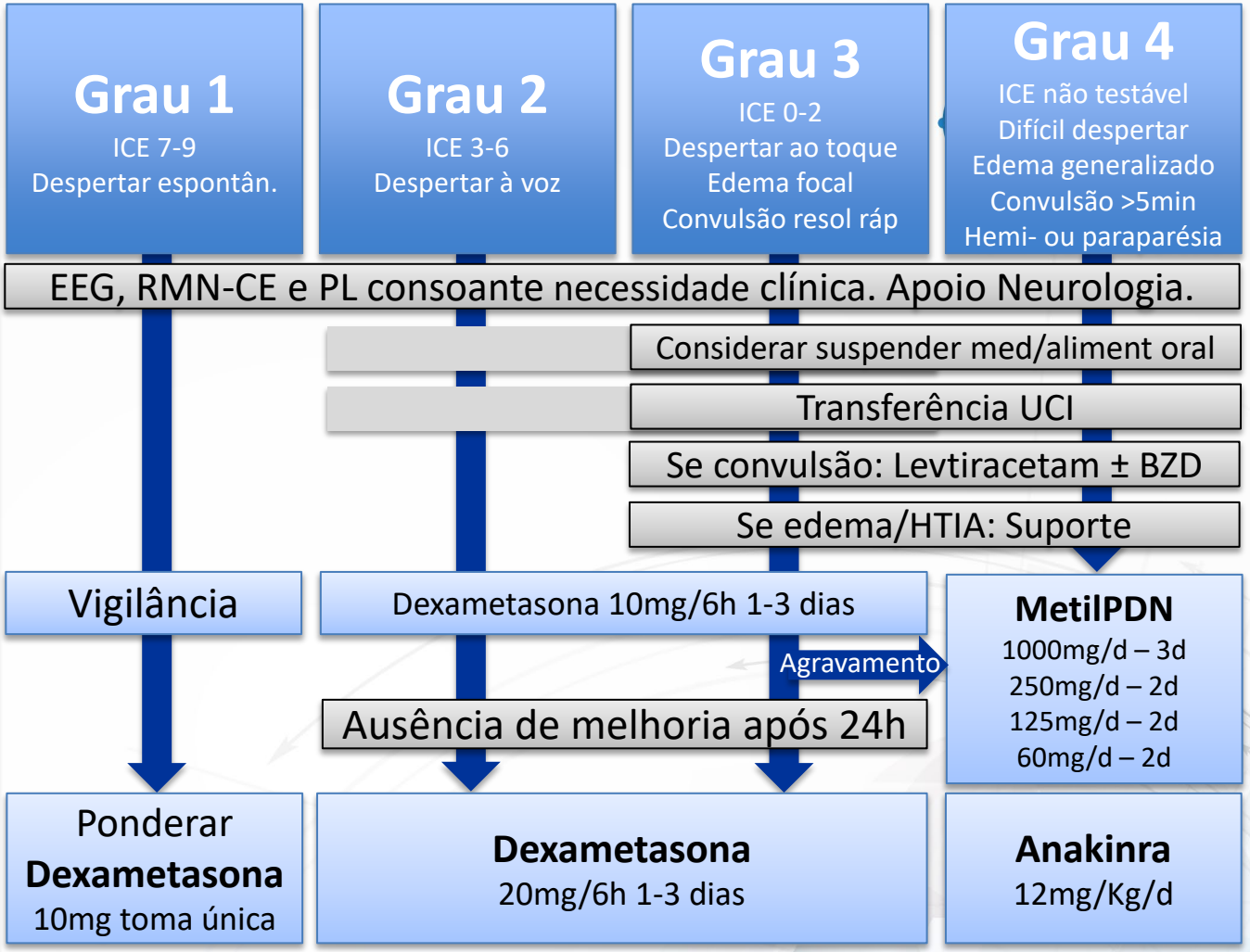
Grau 4

- ICE 0
- Despertar a estimulo vigoroso ou não despertável
- Edema generalizado em exame de imagem
- Postura descorticada, paralisia VI, edema papilar, Triade Cusching
- Convulsão prolongada (>5min)
- Défices motores focais



Complicações da terapia CAR-T
ICANS

- Abordagem Terapêutica



Adaptado de Hayden, P J et al. "Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)." *Annals of oncology : official journal of the European Society for Medical Oncology* vol. 33,3 (2022)

Complicações da terapia CAR-T
ICANS

- Abordagem Terapêutica

- Abordagem **ABC**
- **Levtiracetam 1500mg** e.v. + escalar manutenção
- **Diazepam 0.15mg/Kg (max 10mg)** ou Midazolam 5mg ou Lorazepam 0.5mg.
- **Dexametasona** 20mg/6h

- <u>Se refratário:</u> **Propofol** (bólus 2mg/Kg → per. 10mg/Kg/h) ± **Midazolam** (bólus 0.2mg/kg → perf. 0.1-0.5mg/Kg/h)

Grau 1
ICE 7-9
Despertar espontân.

Grau 2
ICE 3-6
Despertar à voz

Grau 3
ICE 0-2
Despertar ao toque
Edema focal
Convulsão resol ráp

Grau 4
ICE não testável
Difícil despertar
Edema generalizado
Convulsão >5min
Hemi- ou paraparésia

ecessidade clínica. Apoio Neurologia.

Considerar suspender med/aliment oral

Transferência UCI

Se convulsão: Levtiracetam ± BZD

Se edema/HTIA: Suporte

a 10mg/6h 1-3 dias

Agravamento

melhoria após 24h

MetilPDN
1000mg/d – 3d
250mg/d – 2d
125mg/d – 2d
60mg/d – 2d

ametasona
ng/6h 1-3 dias

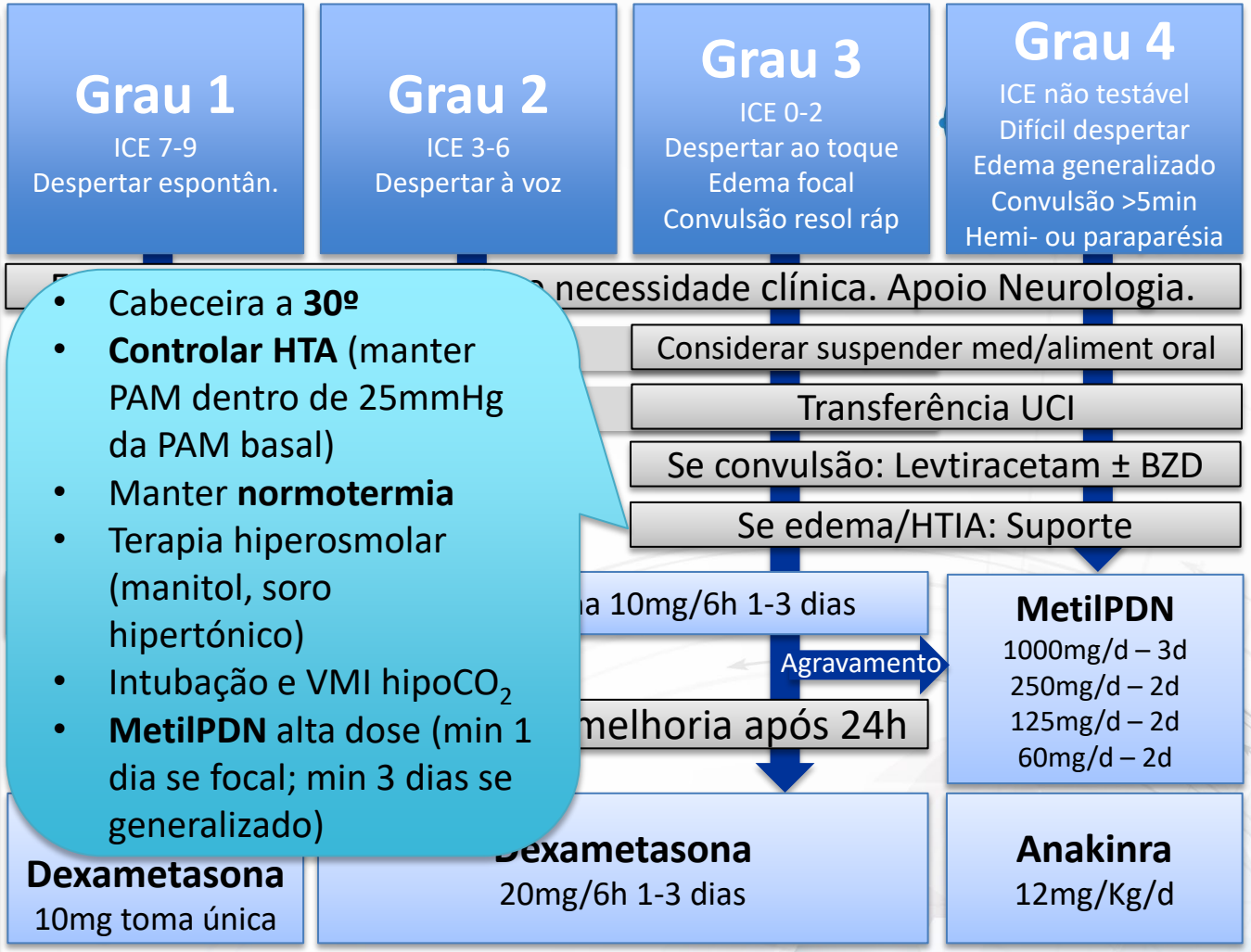
Anakinra
12mg/Kg/d

10mg toma única

Adaptado de Hayden, P J et al. "Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)." *Annals of oncology : official journal of the European Society for Medical Oncology* vol. 33,3 (2022)

Complicações da terapia CAR-T
ICANS

- Abordagem Terapêutica



- Cabeceira a **30º**
- **Controlar HTA** (manter PAM dentro de 25mmHg da PAM basal)
- Manter **normotermia**
- Terapia hiperosmolar (manitol, soro hipertónico)
- Intubação e VMI hipoCO_2
- **MetilPDN** alta dose (min 1 dia se focal; min 3 dias se generalizado)

Adaptado de Hayden, P J et al. "Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)." *Annals of oncology : official journal of the European Society for Medical Oncology* vol. 33,3 (2022)

Complicações da terapia CAR-T
ICANS

- Abordagem Terapêutica

Complicações da terapia CAR-T
Outras Toxicidades Neurológicas

➢ Tumor Inflammation Associated Neurotoxicity (TIAN)

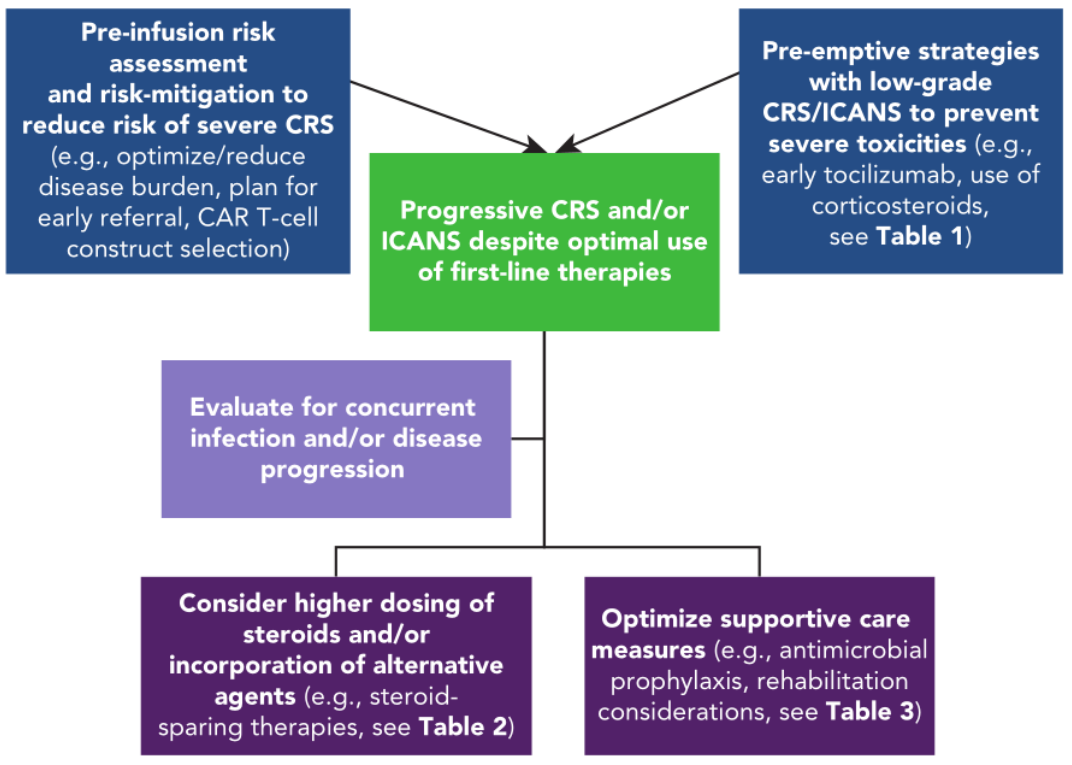
- Doentes com doença SNC+
- *Tumour flare*
- Hipertensão intracraniana, convulsões, etc
- Imagiologia característica

➢ Perturbação neurocognitiva e hipocinética dos movimentos com caraterísticas de Parkinson

- CAR-T anti-BCMA
- Toxicidade *on target off tumor* – Gânglios da base
- Inicio mais tardio (D+27)
- Duração mais prolongada (75 dias)

Complicações da terapia CAR-T

Prevenção



Jain, Michael D et al. “How I treat refractory CRS and ICANS after CAR T-cell therapy.” *Blood* vol. 141,20 (2023)

Complicações da terapia CAR-T

Prevenção

Strategy	Disease/product	Outcome	Comparison*	Comments	Reference
Fractionated CAR T-cell dosing					
Fractionated dosing: day 1 (10% dose), day 2 (30%), and day 3 (60%), with day 2 and day 3 doses allowed to be held for early CRS.	Adult B-ALL treated with CD19 CAR T cells.	Fractionated dose: grade ≥4 CRS, 5% (Penn grading scale) Grade ≥3 neurotoxicity, 6%.	High fixed dose: grade ≥4 CRS, 50%; 3 of 6 patients died.	Difficult to implement with fixed-dose commercial CAR T-cell products.	Frey et al[25] NCT02030847
Prophylaxis					
Prophylactic tocilizumab given on day 2.	Adult DLBCL treated with axi-cel.	Prophy toci: grade ≥3 CRS, 3%. Grade ≥3 ICANS, 41%. One case of cerebral edema.	No prophy toci (ZUMA-1 cohorts 1-2)[26]: grade ≥3 CRS, 13%. Grade ≥3 ICANS, 28%.	Peak IL-6 levels were higher in the prophy toci group, possibly because IL-6R antagonists increase free IL-6.	Locke et al (ZUMA-1 cohort 3)[27] NCT02348216
Prophylactic dexamethasone 10 mg on days 0, 1, and 2.	Adult DLBCL treated with axi-cel.	Prophy dex: grade ≥3 CRS, 0%. Grade ≥3 ICANS, 13%.	No prophy dex (ZUMA-1 cohorts 1-2): grade ≥3 CRS, 13%. Grade ≥3 ICANS, 28%.	Lower baseline tumor burden than ZUMA-1 cohorts 1-2.	Oluwole et al (ZUMA-1 cohort 6)[28] NCT02348216
Prophylactic anakinra given on days 0-7.	Adult DLBCL treated with axi-cel.	Prophy anakinra: grade ≥2 CRS, 40%. Grade ≥3 ICANS, 20%	No prophy anakinra, tumor burden–matched retrospective cohort: grade ≥2 CRS, 70%. Grade ≥3 ICANS, 50%.	Early follow-up suggests efficacy preserved.	Strati et al[29] NCT04432506
Prophylactic anakinra. Started at first fever, or day 2 if no fever. Continued for a minimum of 10 days.	Adult DLBCL and MCL treated with axi-cel, tisa-cel, and brexu-cel.	Prophy anakinra: grade ≥3 CRS, 6%. Grade ≥3 ICANS, 6%.	No specific comparison cohort.	Early follow-up suggests efficacy preserved.	Park et al[30] NCT04148430
Concurrent BTK inhibition					
Ibrutinib + CAR T cells.	Adult CLL treated with CD19 CAR T cells.	Concurrent ibrutinib: grade ≥3 CRS, 0%. Grade ≥3 ICANS, 26%.	No concurrent ibrutinib, earlier cohort of same trial: grade ≥3 CRS, 11%. Grade ≥3 ICANS, NA.	Better CAR T-cell expansion with concurrent ibrutinib, no difference in efficacy.	Gauthier et al[32] NCT01865617
Concurrent JAK inhibition					
Itacitinib + CAR T cells.	Adult DLBCL or MCL (90% of patients) treated with axi-cel, tisa-cel, or brexu-cel.	Concurrent itacitinib: grade ≥3 CRS 2%. Grade ≥3 ICANS, 13%.	No specific comparison cohort.	Randomized phase 2 (itacitinib vs placebo) underway, treating DLBCL/FL with axi-cel.	Pratta et al[33] NCT04071366

Jain, Michael D et al. "How I treat refractory CRS and ICANS after CAR T-cell therapy." *Blood* vol. 141,20 (2023)

Complicações Imunológicas Precoces

Hematotoxicidade

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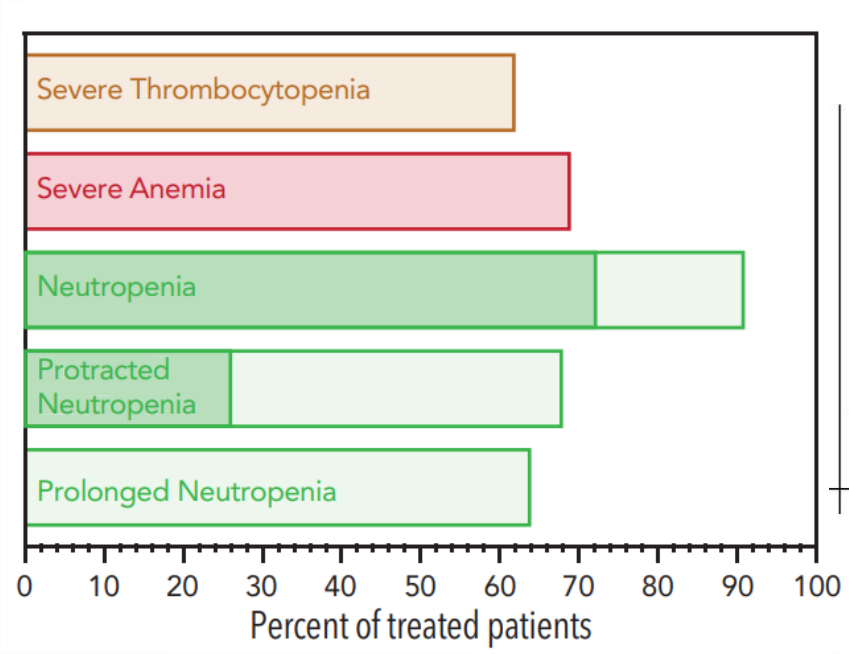
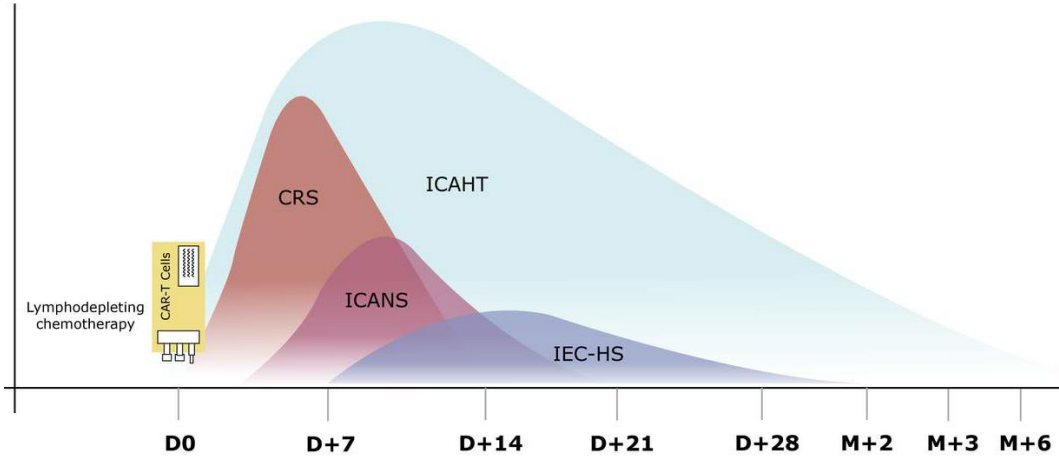
Innovative Medicine

Complicações da terapia CAR-T

Hematotoxicidade (ICAHT)

- Prevalência e Factores de Risco





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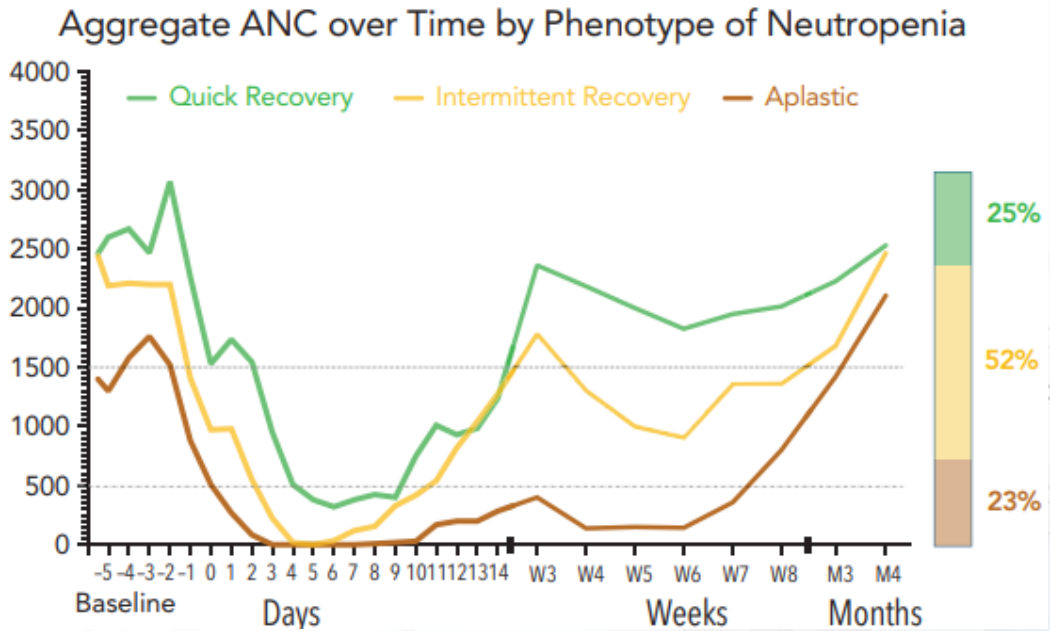
Rejeski, Kai et al. "CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma." *Blood* vol. 138,24 (2021)

Complicações da terapia CAR-T
Hematotoxicidade (ICAHT)

➢ Prevalência e Factores de Risco

3 Fenótipos distintos:

- Recuperação Rápida
  - Reparação sustentada sem nova descida < 1000/uL
- Recuperação Intermitente
  - Recuperação seguida de nova descida < 1000/uL após D+21
- Aplástico
  - Neutrofilos <500/uL durante ≥14 dias



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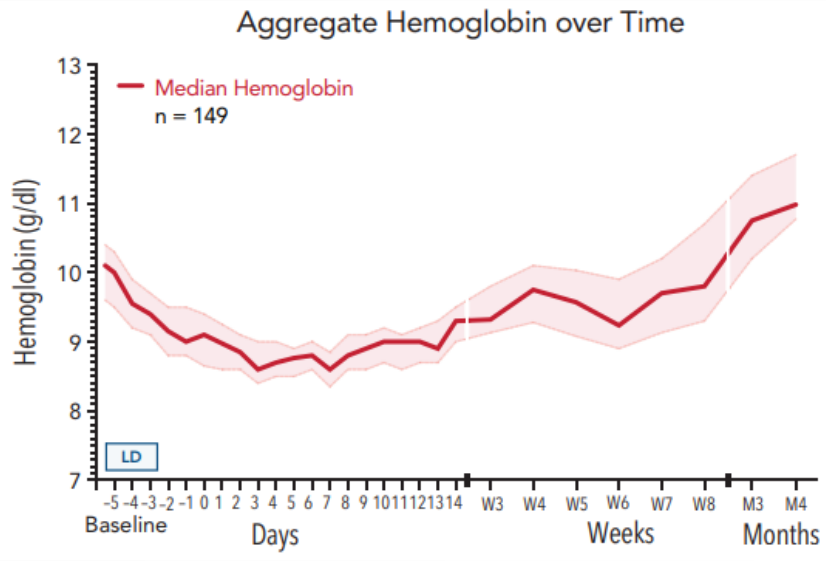
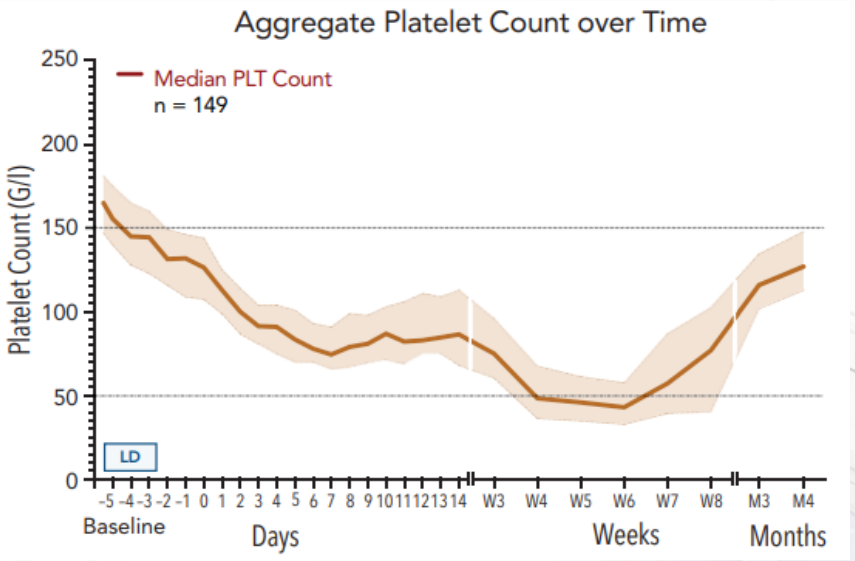
Complicações da terapia CAR-T

Hematotoxicidade (ICAHT)

- Prevalência e Factores de Risco





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Hematotoxicidade (ICAHT)

➢ Prevalência e Factores de Risco

- Tipo de CAR-T cell
  - Coestimulador CD28 > 41BB
- Tipo de neoplasia e carga tumoral
- Reserva medular
  - Infiltração
  - Nº linhas prévias
  - Citopénias prévias
  - CHIP (?)
- Estado Inflamatório
  - Basal (PCR, Ferritina)
  - CRS, IEC-HS, Infeções

Complicações da terapia CAR-T
Hematotoxicidade (ICAHT)

➢ *Scores* de Risco

Prior to lymphodepleting chemotherapy (day -5)

→ Determine patient-individual risk of heme-tox and infections using the **CAR-HEMATOTOX score**

- Leniency time period for lab values: 3 days

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			

Low risk (HT 0-1)

High risk (HT 2-7)

Risk profile	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Median duration of severe neutropenia (ANC<500/µL, D0-60)	5.5 days (95% CI 5-8 days)	6 days (95% CI 5-7 days)	3 days (95% CI 2-5 days)
Aplastic phenotype	2.6%	0%	3%

	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Duration of severe neutropenia (ANC<500/µL, day 0-60)	12 days (95% CI 10-16 days)	14 days (95% CI 9-18 days)	9 days (95% CI 7-13 days)
Aplastic phenotype	36%	47%	32%

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Rejeski, Kai et al. "CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma." *Blood* vol. 138,24 (2021)

Complicações da terapia CAR-T
Hematotoxicidade (ICAHT)

➢ *Scores* de Risco

Transplantation and Cellular Therapy 30 (2024) 404–414

Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article
Cellular Therapy

Clinical Impact of Cytokine Release Syndrome on Prolonged Hematotoxicity after Chimeric Antigen Receptor T Cell Therapy: KyoTox A-Score, a Novel Prediction Model

Naokazu Nakamura[1], Tomoyasu Jo[1,2], Yasuyuki Arai[1,2,*], Toshio Kitawaki[1], Momoko Nishikori[1,3], Chisaki Mizumoto[1], Junya Kanda[1], Kouhei Yamashita[1], Miki Nagao[2], Akifumi Takaori-Kondo[1,2]

Variável	0 Pontos	1 Ponto	2 Pontos
m-CRS	Grau ≤ 1a	–	Grau ≥ 1b
Valor max PCR	< 10 mg/mL	≥ 10 mg/dL	–
Duração elevação PCR	< 10 d	≥ 10 d	–
↓ Fosfato	Não	Sim	–

KyoTox A-Score Baixo (0-1 Pontos)

KyoTox A-Score Alto (2-5 Pontos)

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Complicações da terapia CAR-T

Hematotoxicidade (ICAHT)

➢ Graduação

	Grau 1	Grau 2	Grau 3	Grau 4
ICAHT Precoce (D0–30)				
Neut ≤500/µL	< 7 dias	7 – 13 dias	≥ 14 dias	Nunca >500/µL
Neut ≤100/µL	—	—	≥ 7 dias	≥ 14 dias
ICAHT Tardio (após D30)				
Neut	≤ 1500/µL	≤ 1000/µL	≤ 500/µL	≤ 100/µL

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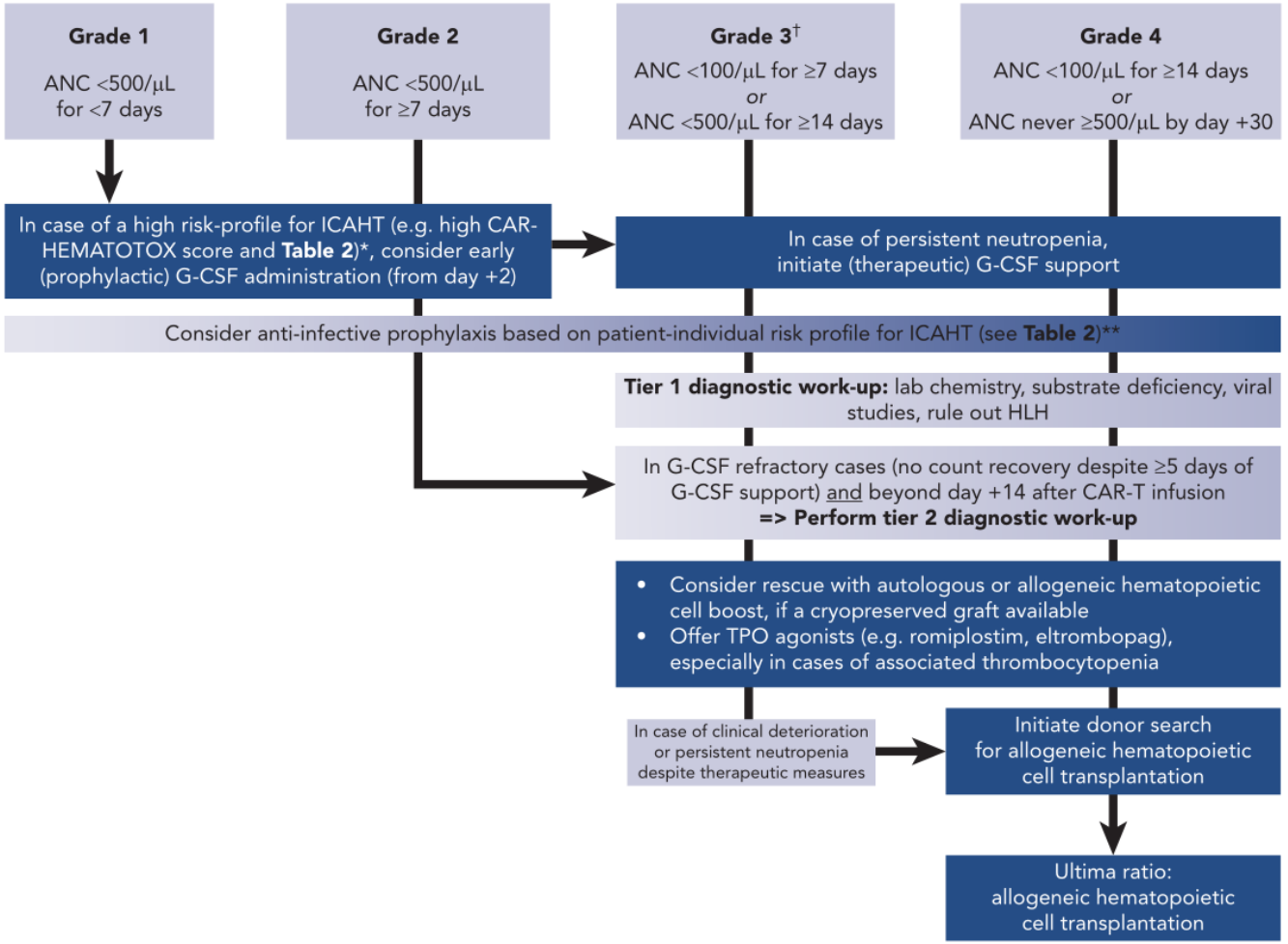
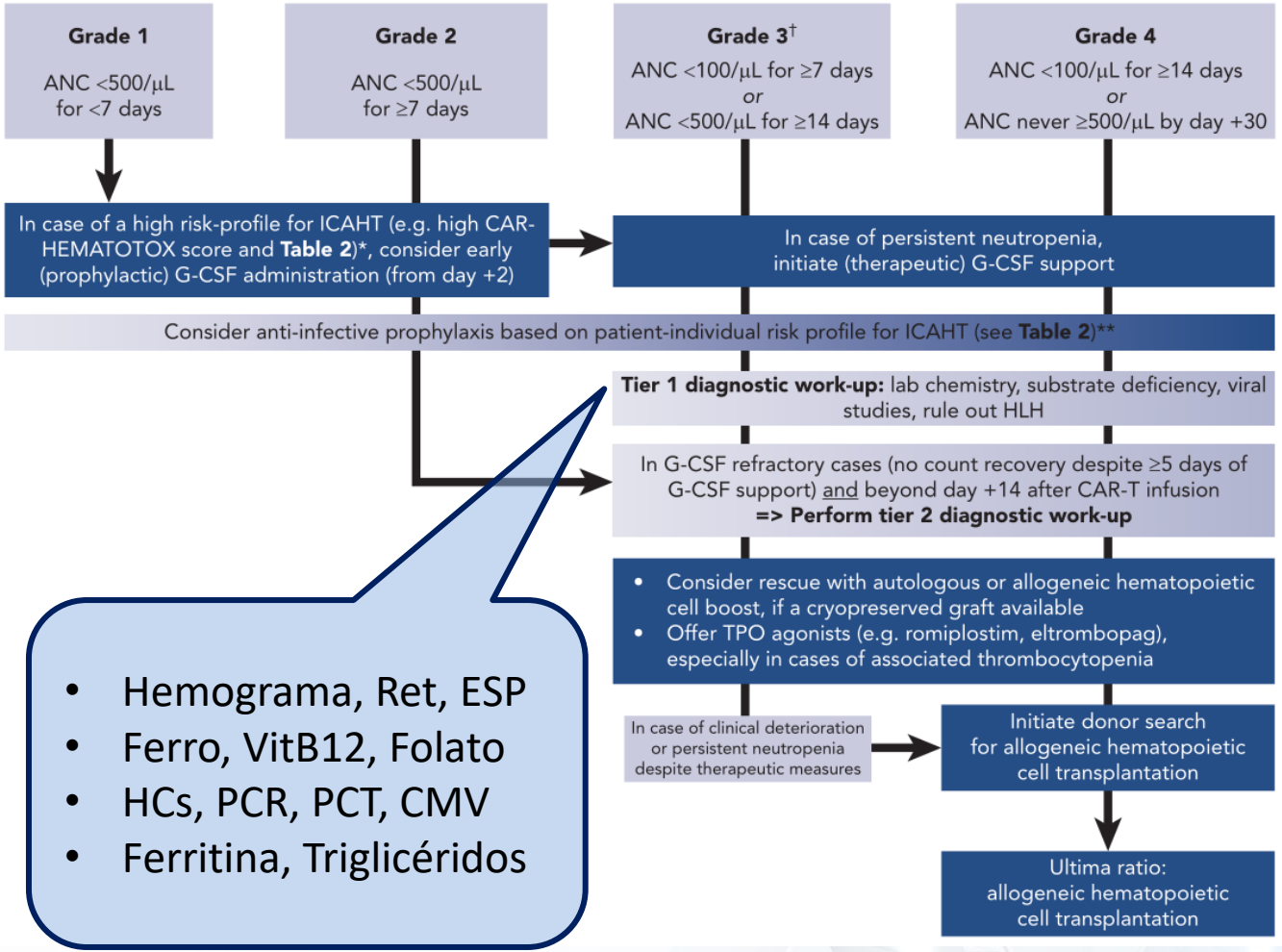
Complicações da terapia CAR-T
ICATH

- Abordagem Terapêutica



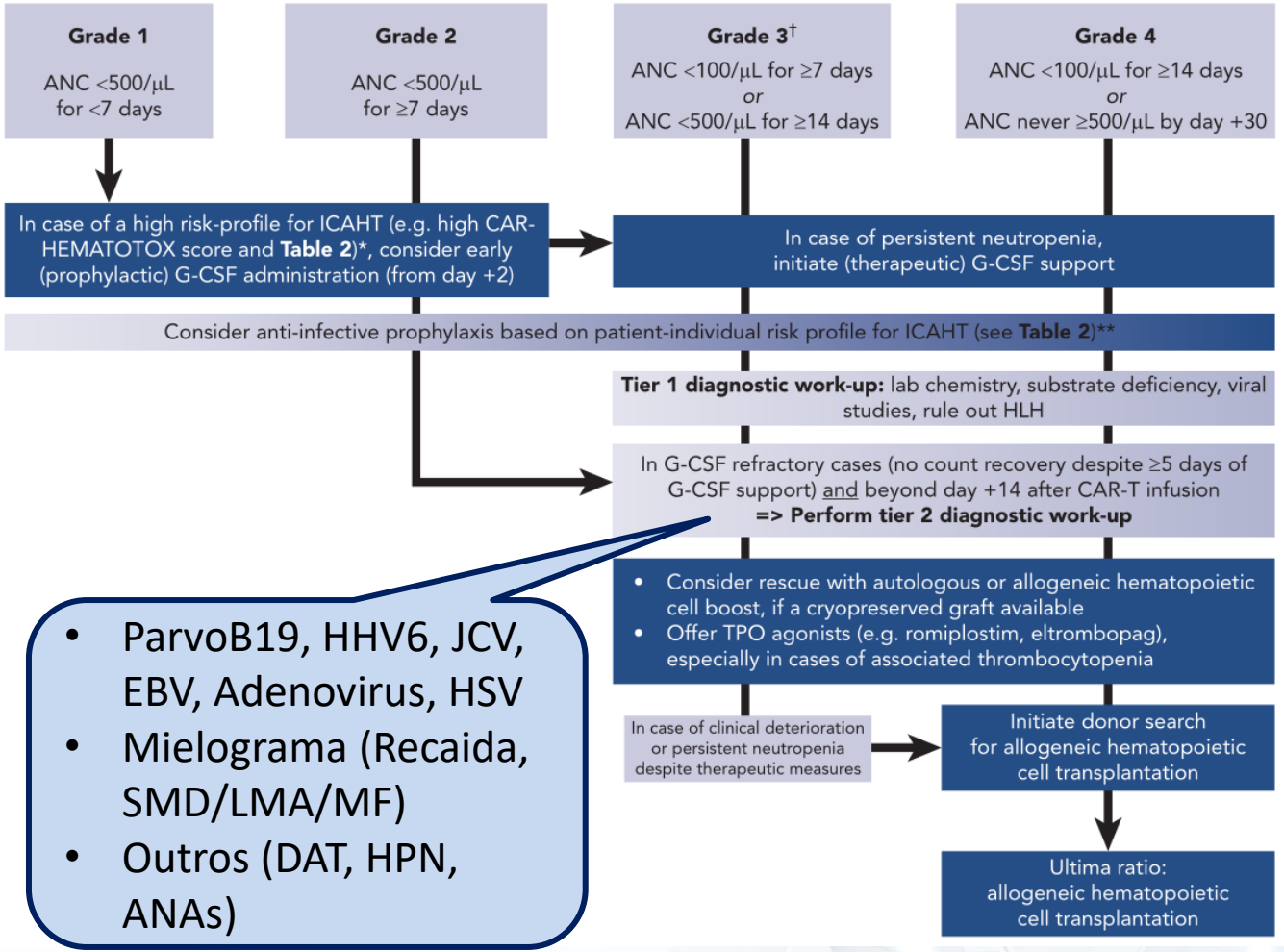
Complicações da terapia CAR-T
ICATH

- Abordagem Terapêutica



Complicações da terapia CAR-T
ICATH

- Abordagem Terapêutica



- ParvoB19, HHV6, JCV, EBV, Adenovirus, HSV
- Mielograma (Recaida, SMD/LMA/MF)
- Outros (DAT, HPN, ANAs)

Toxicidades imunológicas e risco de infeção

Francys Llanos

Índice

Não conflitos de interesses

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Innovative Medicine

OS DOENTES QUE RECEBEM INFUSÃO DE CÉLULAS CAR-T TÊM RISCO DE INFEÇÃO?

Infection. 2020 Sep 26;49(2):215–231. doi: 10.1007/s15010-020-01521-5

Recommendations for screening, monitoring, prevention, and prophylaxis of infections in adult and pediatric patients receiving CAR T-cell therapy: a position paper

Ibai Los-Arcos [1,2], Gloria Iacoboni [3,4], Manuela Aguilar-Guisado [5], Laia Alsina-Manrique [6], Cristina Díaz de Heredia [7], Claudia Fortuny-Guasch [8], Irene García-Cadenas [9], Carolina García-Vidal [10], Marta González-Vicent [11], Rafael Hernani [12], Mi Kwon [13], Marina Machado [14], Xavier Martínez-Gómez [15], Valentín Ortiz Maldonado [16,17], Carolina Pinto Pla [18], José Luis Piñana [19], Virginia Pomar [20], Juan Luis Reguera-Ortega [21], Miguel Salavert [22], Pere Soler-Palacín [23], Lourdes Vázquez-López [24], Pere Barba [3,4,✉], Isabel Ruiz-Camps [1,2]

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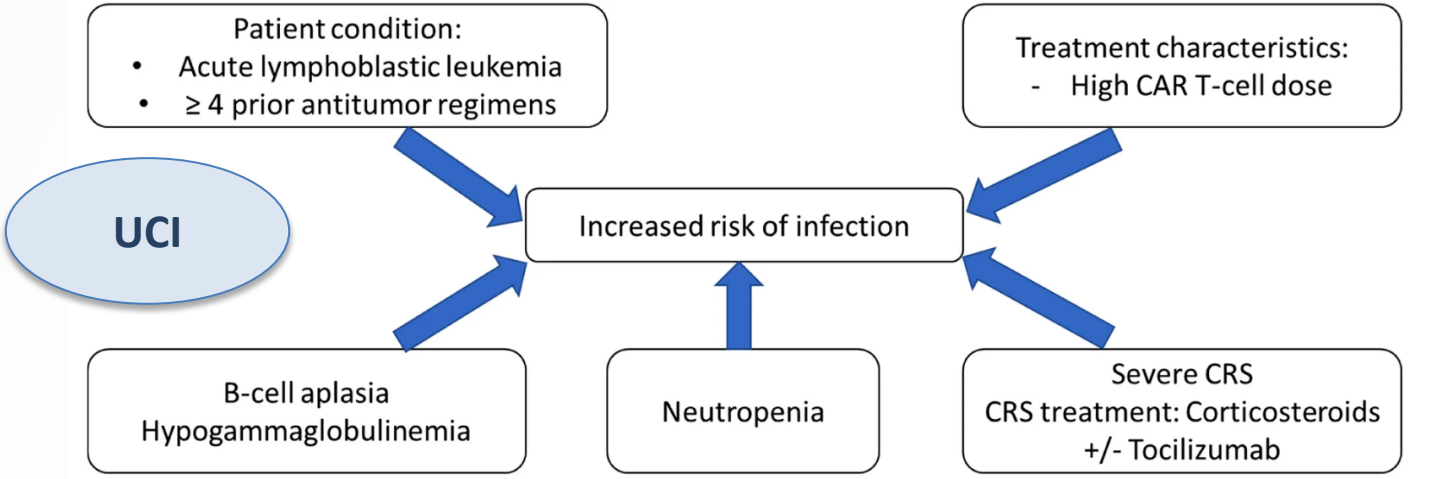

Risk factors for infection in patients receiving CAR T cells

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QUAIS SÃO OS FATORES DE RISCO ASSOCIADOS A INFEÇÕES GRAVES?

IMMUNOBIOLOGY AND IMMUNOTHERAPY | JANUARY 4, 2018

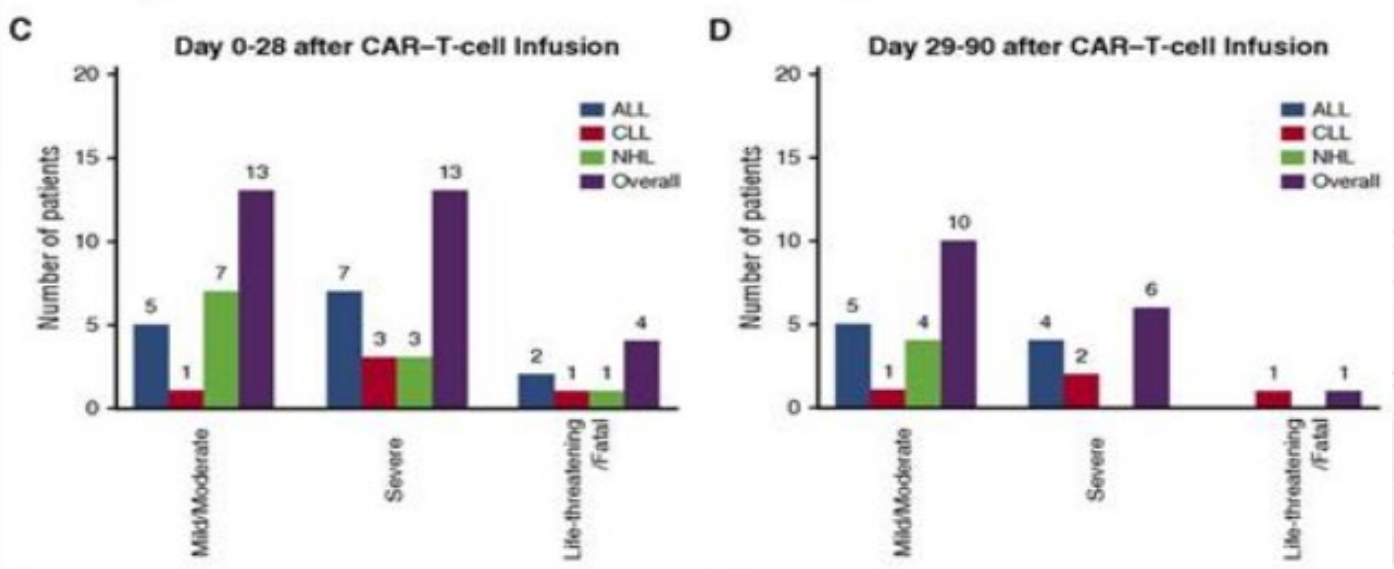
Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy

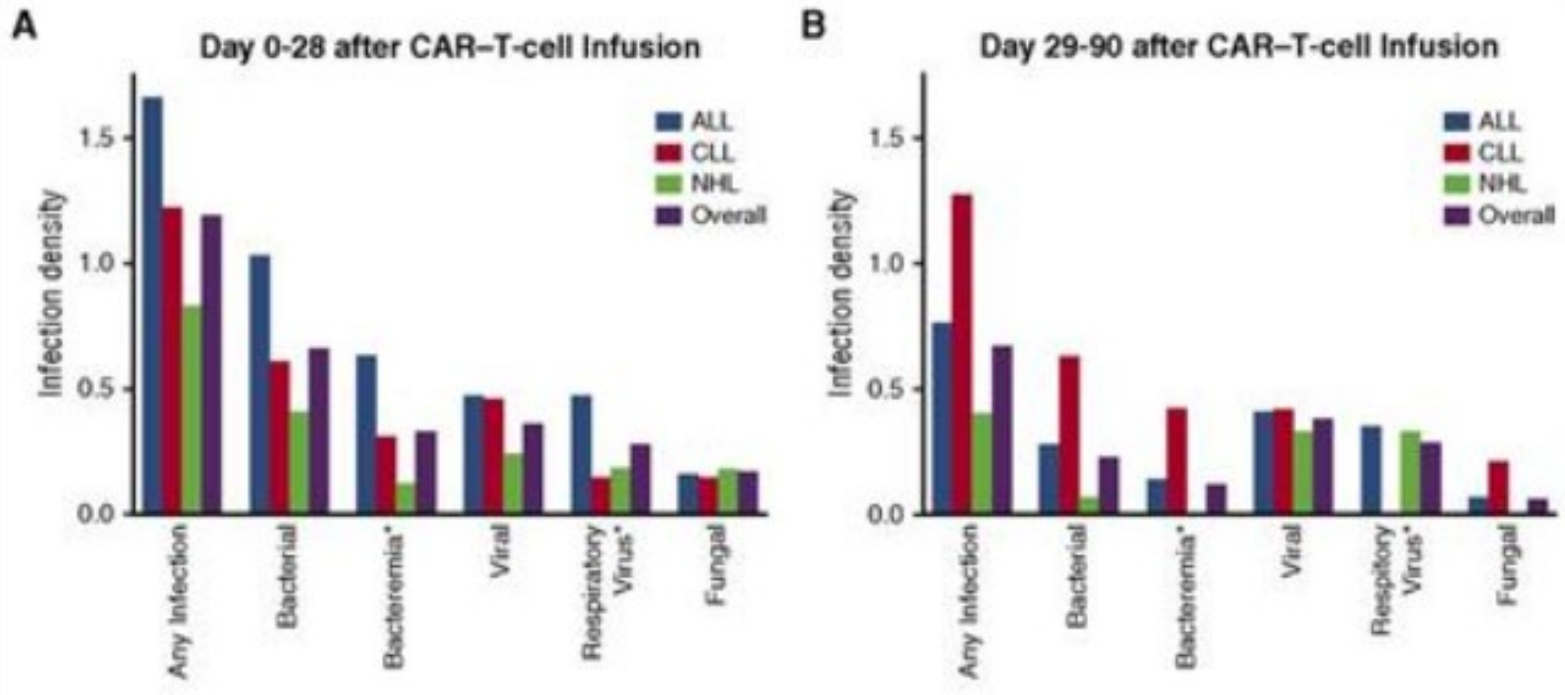
Clinical Trials & Observations

Joshua A. Hill, Daniel Li, Kevin A. Hay, Margaret L. Green, Sindhu Cherian, Xueyan Chen, Stanley R. Riddell, David G. Maloney, Michael Boeckh, Cameron J. Turtle

Check for updates

Blood (2018) 131 (1): 121–130.





Hill J et al. Infections of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood (2018) 131 (1): 121-130

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Blood Cancer J. 2020 Aug 5;10(8):79. doi: 10.1038/s41408-020-00346-7

Infection during the first year in patients treated with CD19 CAR T cells for diffuse large B cell lymphoma

Kitsada Wudhikarn [1,2,#], M Lia Palomba [3,4,#], Martina Pennisi [1,5], Marta Garcia-Recio [1], Jessica R Flynn [6], Sean M Devlin [6], Aishat Afuye [1], Mari Lynne Silverberg [1], Molly A Maloy [1], Gunjan L Shah [1,4], Michael Scordo [1,4], Parastoo B Dahi [1,4], Craig S Sauter [1,4], Connie L Batlevi [3,4], Bianca D Santomasso [4,7], Elena Mead [4,8], Susan K Seo [4,9], Miguel-Angel Perales [1,4,✉]

Variáveis	HR (95% IC)	p-Valeu	Risco
Uso do corticoide sistémico durante o CAR-T	2.22 (1.05-4.67)	0.03	Fator preditor de risco para complicações infeciosas
ECOG-PS (≥2 vs. 1).	2.84 (1.01-8.06)	0.05	Associadas a infeções bacterianas graves
Infeções antes do CAR-T	3.98 (1.30-12.20)	0.01	
IgG <400mg/dL antes do CAR-T	5.73 (2.29-14.30)	<0.001	Maior risco de infeções virais

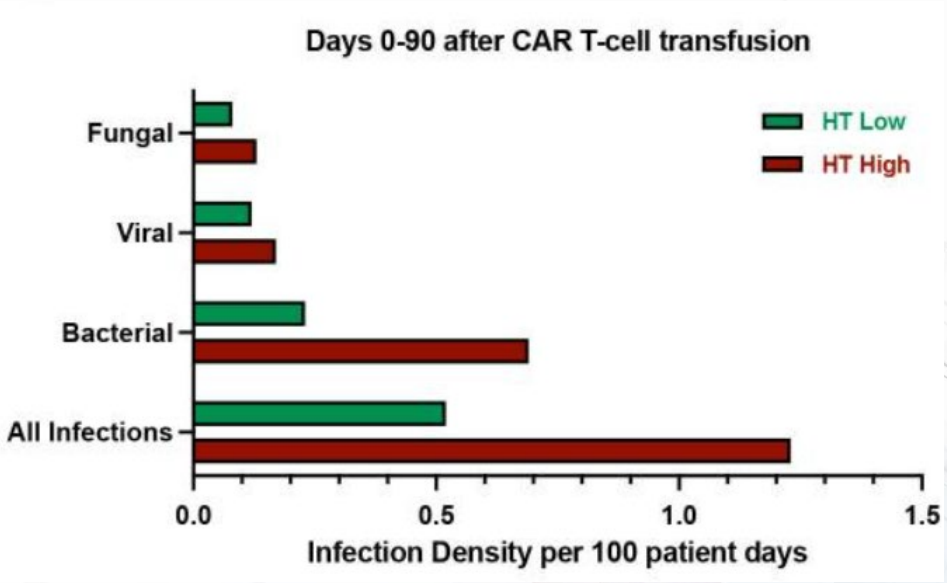
J Immunother Cancer. 2022 May 17;10(5):e004475. doi: 10.1136/jitc-2021-004475

The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CAR-T in R/R LBCL

Kai Rejeski [1,2,3], Ariel Perez [4,5], Gloria Iacoboni [6], Olaf Penack [7,8], Veit Bücklein [1,2], Liv Jentzsch [9], Dimitrios Mougiakakos [10], Grace Johnson [11], Brian Arciola [11], Cecilia Carpio [6], Viktoria Blumenberg [1,2], Eva Hoster [12], Lars Bullinger [7,8], Frederick L Locke [4], Michael von Bergwelt-Baildon [1,3], Andreas Mackensen [10], Wolfgang Bethge [9], Pere Barba [6], Michael D Jain [4], Marion Subklewe [1,2,3]

- Calcular antes da LD (dia -5).
- Compreende 5 marcadores de hemato-toxicidade (P; N; Hb; PCR; Ft).
- Discrimina entre risco elevado (pontuação CAR-HEMATOTOX ≥2) e baixo (0-1).

https://www.german-lymphoma-alliance.de/Scores.html



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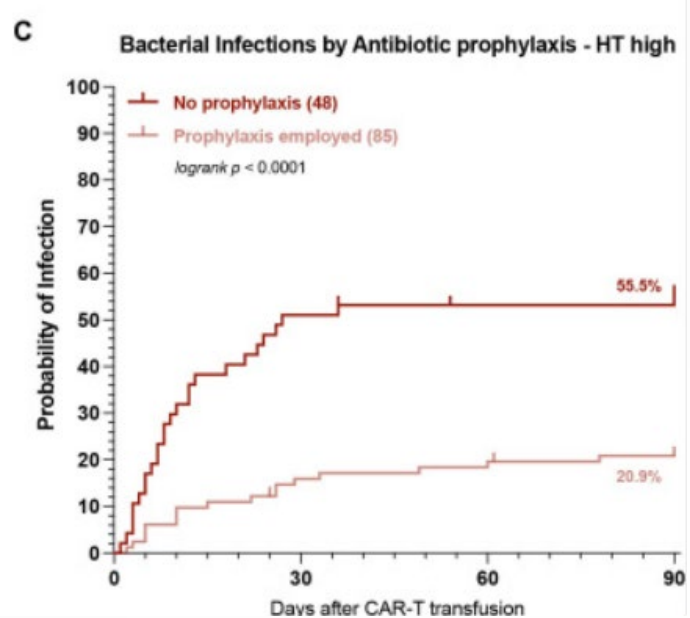

FLUOROQUINOLONAS

Variáveis	HR (95% IC)	p-Valeu	Risco
CAR-HEMATOTOX (≥2)	6.14 (2.93-12.87)	<0.0001	Infeções de grau ≥3
N grave ≥14 dias (<500/µL D0-D+60)	3.13 (1.74-5.62)	<0.001	

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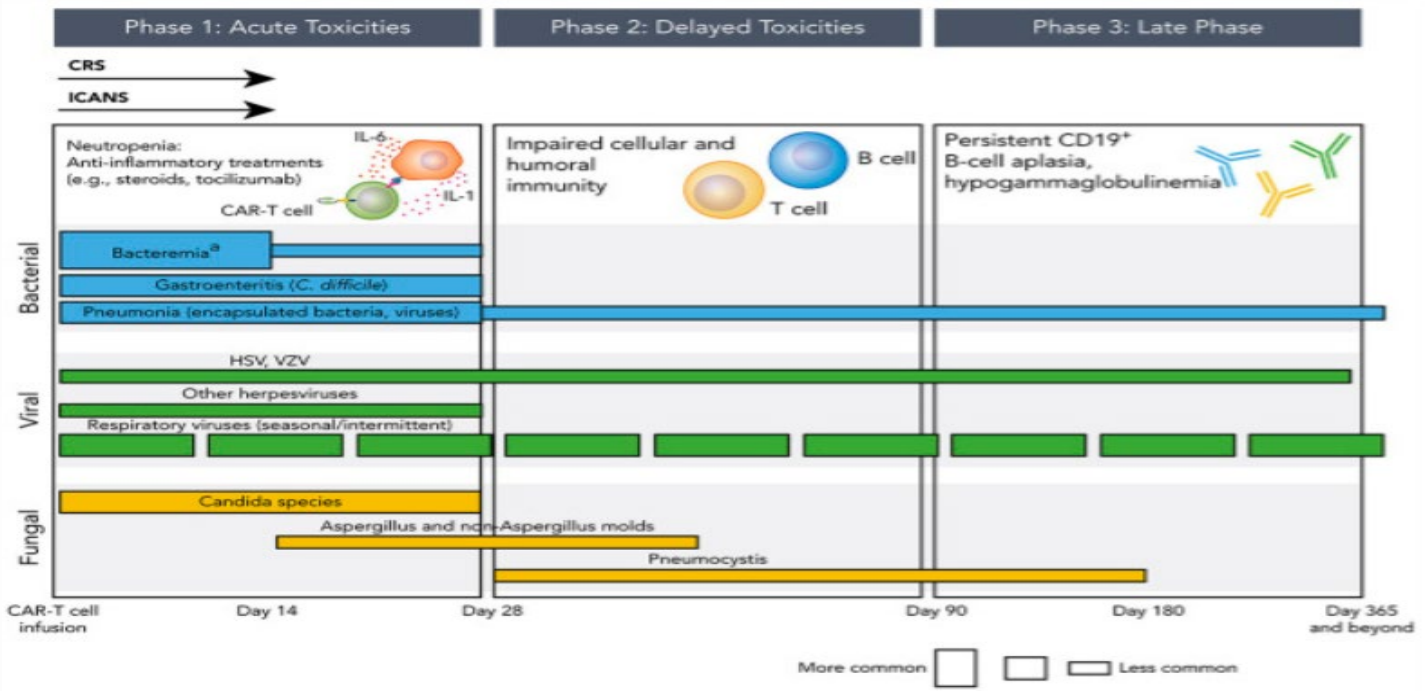
Rejeski K et al. The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CD19 CAR-T in R/R LBCL. JIC 2022 May 17; 10(5):e004475

QUAIS SÃO ESSAS INFEÇÕES?
EPIDEMIOLOGIA DAS INFEÇÕES

Review > Blood. 2020 Aug 20;136(8):925-935. doi: 10.1182/blood.2019004000.

How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies

Joshua A Hill [1 2 3 4], Susan K Seo [5 6]



TRANSPLANT INFECTIOUS DISEASE

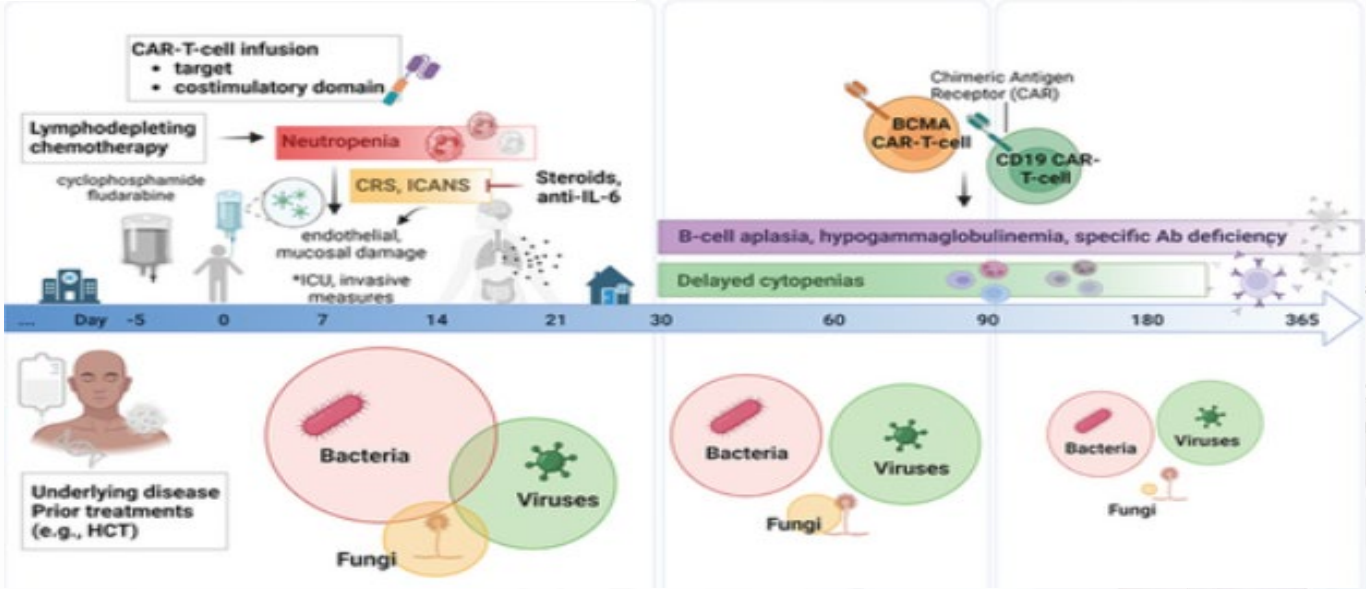
InternNet CLUB
FÓRUM 2025 • 9ª EDIÇÃO

REVIEW ARTICLE | Open Access

Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies

Eleftheria Kampouri, Jessica S. Little, Kai Rejeski, Oriol Manuel, Sarah P. Hammond, Joshua A. Hill

First published: 03 October 2023 | https://doi.org/10.1111/tid.14157 | Citations: 3



Infection risk and epidemiology during different time intervals after chimeric antigen receptor (CAR)-T-cell therapy

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Infeções Precoces

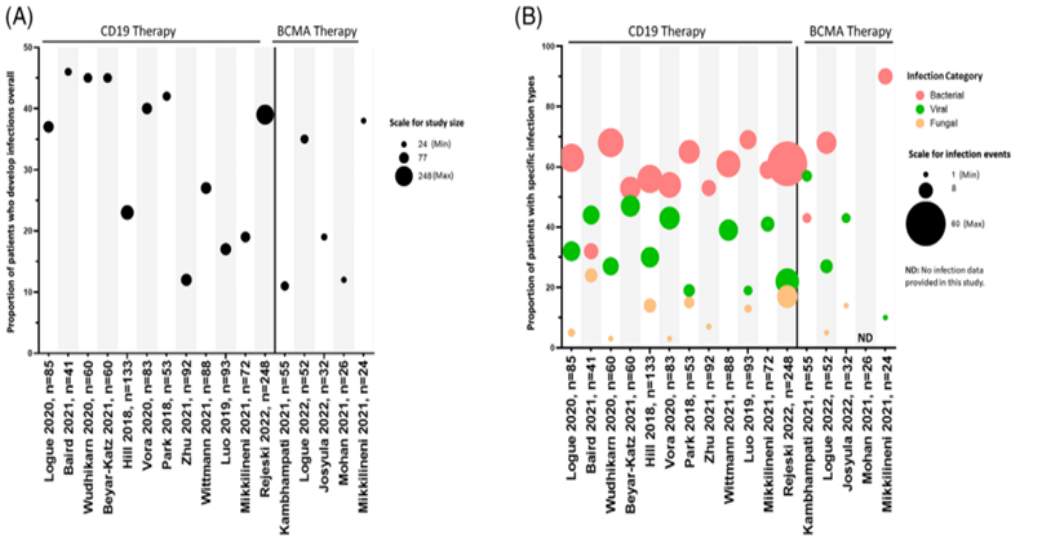

FIGURE 2 Early infections after CD19 and B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR)-T-cell therapy (within 30 days).

- Incidência ~12-46% no 1ºM.
- As infeções bacterianas predominam durante o 1ºM, (32 a 68% de todos os eventos).
- As infeções virais representam 19 a 47% de todas as infeções, incluem vírus respiratórios.

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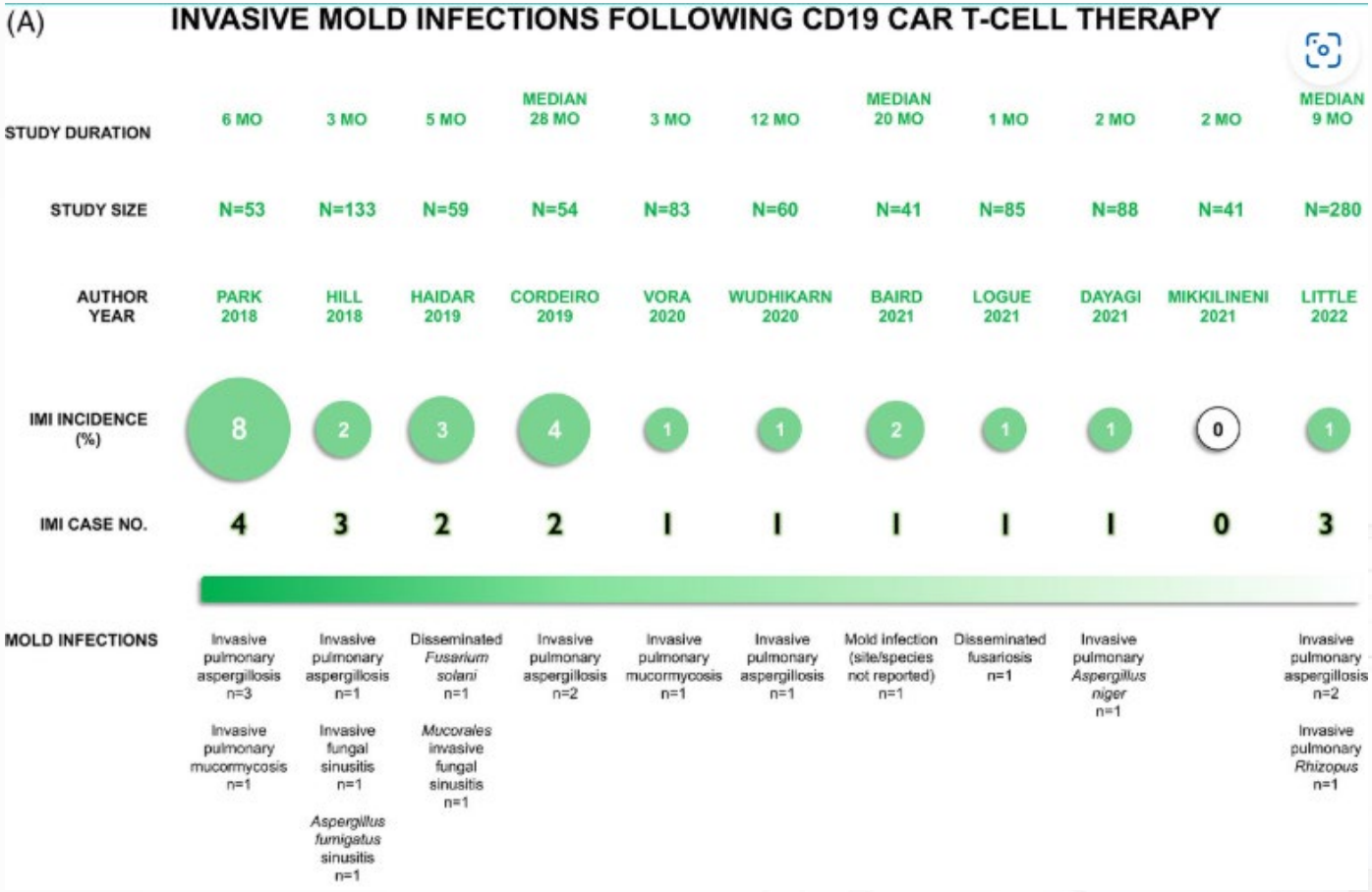
Kampouri E et al. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. TID. 03 october 2023



As infeções fúngicas são menos comuns. (3 a 14%)

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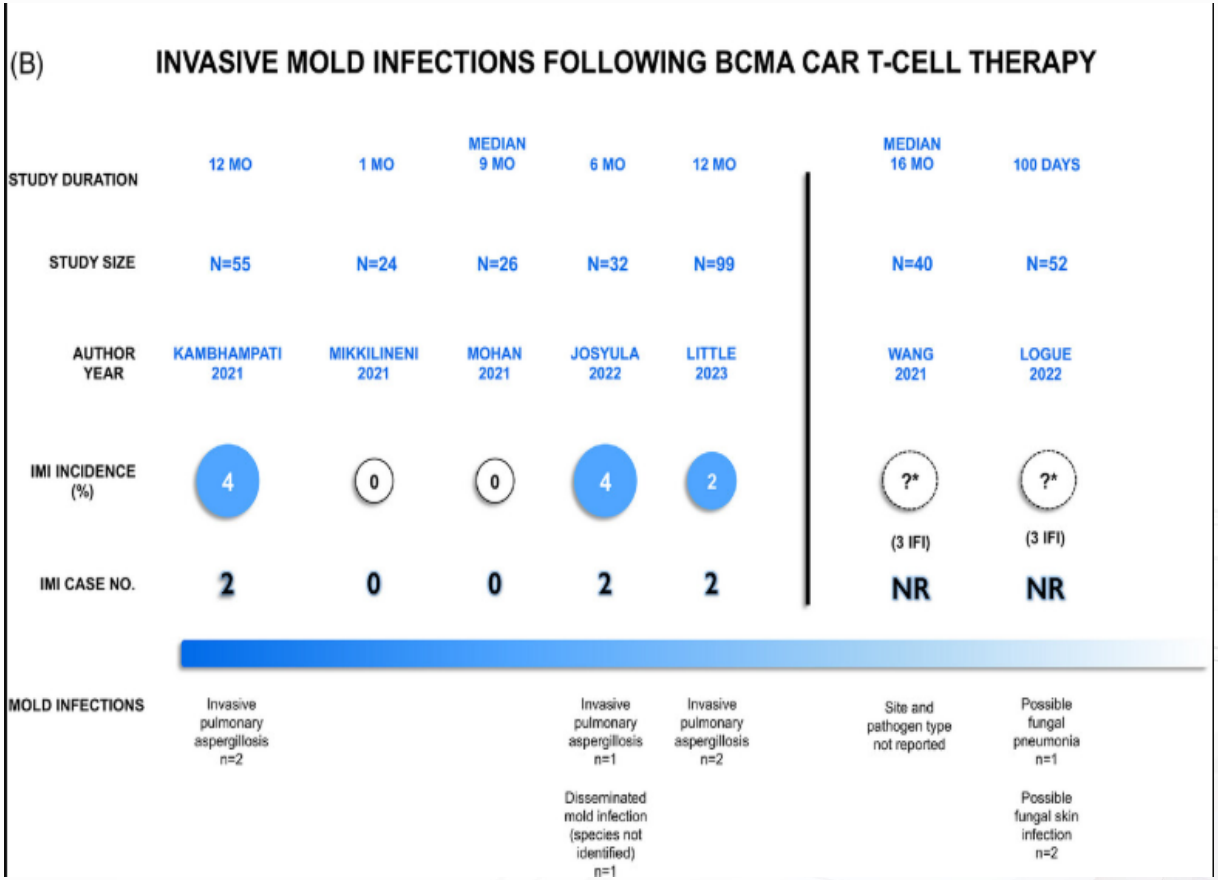
Kampouri E et al. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. TID. 03 october 2023



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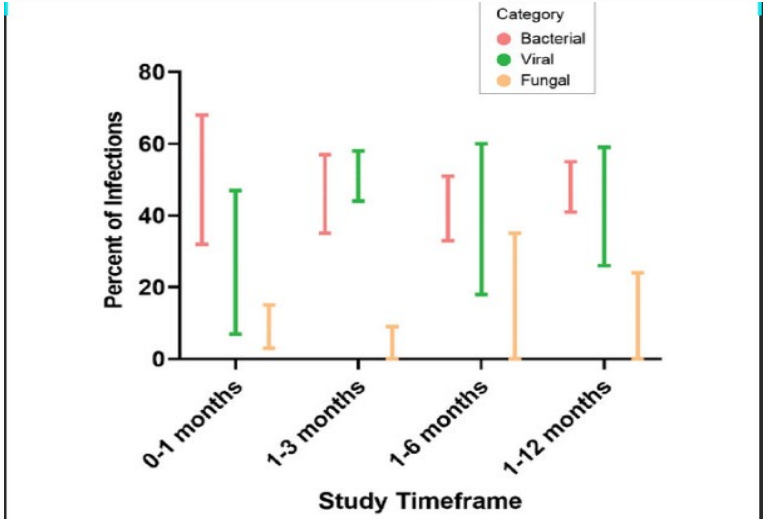
Kampouri E et al. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. TID. 03 october 2023

Infeções Tardias



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

Relative frequency of infection types (bacterial, viral and fungal) as percentage of all infections after CD19 CAR-T-cell therapy during different time intervals

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Kampouri E et al. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. TID. 03 october 2023

Review > Nat Rev Clin Oncol. 2024 Jul;21(7):501-521. doi: 10.1038/s41571-024-00903-0. Epub 2024 May 20.

Current understanding and management of CAR T cell–associated toxicities

Jennifer N Brudno [1], James N Kochenderfer [2]

- Infeções grau ≥3 (~5-32%).
- A morte relacionada com infeções após de CAR-T (~1-12% dos doentes em coortes com follow-up de 10-16M)
- Os fatores de risco pré-CAR-T para infeção incluem: o tipo de doença (LLA-B > LNH), > Nº LT, alo-TPH, QT ponte, CAR-HEMATOTOX ≥2
- N (<500células/µl x≥14D) e corticoides (DMX 10mg/dia x≥9D entre D0-D+21), são fatores de risco para infeção.

Table 1 | Rates of major CAR T cell-related toxicities for approved CAR T cell products

Product and indication	Grade 3–5 CRS (%)[a]	Vasopressor requirement (%)	Hypoxia and/or supplemental oxygen (%)	Grade 3–5 neurological toxicity (%)[b]	Ongoing B cell aplasia at 1 year in evaluable responders (%)[c]	Prolonged grade 3–4 cytopenias (%)[d]	Grade 3–5 infections (%)	Treatment-related mortality (%)	Refs.
CD19-directed CAR T cell products for large B cell lymphoma									
Axi-cel	6.5–16	6–17	22–31	21–35	47–50	29–38	16–28	1.9–5.7	4,23,42,88, 89,91,121
Tisa-cel	4.5–17[m]	1.9–3.6[l]	8.4–13.5	5.1–12[g]	NR	32	20	0–1.3	2,124,172
Liso-cel	1.1–2.2	0–2.6	10	4.3–10	73	37–43	12–15	2.2–2.6	6,173
CD19-directed CAR T cell products for follicular lymphoma									
Axi-cel	6.5	4.7[h]	22	15	52[h]	33	15	0.8	5
Tisa-cel	0	3.1	9.3	3.1	NR	Reported by individual lineages: neutropenia 15.5; thrombocytopenia 16.5; anaemia 3.1	5.2	0	3
CD19-directed CAR T cell products for mantle cell lymphoma									
Brexu-cel	3.0–15[e]	16	34	31–36[i]	55	26 at >90 days	32	2.9–15	8,90
CD19-directed CAR T cell products for B cell acute lymphoblastic leukaemia									
Tisa-cel (children and young adults)	16–47[j]	12–25[f]	17–44	9.0–13[g]	71	32	24	1.3	1,124,174
Brexu-cel (adults aged ≥18 years)	24	40	29	25	50 at 15 months	36	25	3.6	9
CD19-directed CAR T-cell products for chronic lymphocytic leukaemia									
Liso-cel	8.6	NR	14	19	74	54	17	0.73	7,175
BCMA-directed CAR T cell products for multiple myeloma									
Ide-cel	3.1–5.5[n]	NR	NR	3.1–5.7[l]	NA	Neutropenia 41–60; thrombocytopenia 48–59	23	1.9–3.1	10,24
Cilta-cel	5.2[k]	4.1	6.2	10.3[i]	NA	Neutropenia 30; thrombocytopenia 41	23	6.2	11,81

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COMO DIFERENÇAR A SÍNDROME DE LIBERTAÇÃO DE CITOCINAS DE UMA INFEÇÃO?

Open Forum Infect Dis. 2024 Jul 11;11(7):ofae398. doi: 10.1093/ofid/ofae398

Chimeric Antigen Receptor T-Cell Postinfusion Fever: Infection Profile, Clinical Parameters, and Biomarkers Trends to Assist Antibiotic Stewardship

Olivier Peyrony [1,2,#,✉], Nicole Garcia-Pouton [3,#], Mariana Chumbita [4,#], Christian Teijon-Lumbreras [5], Tommaso Francesco Aiello [6], Patricia Monzó-Gallo [7], Antonio Gallardo-Pizarro [8], Valentín Ortiz-Maldonado [9], Núria Martinez-Cibrian [10], Julio Delgado [11], Carlos Fernandez de Larrea [12], Josep Mensa [13], Pedro Puerta-Alcalde [14], Alex Soriano [15,16], Carolina Garcia-Vidal [17,✉,3]

Antibiotic	No. (%)
No.	87
Meropenem	55 (63.2)
Piperacillin-tazobactam	24 (27.6)
Teicoplanin	20 (23.0)
Levofloxacin	20 (23.0)
Ertapenem	5 (5.7)
Amikacin	5 (5.7)
Vancomycin	4 (4.6)
Others	12 (13.8)

Documented Infections in Patients With Initial Fever Post–Chimeric Antigen Receptor T-Cell Infusion

Patient	Bacteria	Virus	Fungi
1	*Staphylococcus epidermidis* (BC and catheter)	...	...
2	...	Coronavirus (BAL)	...
3	...	SARS-CoV-2 (NPS)	...
4	...	SARS-CoV-2 (NPS)	*Candida parapsilosis* (BC)
5	...	RSV (NPS)	...
6	*Enterococcus faecium* (BC)	...	...
7	*Enterococcus faecalis* (BC)	...	...
8	*Staphylococcus haemolyticus* (BC)	...	...
9	...	SARS-CoV-2 and other coronavirus (NSP)	...

No início da febre, não houve diferenças dos parâmetros clínicos e biomarcadores entre doentes sem infeção e com infeção bacteriana documentada, exceto para o score NEWS, que foi maior em doentes sem infeção (HR 5 [4–6] vs HR 3 [3–3]; p= 0,03)

- **Estudo retrospetivo, observacional – HCB**
- **152 doentes tratados com CAR-T**
- **87 (57,2%) febre – 30D após infusão**
- **Tempo médio (infusão e febre): 3D (2-5)**
- **82 (94.3%) AB amplo espectro**
- **9 (10,3) documentada infeção**
- **4 (4.6%) infeções bacterianas**

Johnson&Johnson
Innovative Medicine

Puerta P, et al. Paquete de medidas para reducir el uso de antibióticos y sus complicaciones en pacientes que reciben terapia CAR-T y presentan fiebre. FIS 2022

CAR-T cell infusion

Fever

- □ No specific signs or symptoms of infection
- □ No changes in NEWS score
- □ Negative blood cultures (at least 48h)

ANTIBIOTIC DISCONTINUATION OR DE-ESCALATION REGARDLESS OF FEVER

Johnson&Johnson
Innovative Medicine

Article | Published: 19 February 2021

CRS-related coagulopathy in BCMA targeted CAR-T therapy: a retrospective analysis in a phase I/II clinical trial

Mi Shao, Qin Yu, Xinyi Teng, Xin Guo, Guoqing Wei, Huijun Xu, Jiazhen Cui, A. H. Chang, Yongxian Hu & He Huang

Bone Marrow Transplantation **56**, 1642–1650 (2021) | Cite this article

InternNet CLUB
FÓRUM 2025 • 9ª EDIÇÃO

- Os parâmetros de coagulação e os níveis de algumas citocinas (IL-6, IL-10 e interferon [IFN]-γ) correlacionaram-se positivamente com a gravidade da CRS.
- Doentes com CRS grave apresentam níveis séricos elevados de angiopoietina 2 (ANGPT2) e fator de Von Willebrand (FVW)

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COMO PREVENIR AS INFEÇÕES?

Table 5 (continued) | Prevention, monitoring, evaluation and treatment of CAR T cell-related haematological and immunological toxicities

Pretreatment assessment	Preventive measures	Post-treatment monitoring	Diagnostic evaluation if toxicity occurs	Supportive care measures	Pharmacological and/or immunological management[a]
Immunosuppression and infections, except COVID-19 (refs. 22,26,47,48,129,130,179)					
Pre-leukapheresis serologies for EBV, HBV, HCV, HIV, HSV, VZV and CMV; HBV PCR for viral DNA if HBV surface antigen or core antibody-positive, and HCV PCR for viral RNA if HCV antibody-positive Consider PCR testing for EBV, CMV and HBV regardless of serology results Treatment of individuals with HIV infection can be made on a case-by-case basis[b]	Delay lymphodepletion and/or CAR T cell infusion if patient is febrile and has evidence of infection and give appropriate antimicrobial treatment; resume CAR T cell therapy when patient is afebrile for at least 48 h and clinical evidence suggests that the infection is controlled and symptoms have improved Delay treatment in patients with detectable HBV or HCV DNA/RNA or HBV surface antigen positivity until infection is treated Entecavir or tenofovir prophylaxis in patients with HBV core antibodies, for at least 6 months to 1 year after cell infusion; consider longer in those with continued B cell aplasia All patients should receive prophylactic antimicrobials for pneumocystis and HSV and VZV infection for 6 months to 1 year after cell infusion; consider longer if blood $CD4^+$ cell counts are <200 cells/μl; re-vaccinate with killed/inactivated and live attenuated vaccines >6 months and ≥12 months after CAR T cell infusion, respectively, and when $CD4^+$ and B cell counts are >200 cells/μl. Immunosuppressive treatments, such as systemic chemotherapy, or immunoglobulin replacement therapy for hypogammaglobulinaemia should have been discontinued for ≥2 months prior to re-vaccination with killed/inactivated vaccines and for ≥8 months when using live attenuated vaccines, with the exception influenza and COVID-19 vaccines (see guidance below)	Check immunoglobulin levels monthly Check $CD4^+$ cell count and B cell count every ~3 months HBV viral DNA monitoring in core antibody-positive patients Consider weekly CMV PCR monitoring in seropositive individuals who have received >3 days of glucocorticoids, until 1 month after last dose of glucocorticoids	Rule out infectious causes of fever: blood cultures; depending on symptomatology, nasal swab for SARS-CoV-2 and other respiratory viruses, urine cultures and sputum cultures	Immunoglobulin replacement therapy for serum IgG levels <400–600 mg/dl or recurrent infections; replacement given more routinely in children; can consider cessation of replacement in adults >3 months after CD19-directed CAR T cell infusion Consider antifungal and gram-negative antibacterial prophylaxis in the following circumstances: intensive lymphodepletion regimens (for example, containing an anti-CD52 antibody), prolonged glucocorticoid use and/or prolonged neutropenia	Treat identified bacterial, fungal or influenza infections according to institutional guidelines in immunosuppressed individuals Empiric antibiotics for neutropenic fever

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Innovative Medicine

Brudno J et al. Current understanding and management of CAR-T cell-associated toxicities. NRCO. 2024 Jul;21(7);501-521

Table 5 (continued) | Prevention, monitoring, evaluation and treatment of CAR T cell-related haematological and immunological toxicities

Pretreatment assessment	Preventive measures	Post-treatment monitoring	Diagnostic evaluation if toxicity occurs	Supportive care measures	Pharmacological and/or immunological management[a]
COVID-19 infection[136,178,180]					
PCR testing for SARS-CoV-2 2–3 days before lymphodepletion chemotherapy	Delay lymphodepletion chemotherapy for at least 14–20 days and until symptom improvement in patients with SARS-CoV-2 infection/ COVID-19 Counsel masking and social distancing during periods of high community infection rates Prior to CAR T cell infusion, vaccinate against influenza and COVID-19, if patient's vaccinations are not already up to date Care-givers should follow CDC guidelines for COVID-19 vaccination based on age and health status Re-vaccination for COVID-19 and influenza ≥90 days after CAR T cell infusion	Counsel patients and care-givers to monitor for symptoms and seek care promptly	SARS-CoV-2 PCR testing, with concurrent testing for influenza and RSV in patients with respiratory symptoms In patients with COVID-19 symptoms and negative nasal PCR testing for SARS-CoV-2, consider repeat testing and chest CT imaging ± bronchoscopy to evaluate for lower respiratory infection and other infectious causes	Consider early hospital admission of symptomatic patients for monitoring, depending on institutional resources	Nirmatrelvir and ritonavir or best available antiviral therapy for prevention of hospitalization and death in outpatients with COVID-19 infection; remdesivir or best available antiviral therapy for inpatients with COVID-19, except those with critical illness; dexamethasone for inpatients with COVID-19 requiring supplemental oxygen; anti-cytokine therapy (tocilizumab) or JAK inhibitors can be considered in those with worsening illness (infectious disease consultation recommended) High-titre convalescent plasma can be considered in outpatient or inpatient settings, with most benefit early in the course of illness, or in patients with protracted illness

Brudno J et al. Current understanding and management of CAR-T cell-associated toxicities. NRCO. 2024 Jul;21(7);501-521

TABLE 1 Guidelines and local practices for infection prevention in chimeric antigen receptor (CAR)-T-cell therapy recipients at the authors' centers and from published guidelines.

	EBMT/EHA (Europe)	Spanish group (Spain)	SFGM-TC (France)	Fred Hutch (US)	Dana Farber (US)	CHUV Lausanne (Switzerland)	LMU Munich (Germany)
Antibacterial prophylaxis	NR	NR	NR	FQ during neutropenia[a]	Levofloxacin 500 mg/day during neutropenia[a]	NR	Risk adapted[b]; FQ during neutropenia[a]
Antifungal prophylaxis	Consider fluconazole, posaconazole,[c] or micafungin if severe or prolonged >14 days neutropenia,[a] and/or long-term or high dose (>3 days) of steroids or post-allo-HCT	Fluconazole (400 mg/day) during neutropenia[a]	Consider fluconazole or micafungin if severe neutropenia[a] >14 days, steroids >3 days, post-allo-HCT	Fluconazole (200 mg/day) during neutropenia[a]	No antifungal prophylaxis	Fluconazole (200 mg/day) during neutropenia[a]	No antifungal prophylaxis
Anti-mold prophylaxis	See above	Posaconazole 300 mg/day,[c] nebulized liposomal amphotericin B or micafungin if ≥4 lines of prior treatment, pre-CAR-T-cell infusion severe neutropenia[a], higher dose of CAR-T-cells ($>2 \times 10^7$), previous IFI, tocilizumab, and/or steroids	Posaconazole (300 mg/day[c]) if post-allo-HCT or steroids or previous IFI	Posaconazole (300 mg/day[c]) if neutropenia[a] >20 days or steroids >3 days for at least 4 weeks after last dose of steroid (and after neutropenia resolution[a])	No anti-mold prophylaxis	Posaconazole (300 mg/day[c]) if post-allo-HCT or steroids or previous IFI	Risk-adapted[b] (posaconazole[c] or micafungin during neutropenia[a] or extended steroid exposure)
Anti-PjP prophylaxis	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for 1-year and until CD4 >200 cells/mm^3	TMP/SMX DS 3×/week Start 1 week pre-infusion (pause during neutropenia), continue until CD4 >200 cells/mm^3	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for 1-year and until CD4 >200 cells/mm^3	TMP/SMX DS 2×/day on 2 consecutive days/week Start 21–28 days post-infusion, continue for at least 6 months	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3	TMP/SMX 1DS 3×/week Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3

	EBMT/EHA (Europe)	Spanish group (Spain)	SFGM-TC (France)	Fred Hutch (US)	Dana Farber (US)	CHUV Lausanne (Switzerland)	LMU Munich (Germany)
Antiviral prophylaxis	Acyclovir 800 mg 2x/day or valacyclovir 500 mg 2x/day Start at LD chemotherapy, continue for 1 year and until CD4 >200 cells/mm^3	Acyclovir 400–800 mg 2x/day At least 60–100 days after infusion	Acyclovir 800 mg 2x/day or valacyclovir 500 mg 2x/day Start at LD chemotherapy, continue for 1-year and until CD4 >200 cells/mm^3	Acyclovir 800 mg 2x/day or valacyclovir 500 mg 2x/day Start at lymphodepleting chemotherapy, continue for at least 1 year	Acyclovir 400 mg 3x/day or valacyclovir 500 mg 2x/day Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3	Valacyclovir 500 mg 2x/day for 6–12 months	Acyclovir 400 mg 2x/day Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3
CMV monitoring	As clinically indicated	NR	Consider in CMV seropositive patients at high risk Weekly monitoring	Patients treated with >3 days of steroids Weekly until 1 month after last dose of steroid	Strongly consider monitoring for patients receiving >5 doses dexamethasone	Consider in CMV seropositive patients at high risk Weekly/biweekly monitoring	NR
Preemptive threshold	–	NR		150 IU/mL (plasma)	None	None	None

Abbreviations: Allo-HCT, allogeneic hematopoietic cell transplant; CHUV, Lausanne University Hospital; CMV, cytomegalovirus; DS, double strength; EBMT, European Society for Blood and Marrow Transplantation; FQ, fluoroquinolone (levofloxacin 750 mg PO daily); IFI, invasive fungal infection; LD, lymphodepleting; LMU, Ludwig Maximilian University of Munich; NR, not recommended; PjP, *Pneumocystis jirovecii* pneumonia; SFGM-TC, Société de Greffe de Moelle et de Thérapie Cellulaire; SS, single strength; TMP/SMX, trimethoprim/sulfamethoxazole.

[a]Neutropenia defined as absolute neutrophil count <500 cell/mm^3; resolution: first of 3 days ≥500 cell/mm^3.

[b]Adapted to baseline CAR-Hematotox score or other pertinent risk factors for prolonged severe neutropenia (absolute neutrophile count <500 cell/mm^3 for ≥7 days) such as underlying bone marrow infiltration.

[c]Posaconazole 200 mg every 12 h on first day then 300 mg/day.

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Overview of infectious complications among CAR T- cell therapy recipients

Swarn Arya [1], Zainab Shahid [1,2,*]

Proposed Antimicrobial Prophylaxis for CAR-T Patients (4, 86–90).

	Agent	Alternative agent (s)	Comment
Antibacterial	Levofloxacin		Start when ANC < 500 and continue until neutrophil recovery (ANC >500 for at least 3 days)
Antifungal	Fluconazole	Micafungin	Start when ANC<500 and continue until neutrophil recovery (ANC >500 for at least 3 days)
Anti-mold	Voriconazole	Posaconazole	Consider in those at high risk for mold infection: ANC<500 for >21 days, treatment with prednisone >20mg for >2 weeks or equivalent, history of IFI, history of allogeneic HSCT; duration determined case by case
Anti-PJP	Trimethoprilm/ Sulfamethoxazole (TMP/SMX)	Inhaled pentamidine OR dapsone OR atovaquone	Start with lymphodepleting chemotherapy and continue for at least 6 months post- CAR T infusion or until CD4 count >200 cell/mm^3
Antiviral	Acyclovir	Valacyclovir	Start with lymphodepleting chemotherapy and continue for 6–12 months or until CD4 >200 cell/mm^3

Immunosuppressive Agents Used for Treatment Of CRS/ICANS/HLH and their Associated Infection.

Immunosuppressive Therapy	Associated Infection Risk	Prophylaxis Strategy Considerations
Steroids (dexamethasone, methylprednisolone)	Well-known association with fungal infections, viral reactivations, and PJP, which is also noted in some cohorts after CAR T-cell therapy (11, 16, 22, 35, 49, 65)	Mold active prophylaxis HSV/VZV prophylaxis if seropositive Weekly monitoring for CMV reactivation and strong consideration of pre-emptive therapy
IL-1 Receptor antagonist (anakinra)	Well tolerated with extended treatment in the rheumatoid arthritis population (106); no specific association with infectious risk in limited experience after CAR-T (107) In combination with steroids, the risk of infection may be higher (106)	If being administered with steroids, above considerations apply
IL-6 receptor antagonist (tocilizumab, siltuximab)	Safety profile post CAR-T infusion is unclear; in one report, use was associated with infections and death (108). In other populations, it has been associated with tuberculosis (TB), other mycobacterial infections, and fungal infections (39)	Mold active prophylaxis HSV prophylaxis if seropositive CMV preemptive therapy Weekly monitoring for viral reactivation Bacterial prophylaxis when ANC<500
JAK1/2 inhibitor (ruxolitinib)	Safety in CAR T-cell population unclear; associated with higher rates of VZV infection and hepatitis B reactivation (109, 110) in hematological malignancy population; also reports of disseminated TB, cryptococcal infection, toxoplasmosis, CMV disease, mold infections (109, 111).	Mold-active prophylaxis (with attention to drug-drug interactions between ruxolitiib and azoles) PJP prophylaxis VZV prophylaxis if seropositive Weekly monitoring for CMV reactivation among those on multiple and strong consideration of pre-emptive therapy HBV prophylaxis if HBSAg+ and/or HBV DNA PCR is detectable Bacterial prophylaxis when ANC<500
Chemotherapy (etoposide)	Bacterial infections with neutropenia	Attention to bacterial prophylaxis when ANC<500
Anti-IFN-gamma monoclonal antibody (emapalumab)	Viral reactivations, fungal infections, TB reactivation and other mycobacterial infections have been reported in other populations (112, 113)	Fungal prophylaxis on case by case basis PJP prophylaxis VZV prophylaxis if seropositive Weekly monitoring for CMV reactivation and consideration of pre-emptive therapy

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Vaccines For CAR T-cell Therapy Recipients.

	Killed/inactivated vaccines	Live and non-live adjuvant vaccines
Eligibility	6 months post-CAR-T 2 months since last IGRT	1-year post-CAR-T
Contraindications	• IGRT within the past 2 months • Receiving T-cell or B-cell directed immunosuppressive therapy. • Receipt of anti-CD20 or anti-CD19 in the prior 6 months • Actively receiving chemotherapy	• Received anti-CD19 or anti-CD20 therapy within the past 6 months. • 1 year post CAR T-cell therapy • 2 years post autologous or allogeneic HCT • <1 y off of all systemic immunosuppressive therapy • < 8 months after the last dose of IGRT • Absolute CD4 count < 200 cells/mm^3 • Absolute CD19+ or CD20+ B cell count < 20 cells/mm^3 • Actively receiving chemotherapy
Vaccinations to consider	Influenza Covid-19 Pneumococcal conjugate Pneumococcal polysaccharide Diphtheria, tetanus, and acellular pertussis (DTaP) Hepatitis A virus Hepatitis B virus	Varicella Zoster Virus

- O momento ideal da vacinação não é claro, depende do tempo da reconstituição da imunidade celular e humoral após CAR-T.
- A vacina contra SARS CoV-2 pode ser iniciada no D+90 pós-infusão.
- As principais vacinas a serem consideradas incluem influenza anual, Strept. pneumoniae, Haemophilus influenza tipo B, toxinas de Corynebacterium diphtheriae e Clostridium tetani, Bordetella pertussise vírus da Hepatite A e B
- Doentes com >50ª, soropositivos para VZV ou histórico de herpes zóster, a vacina zóster recombinante (Shingrix) deve ser considerada

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QUIZ

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Quiz

15 questões

- 5 sobre o tema grupo 1
- 5 sobre o tema grupo 2
- 5 sobre conceitos básicos aplicados em hematologia

Estrutura das questões

- Escolha múltipla
- 4 opções de resposta
- Apenas 1 opção correta

Quiz

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Aceder ao *Quiz*

- Leitura do QR code ou pelo link.
- Cada participante tem de escrever o seu nome.
- As questões serão apresentadas 1 a 1.
- 60 segundos para responder a cada questão
- Após todos os participantes responderem é apresentado o quadro com as pontuações, e passa-se à próxima questão.
- No fim das 15 questões é apresentado o quadro final com as pontuações.

Pontuação

- Por cada resposta correta o sistema atribui uma pontuação
- A pontuação é ajustada pela rapidez de resposta

LEIA O ***QR CODE*** PARA INICIAR O **QUIZ**

BOA SORTE!

Resultados do *Quiz*

LEIA O ***QR CODE*** PARA INICIAR
O **QUESTIONÁRIO DE SATISFAÇÃO**

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