ESCMID
MANAGING INFECTIONS
PROMOTING SCIENCE

Infectious complications of CAR T-cell therapies

Pr Claire Roger

Intensive Care Unit

Nimes University Hospital, France

UR UM 103 IMAGINE, School of Medicine, Montpellier University

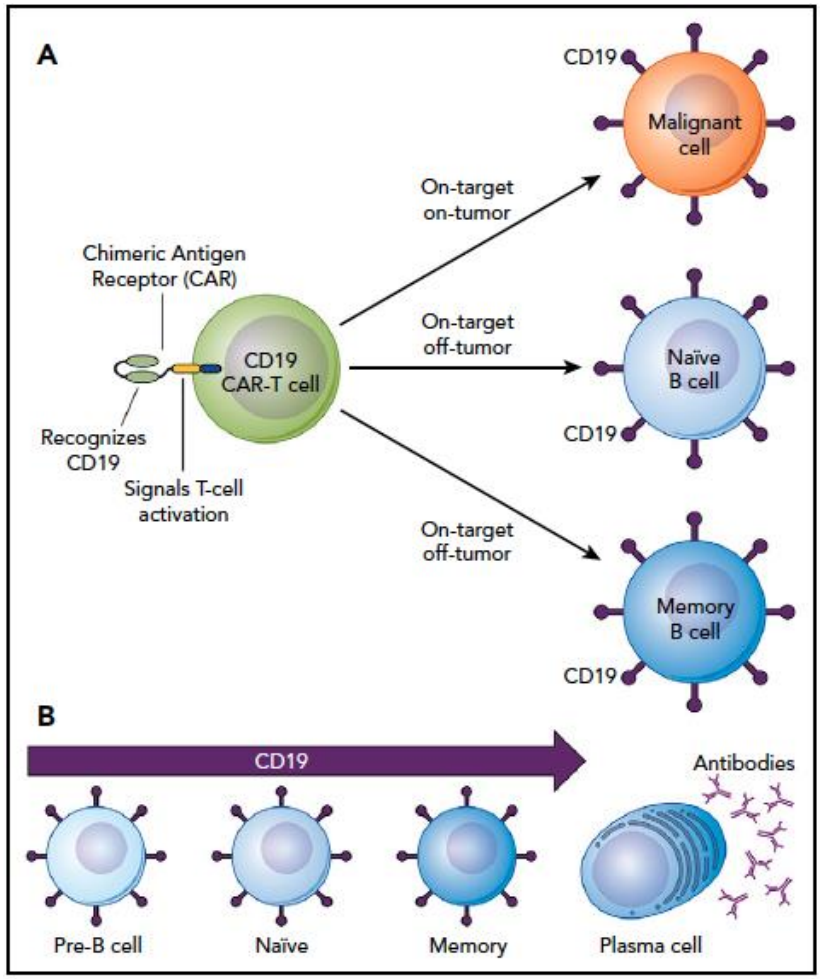
Faculté de Médecine Montpellier-Nîmes

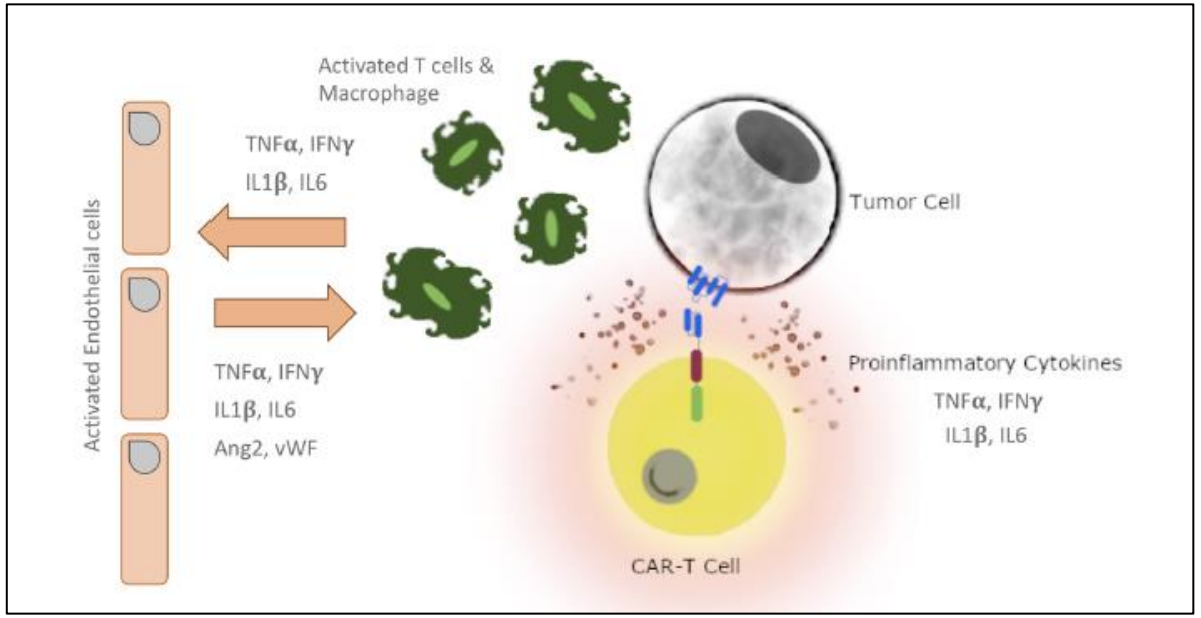
Université Montpellier

SFAR

CHU Nîmes

CAR T-cell therapies





Endothelial cell activation

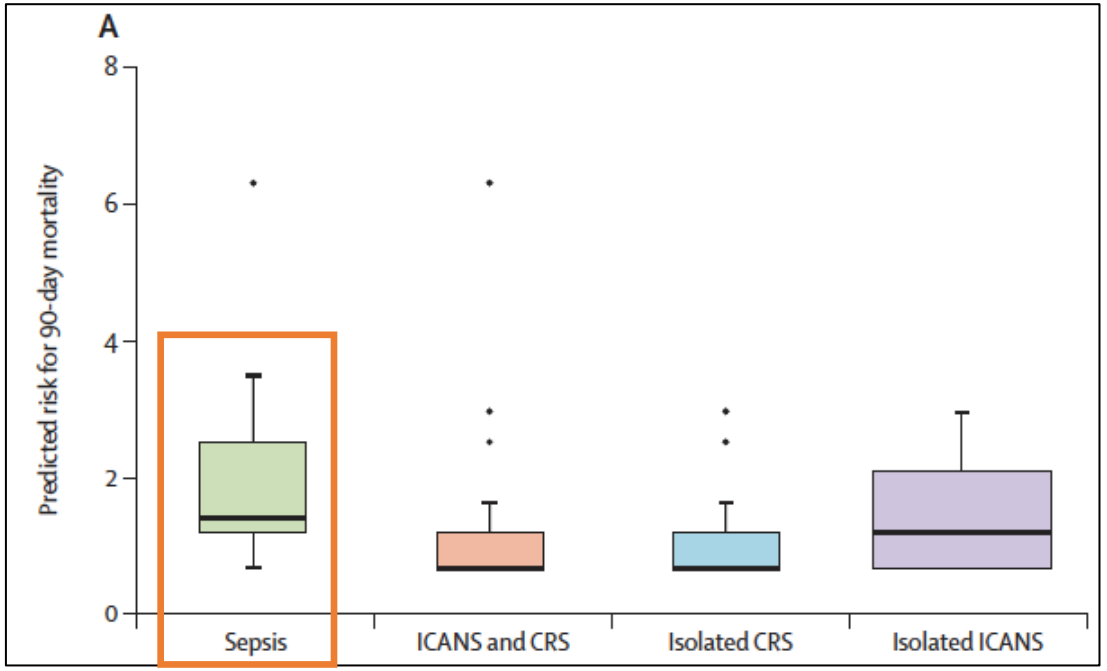
Hill et al. Blood 2020
Bellal et al. Crit Care 2024

Impact of infectious complications on early and late clinical outcomes

Outcomes in patients treated with chimeric antigen receptor T-cell therapy who were admitted to intensive care (CARTTAS): an international, multicentre, observational cohort study

Élie Azoulay, Pedro Castro, Adel Maamar, Victoria Metaxa, Alice Gallo de Moraes, Louis Voigt, Florent Wallet, Kada Klouche, Muriel Picard, Anne-Sophie Moreau, Andry Van De Louw, Amélie Seguin, Djamel Mokart, Sanjay Chawla, Julien Leroy, Boris Böll, Nahema Issa, Bruno Levy, Pleun Hemelaar, Sara Fernandez, Laveena Munshi, Philippe Bauer, Peter Schellongowski, Michael Joannidis, Gabriel Moreno-Gonzalez, Gennadii Galstian, Michael Darmon, Sandrine Valade, on behalf of the Nine-I investigators

Lancet Haematol 2021; 8: e355–64

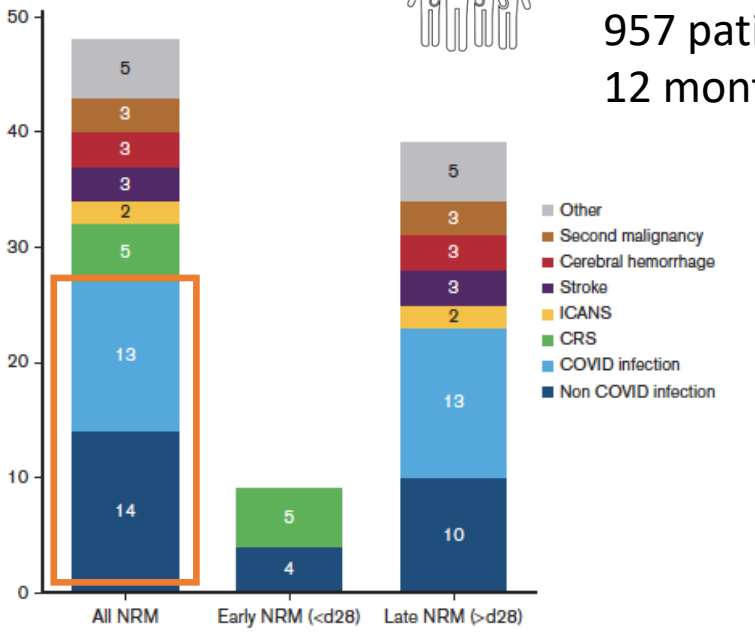


Nonrelapse mortality after CAR T-cell therapy for large B-cell lymphoma: a LYSA study from the DESCAR-T registry

Jean Lemoine,[1] Emmanuel Bachy,[2] Guillaume Cartron,[3] David Beauvais,[4] Thomas Gastinne,[5] Roberta Di Blasi,[6] Marie-Thérèse Rubio,[7] Stéphanie Guidez,[8] Mohamad Mohty,[9] Rene-Olivier Casasnovas,[10] Magalie Joris,[11] Cristina Castilla-Llorente,[12] Corinne Haioun,[13] Olivier Hermine,[14] Michael Loschi,[15] Sylvain Carras,[16] Pierre Bories,[17] Tom Fradon,[18] Charles Herbaux,[3] Pierre Sesques,[2] Steven Le Gouill,[19] Franck Morschhauser,[4] Catherine Thieblemont,[6] and Roch Houot[1]

Blood Adv 2023

DESCAR-T registry
957 patients with LBCL
12 months follow-up



Agenda

Infectious complications after CAR T-cell therapies

- Incidence
- Risk factors
- Diagnosis
- Preventive strategies

Agenda

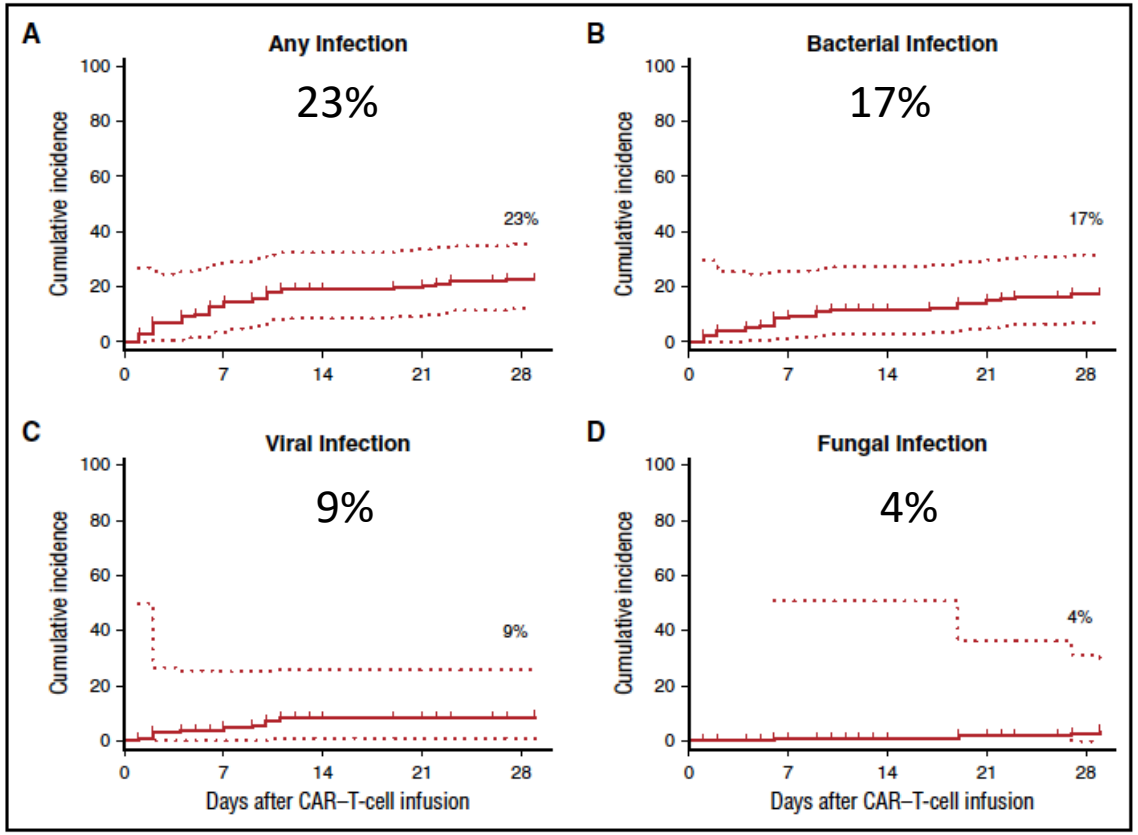
Infectious complications after CAR T-cell therapies

- Incidence
- Risk factors
- Diagnosis
- Preventive strategies

IMMUNOBIOLOGY AND IMMUNOTHERAPY

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

Joshua A. Hill,[1,2] Daniel Li,[3] Kevin A. Hay,[4,5] Margaret L. Green,[1,2] Sindhu Cherian,[6] Xueyan Chen,[6] Stanley R. Riddell,[1,4] David G. Maloney,[1,4] Michael Boeckh,[1,2] and Cameron J. Turtle[1,4]



133 patients with R/R B-cell malignancies
- 35% ALL
- 18% CLL
- 47% NHL

3-month follow up

80% infections <10 days

Hill et al. Blood 2018

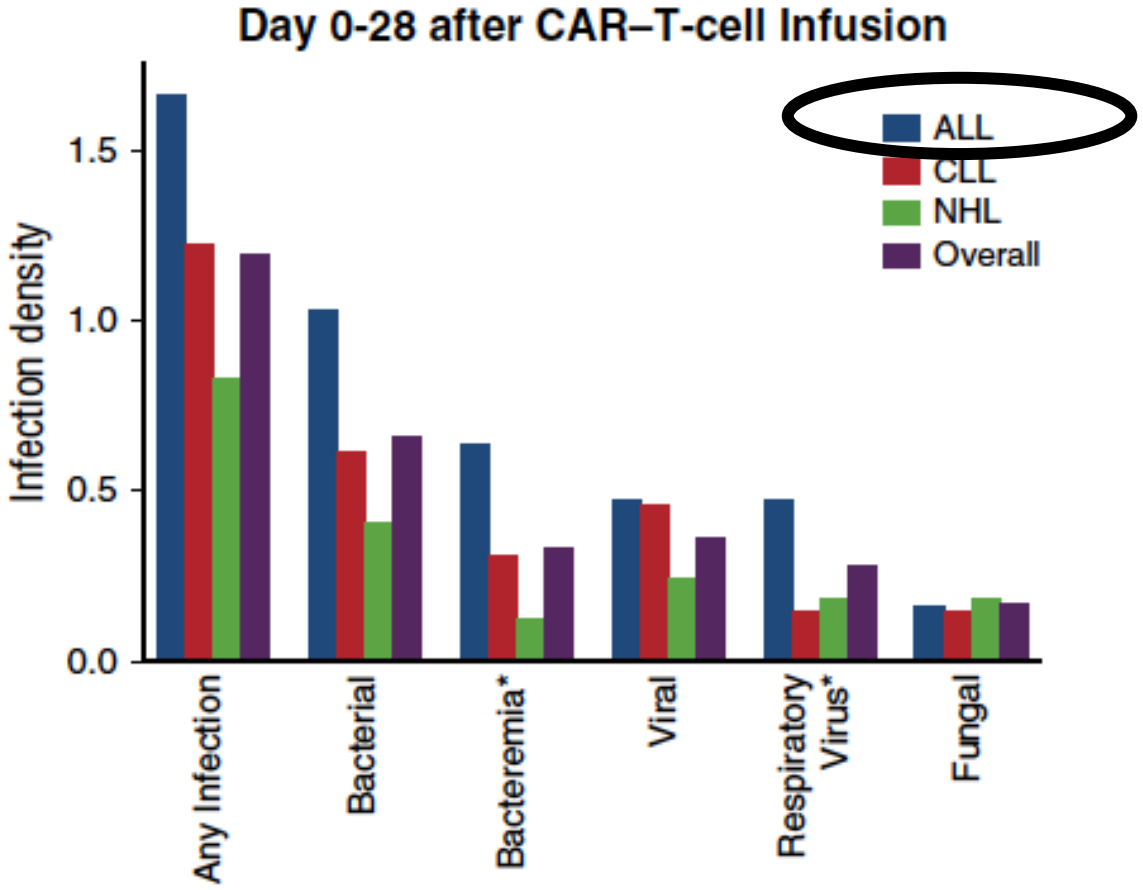
- Overall prevalence varies:
  - 18-56% prospective trials
  - 20-60% retrospective cohorts
- Factors of variation:
  - Patient related factors
  - CAR T-cell related factors
  - Follow up

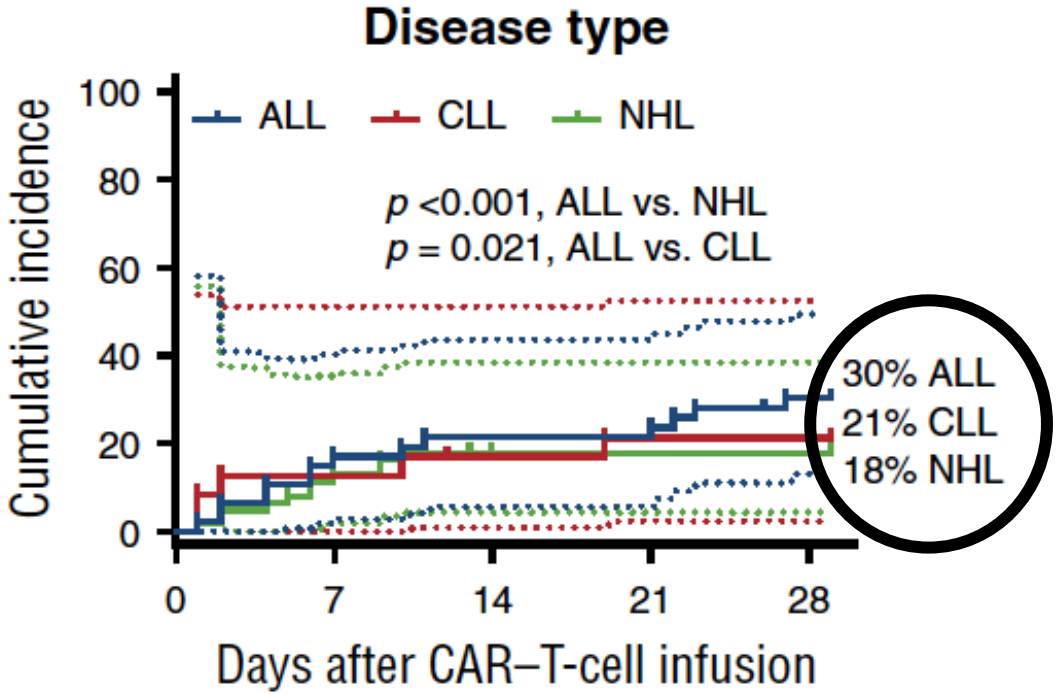
Table 1. Pooled data of infectious complications from CAR-T cell therapy.

Reference	CAR T-cell therapy	*N*	Underlying malignancy	Severity grade	Timepoint	Bacterial infection incidence (*n*, %)	Viral infection incidence (*n*, %)	Fungal infection incidence (*n*, %)
Abramson *et al.*[34]	Lisocabtagene maraleucel	269	R/R B-cell lymphoma	⩾3	12 months	27/269 (10)	4/269 (1)	2/269 (1)
Locke *et al.*[38]	Axicabtagene ciloleucel	108	Refractory B-cell lymphoma	All	12 months	44/108 (40)	11/108 (10)	7/108 (6)
Logue *et al.*[35]	Axicabtagene ciloleucel	85	R/R B-cell lymphoma	All	⩽30 days	26/85 (31)	12/85 (14)	2/85 (2)
					>30 days	13/85 (15)	19/85 (22)	0/85 (0)
Wittmann Dayagi *et al.*[36]	CD28-based CAR T cells	88	R/R B-cell lymphoma	All	⩽30 days	22/85 (25)	14/85 (16)	0/85 (0)
					30–60 days	8/85 (9)	2/85 (2)	1/85 (1)
Baird *et al.*[37]	Axicabtagene ciloleucel	41	R/R B-cell lymphoma	All	⩽28 days	7/41 (17.1)	8/41 (19.5)	4/41 (9.8)
					>28 days	10/41 (24.4)	10/41 (24.4)	9/41 (22)
Wudhikarn *et al.*[22]	Axicabtagene ciloleucel OR tisagenlecleucel	60	R/R DLBCL	All	⩽30 days	20/60 (33)	10/60 (17)	1/60 (2)
					>30 days	14/60 (24)	17/60 (28)	3/60 (5)
Hill *et al.*[21]	Anti-CD19 CAR autologous T cells	133	ALL, CLL, NHL	All	⩽28 days	22/133 (16.5)	11/133 (8.3)	4/133 (3)
					>28 days	7/119 (5.9)	11/119 (9.2)	2/119 (1.7)
Munshi *et al.*[41]	Idecabtagene vicleucel	54	R/R multiple myeloma	All	12 months	13/54 (24)	15/54 (28)	4/54 (7)

Stewart et al. Ther Adv Infectious Dis 2021

Risk of infection and underlying disease: ALL>CLL and NHL





Hill et al. Blood 2018

Infections in haematology patients treated with CAR-T therapies: A systematic review and meta-analysis

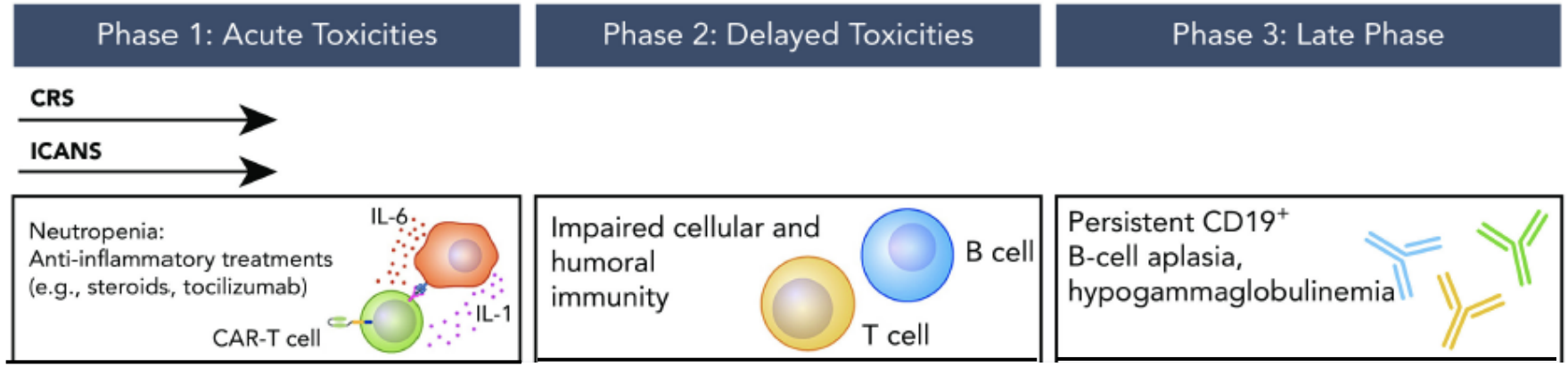
Gemma K. Reynolds [a,c,d,e,*,1], Beatrice Sim [a,d], Tim Spelman [d], Ashmitha Thomas [e], Anthony Longhitano [f], Mary Ann Anderson [b], Karin Thursky [a,c,d], Monica Slavin [a,c,d], Benjamin W. Teh [a,c,d,2]

Summary of microbiologically confirmed infections (bacterial, viral, fungal).

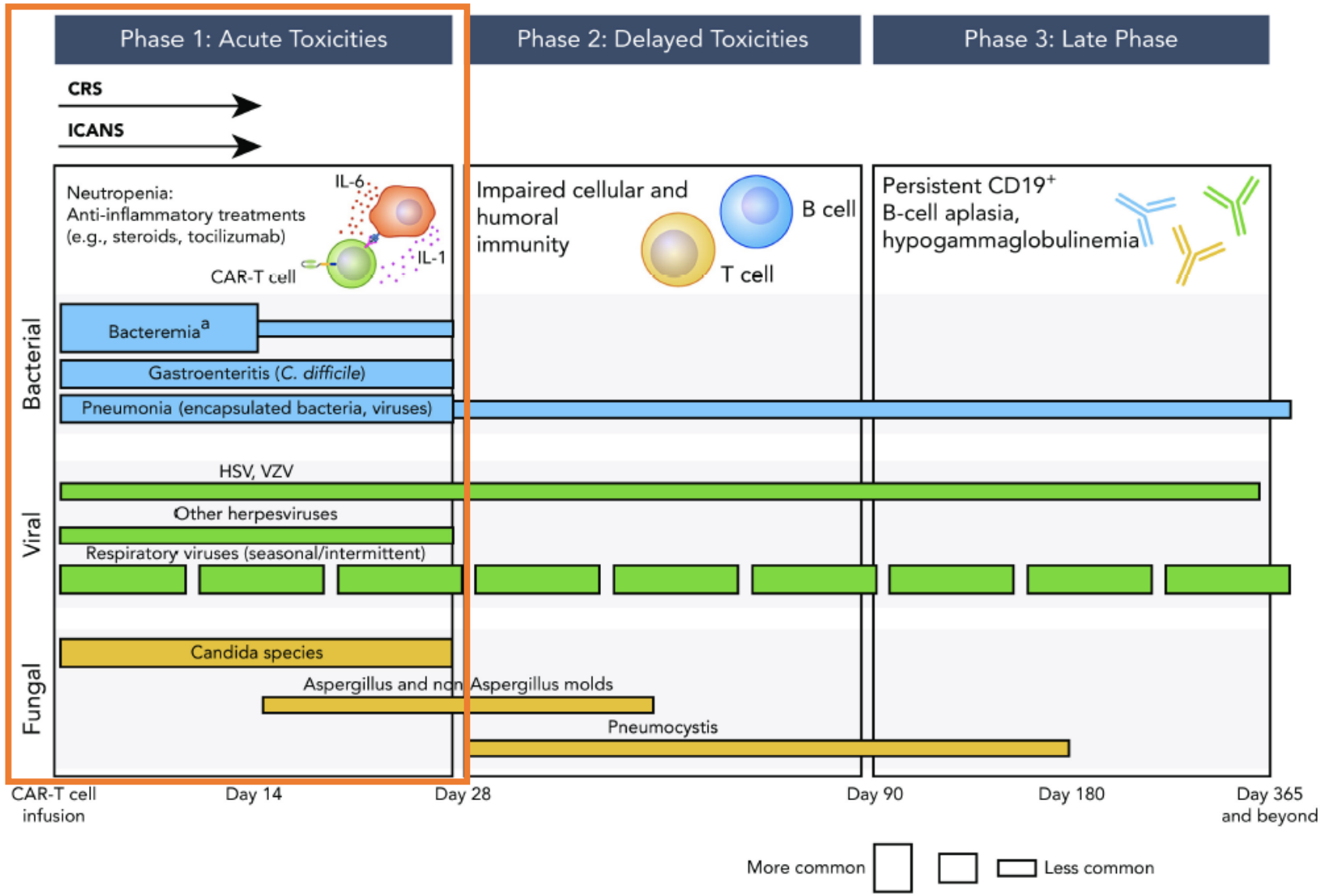
	Non Hodgkin's Lymphoma N (%)	Acute Lymphoblastic Leukaemia N (%)	Multiple Myeloma N (%)	Chronic Lymphocytic Leukaemia N (%)
Incidence of microbiologically confirmed infections amongst CAR-T treated patients, as defined by the studies				
Included Patients	1487	256	265	41
Total Infection Events	834	141	187	24
Incidence	0.56 events / treated patient	0.55 events / treated patients	0.7 events / treated patients	0.58 events / treated patients
	N (% of events)	N (% of events)	N (% of events)	N (% of events)
Bacterial Events	414 (50)	89 (63)	89 (48)	14 (58)
Viral Events	318 (38)	37 (26)	80 (43)	8 (33)
Fungal Events	78 (9)	15 (11)	18 (9)	2 (8)

Reynolds et al. Crit Rev Oncol 2023

3 different phases for infectious complications



Hill et al. Blood. 2020; 136: 925–935.



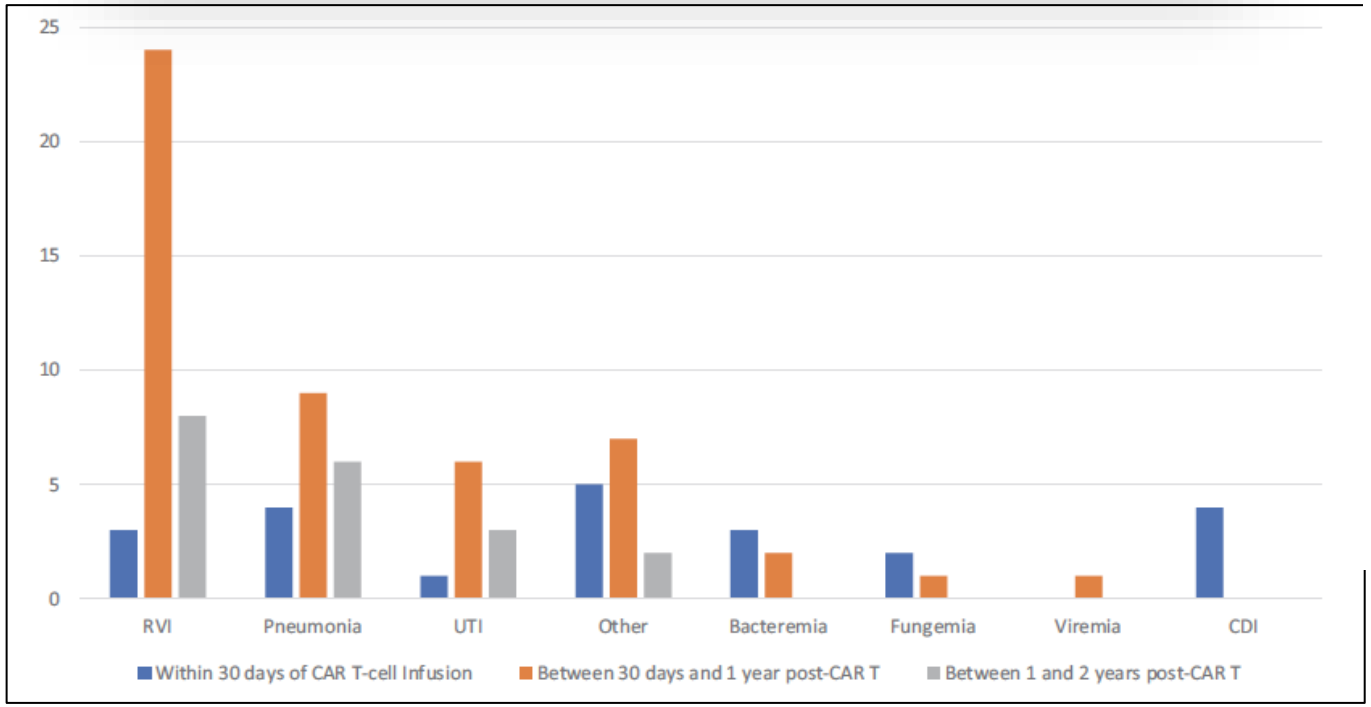
Hill et al. Blood. 2020; 136: 925–935.

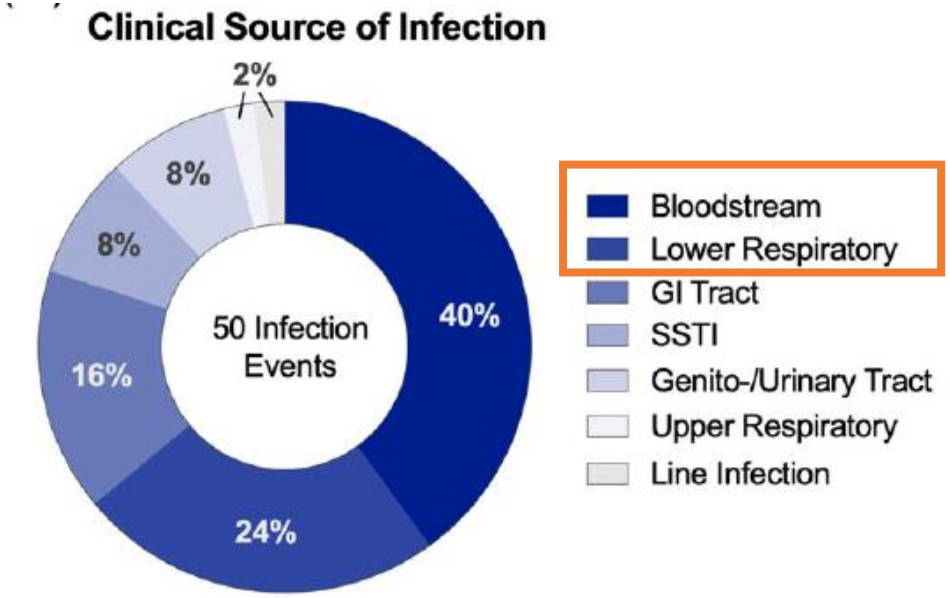
Sources of infection: BSI and pulmonary infections

Infectious complications of car T-cell therapy: A longitudinal risk model

Michael T. Czapka[1] | Peter A. Riedell[2] | Jennifer C. Pisano[1]

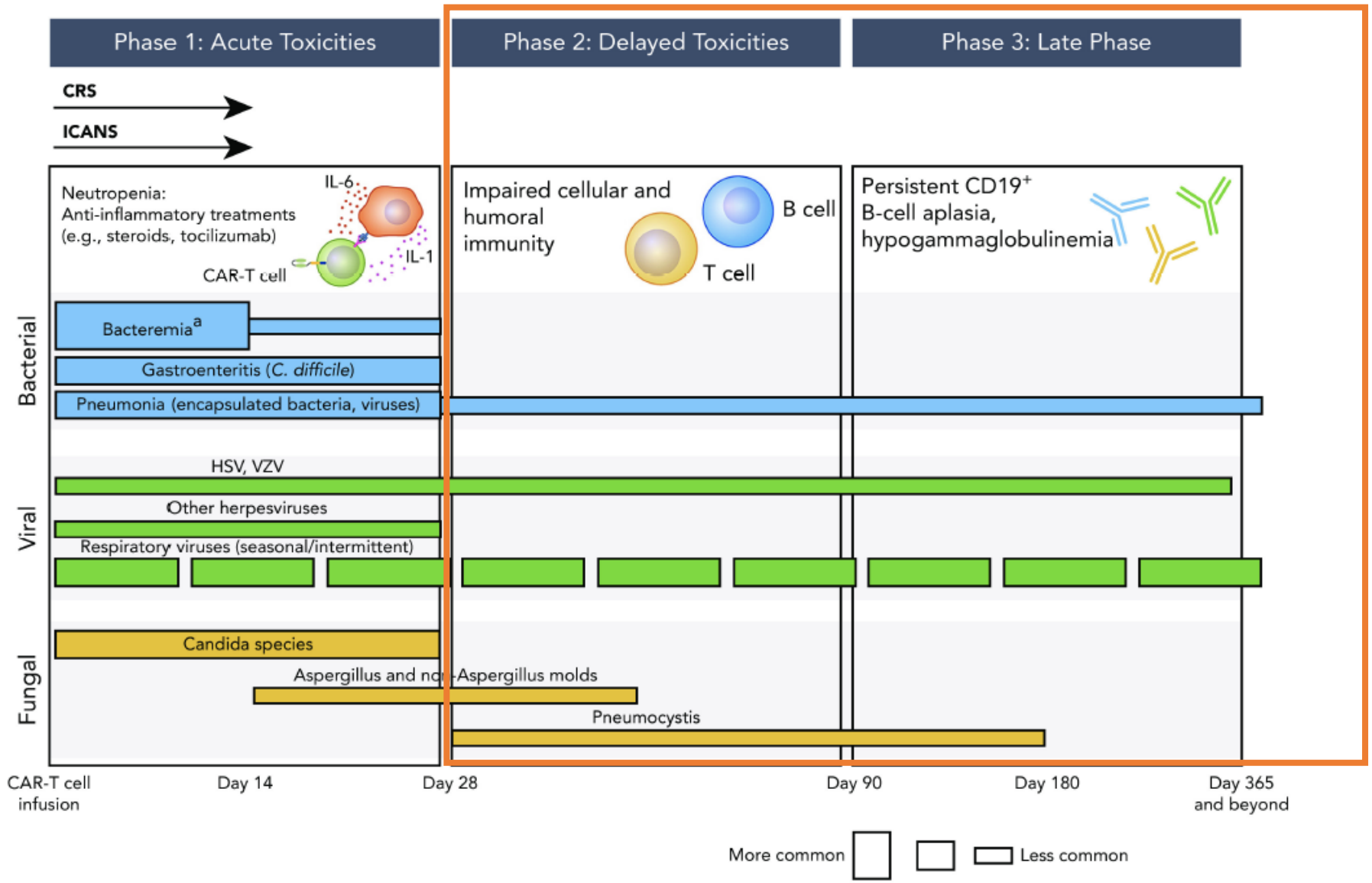
Transplant Infectious Disease





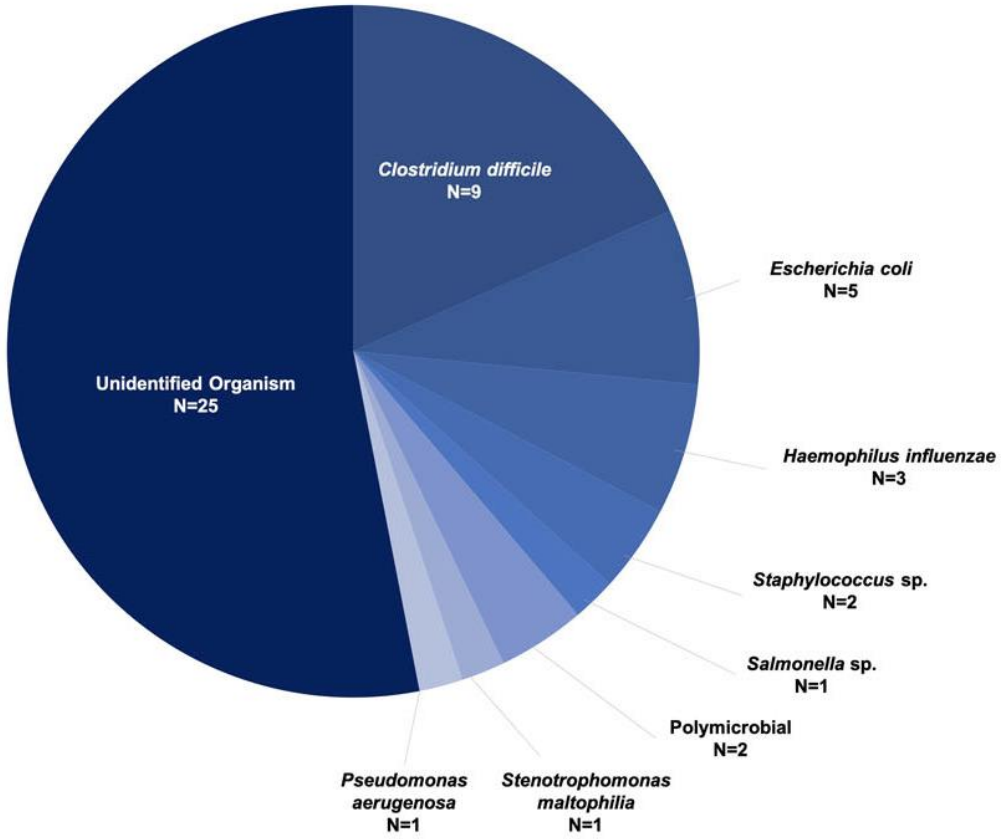
RVI: Respiratory viral infection

Czapka et al. Transpl Infect Dis. 2023
Rejeski et al. Am J Haematol 2023



Hill et al. Blood. 2020; 136: 925–935.

Pathogens distribution in the first year after CAR T-cell therapy



Wudhikarn Blood Cancer J 2020; 10:79.

Viral infections after CAR T-cell therapy: Mostly respiratory viruses

Summary of microbiologically confirmed infections (bacterial, viral, fungal).

	Non Hodgkin's Lymphoma N (%)	Acute Lymphoblastic Leukaemia N (%)	Multiple Myeloma N (%)	Chronic Lymphocytic Leukaemia N (%)
Viral Infection Events	266 N (% of events)	28 N (% of events)	25 N (% of events)	9 N (% of events)
CMV	39 (15)	0	0	0
HSV/VZV reactivation	73 (27)	2 (7)	0	0
Upper respiratory tract viral infections	113 (42)	20 (71)	25 (100)	1 (11)
Polyoma viruses	11 (4)	1 (4)	0	0
EBV	1 (0.4)	0	0	0
HHV-6	1 (0.4)	0	0	0
Viral NOS*	13 (5)	5 (18)	0	8 (89)

Reynolds et al. Crit Rev Oncol 2023

CMV reactivation after CAR T-cell therapy

Cytomegalovirus (CMV) Reactivation and CMV-Specific Cell-Mediated Immunity After Chimeric Antigen Receptor T-Cell Therapy

Eleftheria Kampouri,[1,©] Sarah S. Ibrahimi,[1] Hu Xie,[2] Elizabeth R. Wong,[1] Jessica B. Hecht,[1] Mandeep K. Sekhon,[1] Alythia Vo,[1] Terry L. Stevens-Ayers,[1] Damian J. Green,[3,4] Jordan Gauthier,[2,4] David G. Maloney,[2,4] Ailyn Perez,[5] Keith R. Jerome,[1,5] Wendy M. Leisenring,[2,6] Michael J. Boeckh,[1,2,4] and Joshua A. Hill[1,2,4]

Clinical Infectious Diseases

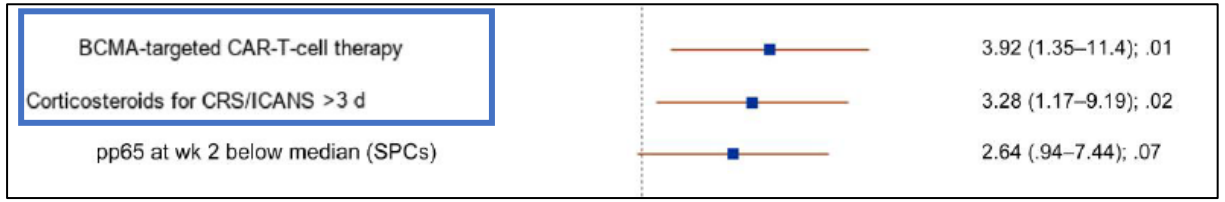
MAJOR ARTICLE

72 CMV positive CD19, CD20, BCMA recipents

CMV testing before and weekly up to 12 weeks post CAR T-cell therapy

Overall incidence of CMV reactivation:
27% (CI 16.8-38.2%)

RISK FACTORS



Kampouri et al. CID 2024; 78: 1022-1032.

- CMV replication was relatively frequent in patients with R/R aggressive B cell lymphoma receiving CAR T cell therapy, but viral load is usually low, self-limited, and not associated with end-organ damage.

- Median onset: 3 weeks after CAR T-cell therapy

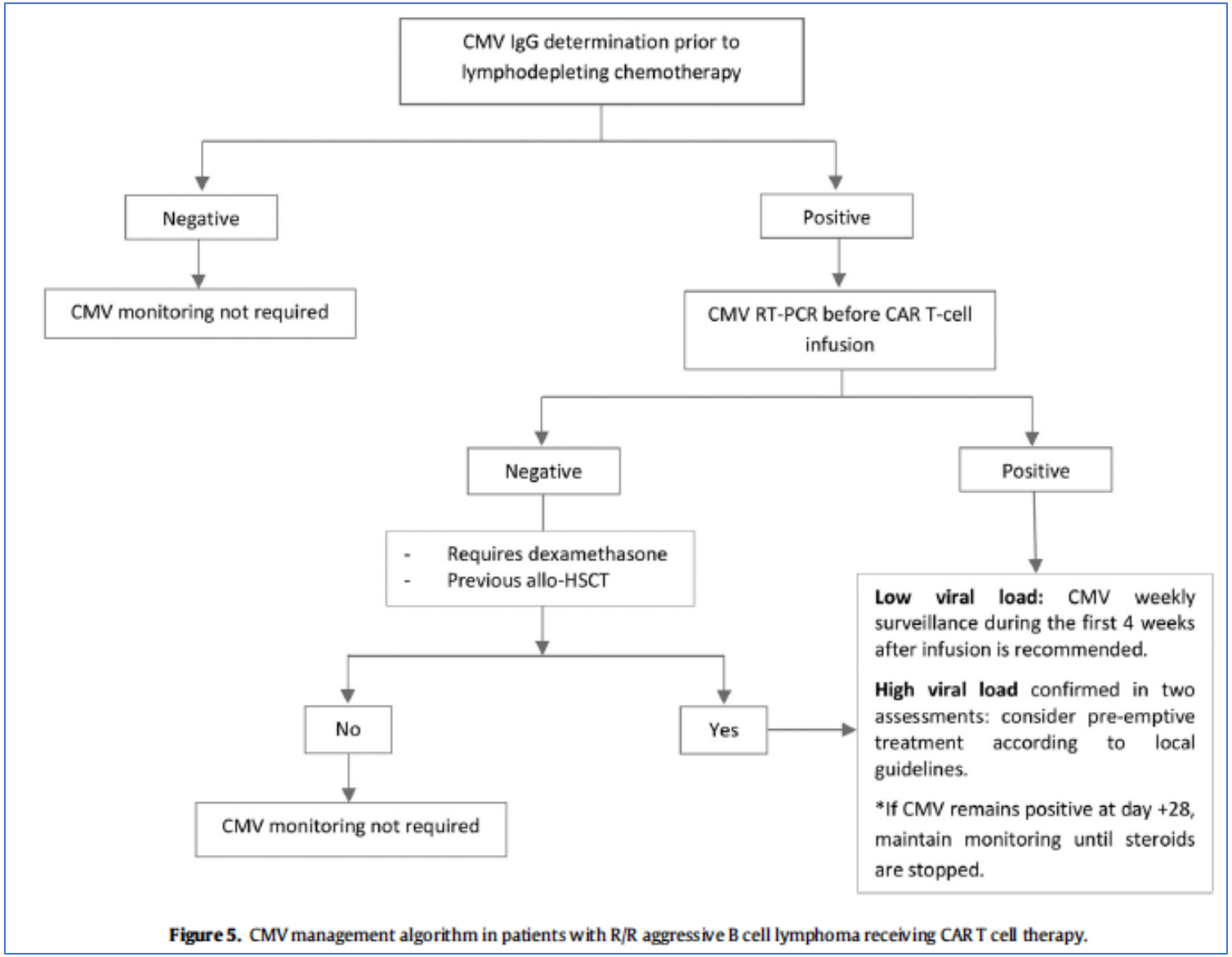
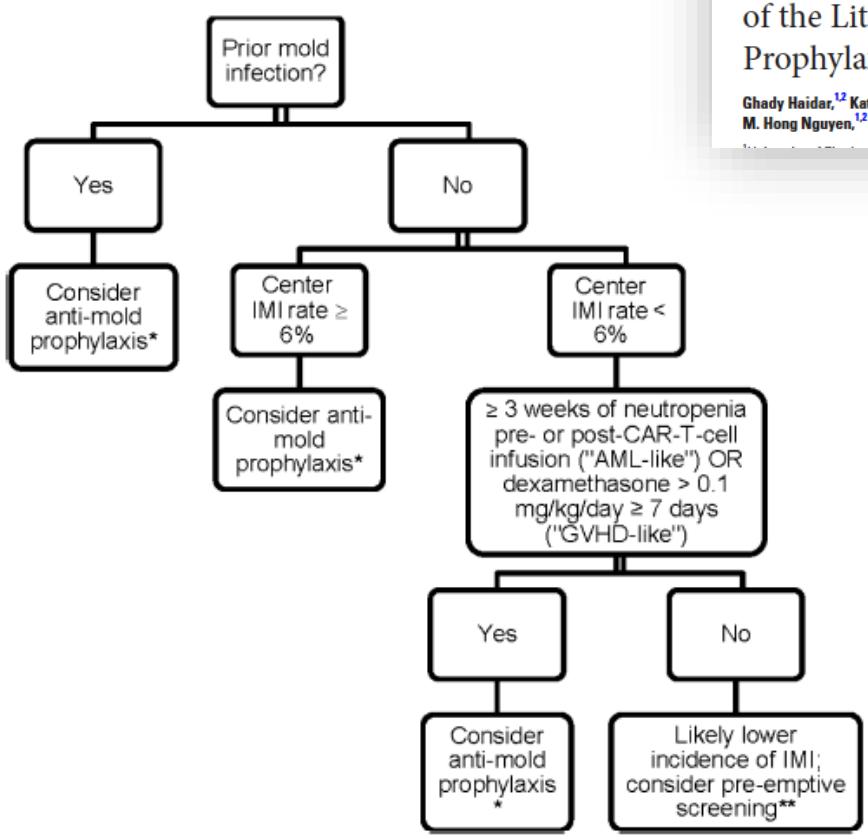


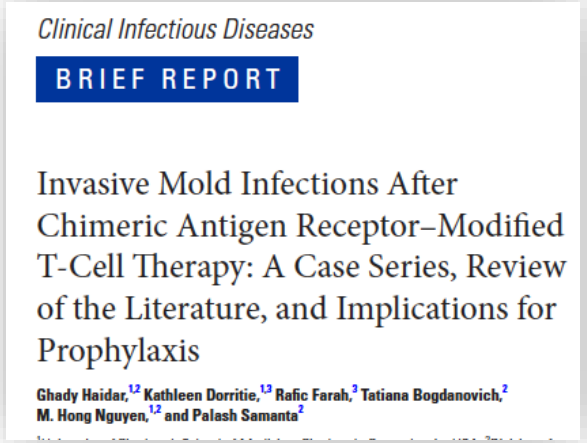
Figure 5. CMV management algorithm in patients with R/R aggressive B cell lymphoma receiving CAR T cell therapy.

Marquez-Algaba et al. Transplant Cell Ther 2022

Low incidence of fungal infections : 1-5%

- Mainly candidemia
  - Risk factors
    - Prolonged course of steroids
    - **Duration of neutropenia**
- Mold infections are rare
  - Aspergillus sp.
  - Pneumocystis jiroveci




Clinical Infectious Diseases

BRIEF REPORT

Invasive Mold Infections After Chimeric Antigen Receptor–Modified T-Cell Therapy: A Case Series, Review of the Literature, and Implications for Prophylaxis

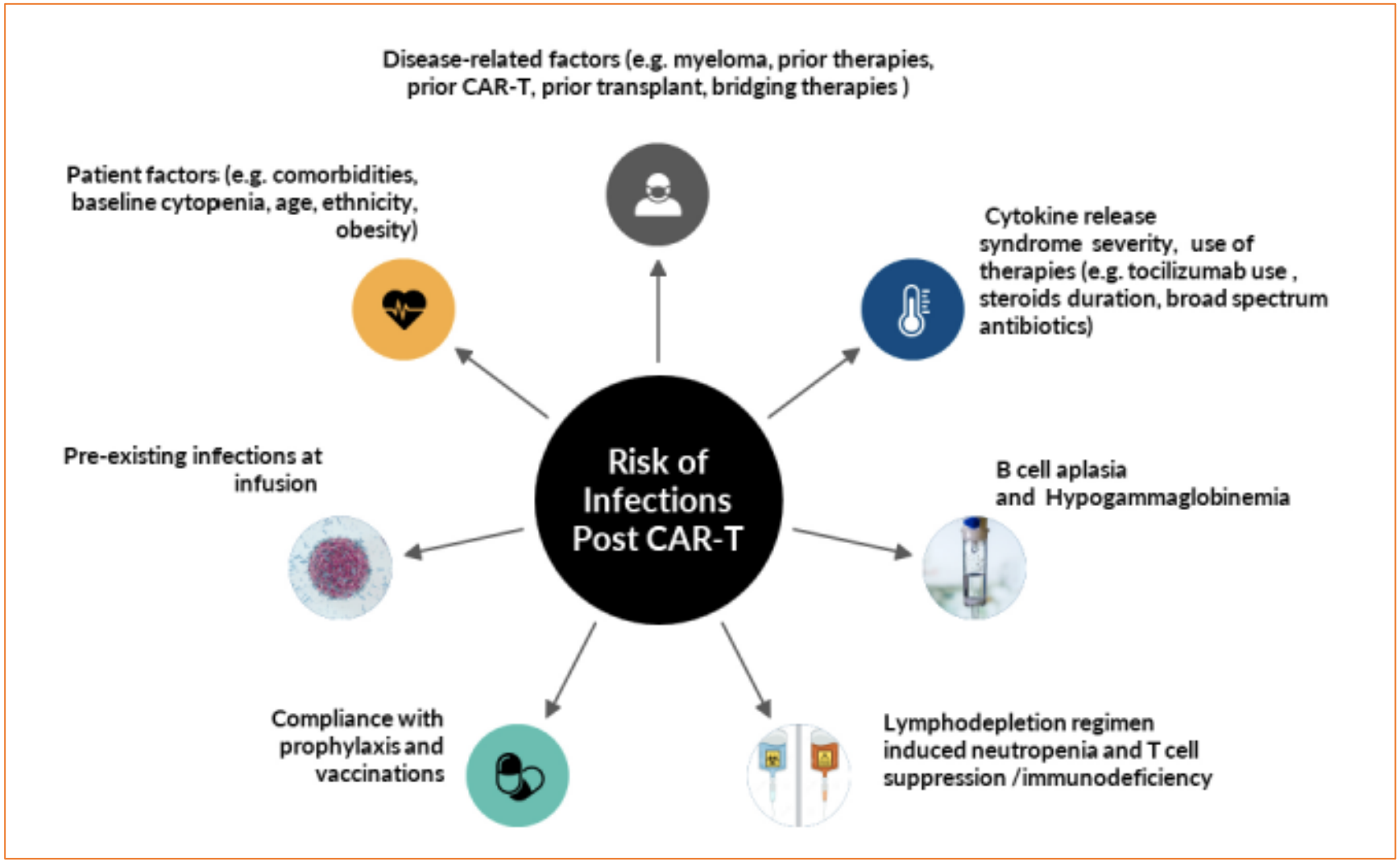
Ghady Haidar,[1,2] Kathleen Dorritie,[1,3] Rafic Farah,[3] Tatiana Bogdanovich,[2] M. Hong Nguyen,[1,2] and Palash Samanta[2]

Hill et al. Blood 2018
Wudhikarn et al. Blood Cancer J 2020
Haidar et al. CID 2020

Agenda

Infectious complications after CAR T-cell therapies

- Incidence
- Risk factors
- Diagnosis
- Preventive strategies



Ahmed et al. Clin Hematol International 2024

Clinical Microbiology and Infection 29 (2023) 1280–1288

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Systematic review

Predicting infections in patients with haematological malignancies treated with chimeric antigen receptor T-cell therapies: A systematic scoping review and narrative synthesis

Gemma Reynolds [1, 2, 3, 4, *], Beatrice Sim [1, 3], Mary Ann Anderson [5], Tim Spelman [3], Benjamin W. Teh [1, 2, 3], Monica A. Slavin [1, 2, 3], Karin A. Thursky [1, 2, 3]

Summary of key pre-treatment post-treatment variables significant associated with all-cause infection in CAR-T-treated patients

	Significant predictors in ≥3 studies	Significant predictors in ≥1 studies
Before CAR-T treatment	Number of lines of prior therapy	Disease bulk Bridging therapy CAR-T dose Prior infections Baseline neutropenia ALL (underlying disease) Adult (vs. paediatric patients) 30-d CAR-T non-response
After CAR-T treatment	Multivariate analyses: Steroid use Treatment-emergent neutropenia Univariate analyses: Cytokine release syndrome Neurotoxicity Tocilizumab (steroid use)	

ALL, acute lymphoblastic leukaemia; CAR-T, Chimeric antigen receptor T.

Reynolds CMI 2023; 29: 1280-8.

Infectious complications after CAR T-cell terapy: Risk factors

Host-related factors

- Underlying disease
  - Type
  - Status
- Previous therapies (cumulative immunosuppression)
- Previous chemotherapy and biological therapy
- Previous HSCT
  - Allogeneic
  - Autologous
- Baseline cytopenia
- Comorbidities
- History of previous infections
- Antimicrobial prophylaxis

Treatment-related factors

- Type of CAR T-cell therapy
  - Dose and administration schedule
  - Resulting cytopenias and other haematological side effects
- Conditioning regimen
- Resulting hypogammaglobulinaemia
- Severe adverse events requiring additional immunosuppression
  - Cytokine release syndrome
  - Neurotoxicity
  - Haemophagocytic lymphohistiocytosis and macrophage activation syndrome

➡ Cumulative immunosuppressive state

Gudiol et al. Lancet Haematol 2021; 8:e216-228.

CRS and ICANS as risk factors for infection

Post-CAR–T-cell infusion variables	Unadjusted HR* (95% CI)	P
CAR–T-cell dose level, cells per kg		
2×10^7 vs 2×10^5	3.19 (1.07-9.51)	.038
2×10^7 vs 2×10^6	3.15 (1.24-8.01)	.016
ANC < 500 cells per mm^3 on day of infection	2.04 (0.85-4.89)	.11
CRS grade		
0 vs 1-3 vs 4-5†	3.38 (1.99-5.73)	<.001
Neurotoxicity grade		
0 vs 1-2 vs 3-5‡	1.76 (1.11-2.78)	.015
Tocilizumab use§	3.45 (1.23-9.67)	.019
Corticosteroid use§	1.50 (0.43-5.23)	.5
ICU admission	4.35 (1.78-10.65)	.001

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

Joshua A. Hill[1-4] and Susan K. Seo[5,6]

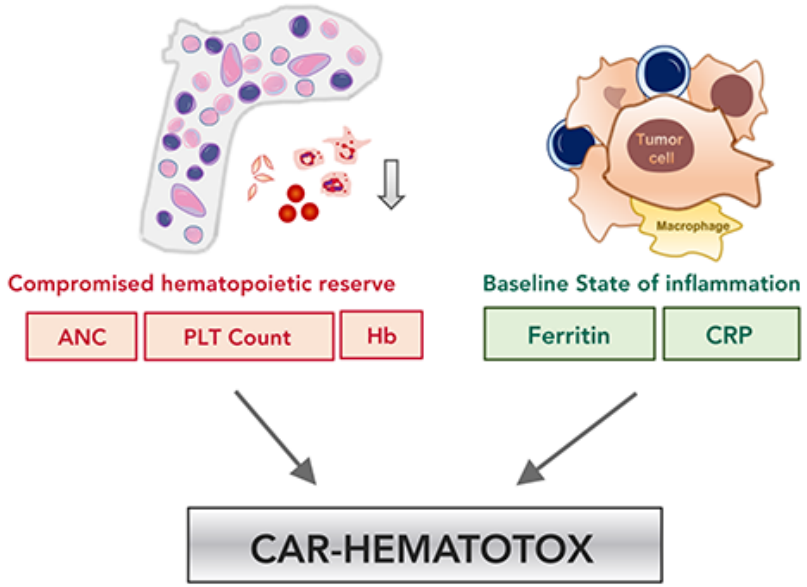
High-risk patients are those who meet any of the below criteria

- Receiving >1 dose of tocilizumab
- Requiring >3 days of ≥10 mg dexamethasone per day within a 7-day period
- Receiving 1 or more doses of methylprednisolone ≥1 g per day
- Receiving second-line agents for management of CRS or ICANS (eg, anakinra, siltuximab)

Hill et al. Blood 2018

Hill et al. Blood 2020

CAR-HEMATOTOX score



Low risk : 0 - 1 **High risk ≥ 2**

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			

Rejeski et al. Blood 2021
Rejeski et al. Blood 2023
Rejeski et al. J ImmunoTher Cancer 2022

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

Kai Rejeski,[1,*] Marion Subklewe,[1,*] Mahmoud Aljurf,[2] Emmanuel Bachy,[3] Adriana Balduzzi,[4] Pere Barba,[5,6] Benedetto Bruno,[7] Reuben Benjamin,[8] Matteo G. Carrabba,[9] Christian Chabannon,[10] Fabio Ciceri,[9] Paolo Corradini,[11] Julio Delgado,[12] Roberta Di Blasi,[13] Raffaella Greco,[9] Roch Houot,[14] Gloria Iacoboni,[5,6] Ulrich Jäger,[15] Marie José Kersten,[16] Stephan Mielke,[17] Amon Nagler,[18] Francesco Onida,[19] Zinaida Peric,[20] Claire Roddie,[21] Annalisa Ruggeri,[9] Fermín Sánchez-Guijo,[22] Isabel Sánchez-Ortega,[23] Dominik Schneidawind,[24] Maria-Luisa Schubert,[25] John A. Snowden,[26] Catherine Thieblemont,[13] Max Topp,[27] Pier Luigi Zinzani,[28] John G. Gribben,[29] Chiara Bonini,[30] Anna Sureda,[31] and Ibrahim Yakoub-Agha[32]

Prior to lymphodepleting chemotherapy (day-5)
Determine individual risk factors of hematox and infection

Low risk (HT 0-1)

	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%
Severe infection rate	8%	5%	5%
Severe bacterial infection rate	0.9%	5%	3%

High risk (HT 2-7)

	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%
Severe infection rate	40%	30%	40%
Severe bacterial infection rate	27%	28%	34%

Rejeski et al. Blood 2023; 10: 865-877.

Impact of cytopenias during CAR T-cell therapy

- Baseline cytopenias are common prior to CAR T-cell therapy
  - Neutropenia occurs in ~30-35% of patients
  - Severe lymphopenia in 80% of patients
  - Low CD4T after 1 year post CAR T-cell infusion
  - Baseline hypogammaglobulinemia in up to 40%

- Cytopenias post CAR T-cell can persist months or years
  - Grade ¾ in 30% of patients
  - Hypogammaglobulinemia in up to 70% of patients, can persist for years

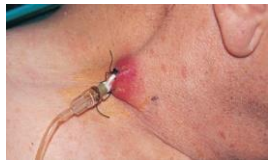
Park CID 2018, Hill Blood 2018, Logue Hematologica 2020.

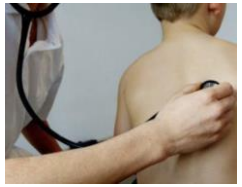
Agenda

Infectious complications after CAR T-cell therapies

- Incidence
- Risk factors
- Diagnosis
- Preventive strategies

CLINICAL ASSESSMENT
PATIENT HISTORY





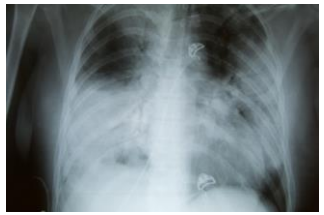
Identify source of infection

APPROPRIATE MICROBIOLOGICAL SAMPLES

Identify pathogens

IMAGING

X RAY US
CT SCAN



LIKELIHOOD OF INFECTION

RAPID MOLECULAR DIAGNOSTIC TEST

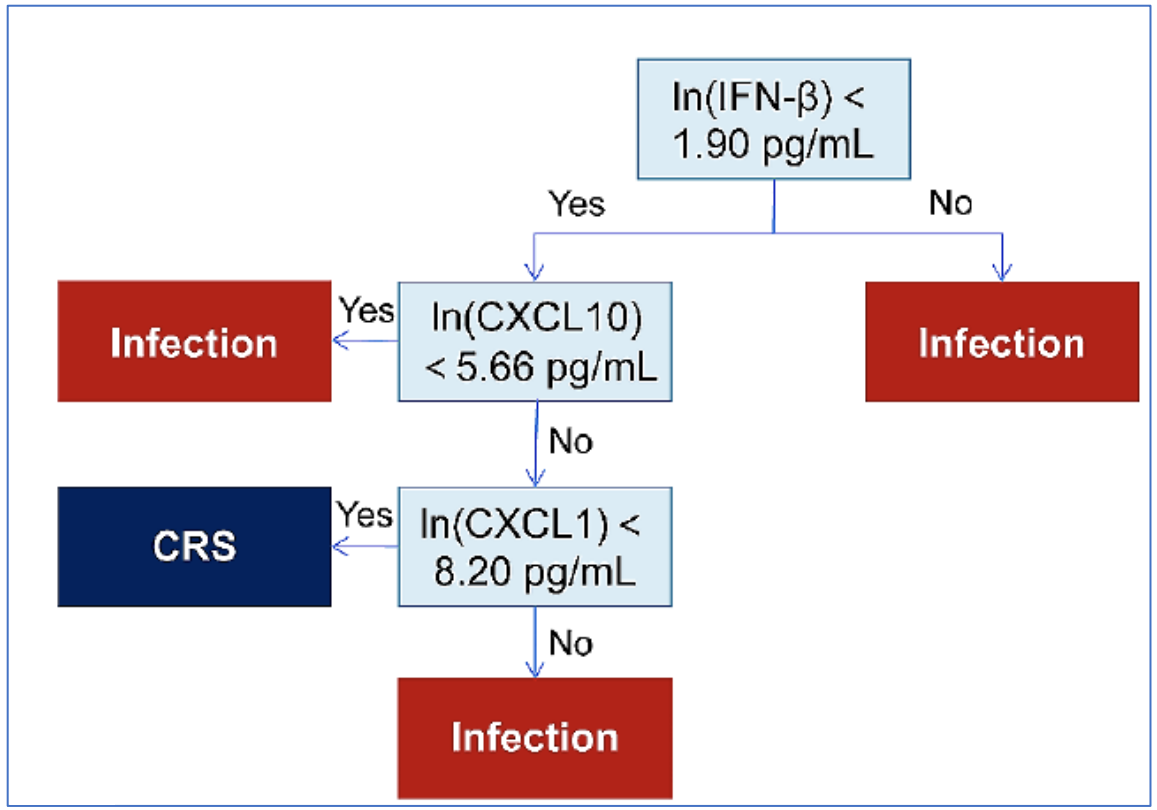
Reduce turnaround time

BIOMARKERS

PCT CRP Interleukins

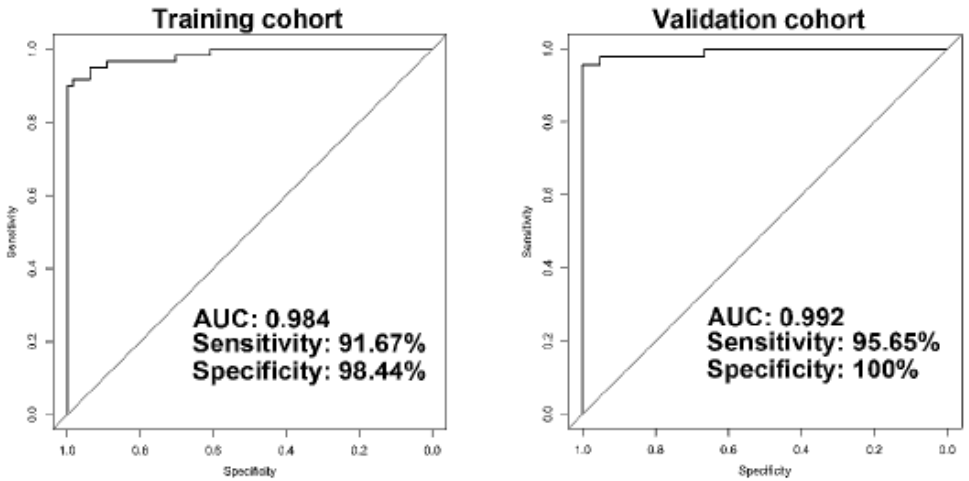
Can biomarkers help distinguishing infection from CRS?

84% r/r multiple myeloma
15% r/r leukemia



Cytokine-based models for efficient differentiation between infection and cytokine release syndrome in patients with hematological malignancies

Linqin Wang[1,2,3,4†], Yuqi Lv[1,2,3,4†], Linghui Zhou[1,2,3,4†], Shenghao Wu[1,5], Yuanyuan Zhu[1,2,3,4], Shan Fu[1,2,3,4], Shuyi Ding[1,2,3,4], Ruimin Hong[1,2,3,4], Mingming Zhang[1,2,3,4], Hanjing Yu[6], Alex H. Chang[7,8], Guoqing Wei[1,2,3,4], Yongxian Hu[1,2,3,4*] and He Huang[1,2,3,4*]

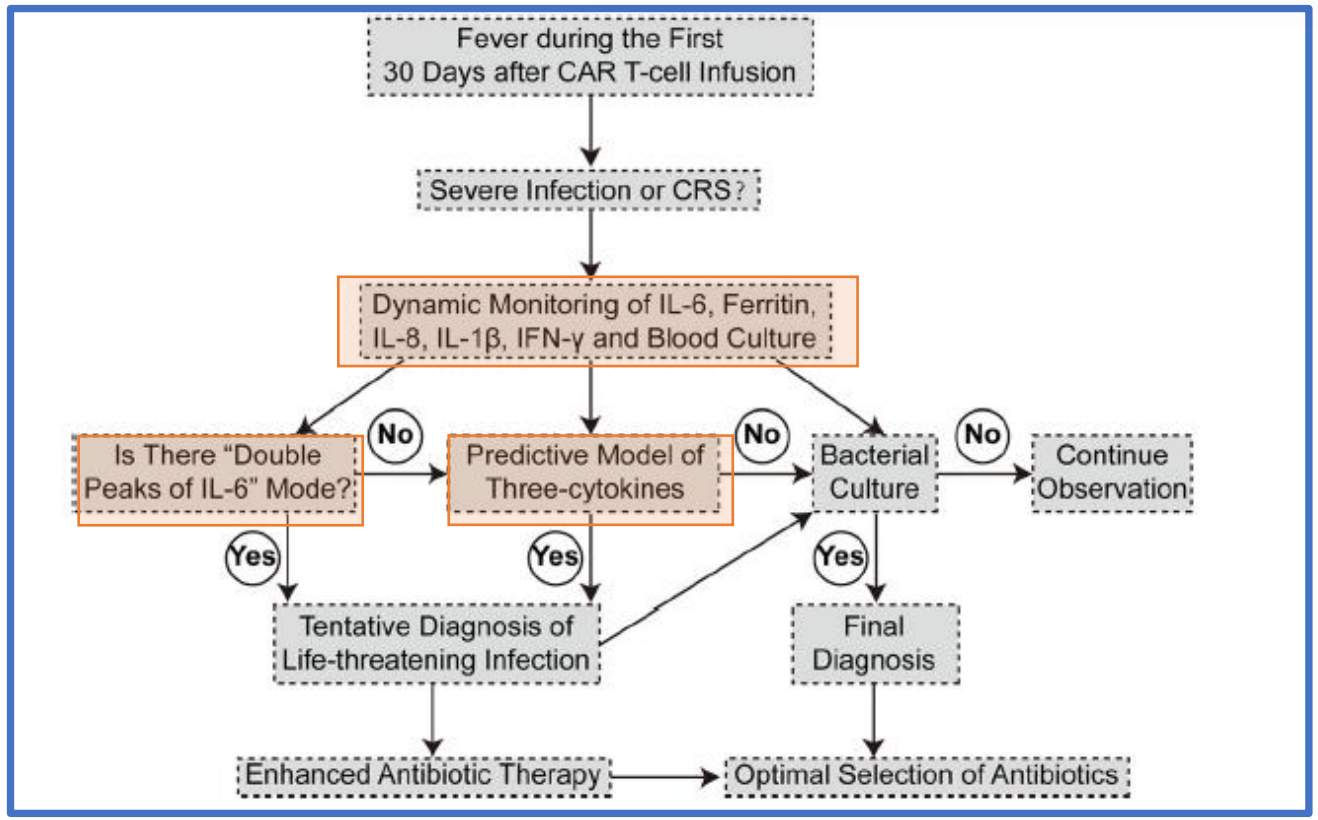


Wang et al. Exp Hematol Oncol 2024; 12:28.

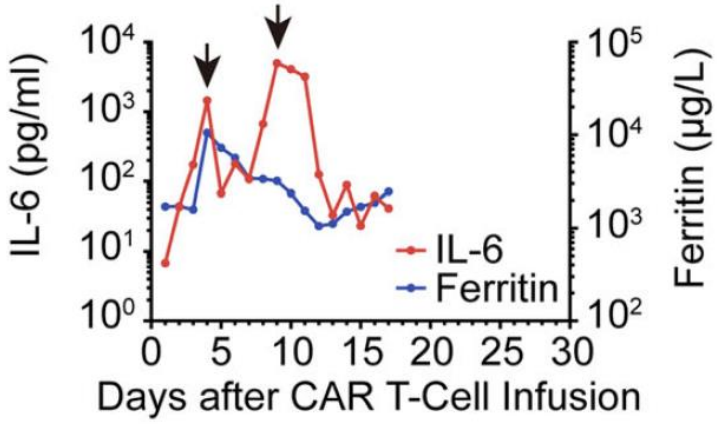
RESEARCH ARTICLE Open Access

Inflammatory signatures for quick diagnosis of life-threatening infection during the CAR T-cell therapy

Hui Luo[1,2], Na Wang[1,2], Liang Huang[1,2], Xiaoxi Zhou[1,2], Jin Jin[1,2], Chunrei Li[1,2], Di Wang[1,2], Bin Xu[1,2], Jinhuan Xu[1,2], Lijun Jiang[1,2], Jue Wang[1,2], Yang Cao[1,2], Yi Xiao[1,2], Qian Zhang[1,2], Xia Mao[1,2], Songya Liu[1,2], Liting Chen[1,2], Min Xiao[1,2] and Jianfeng Zhou[1,2*]



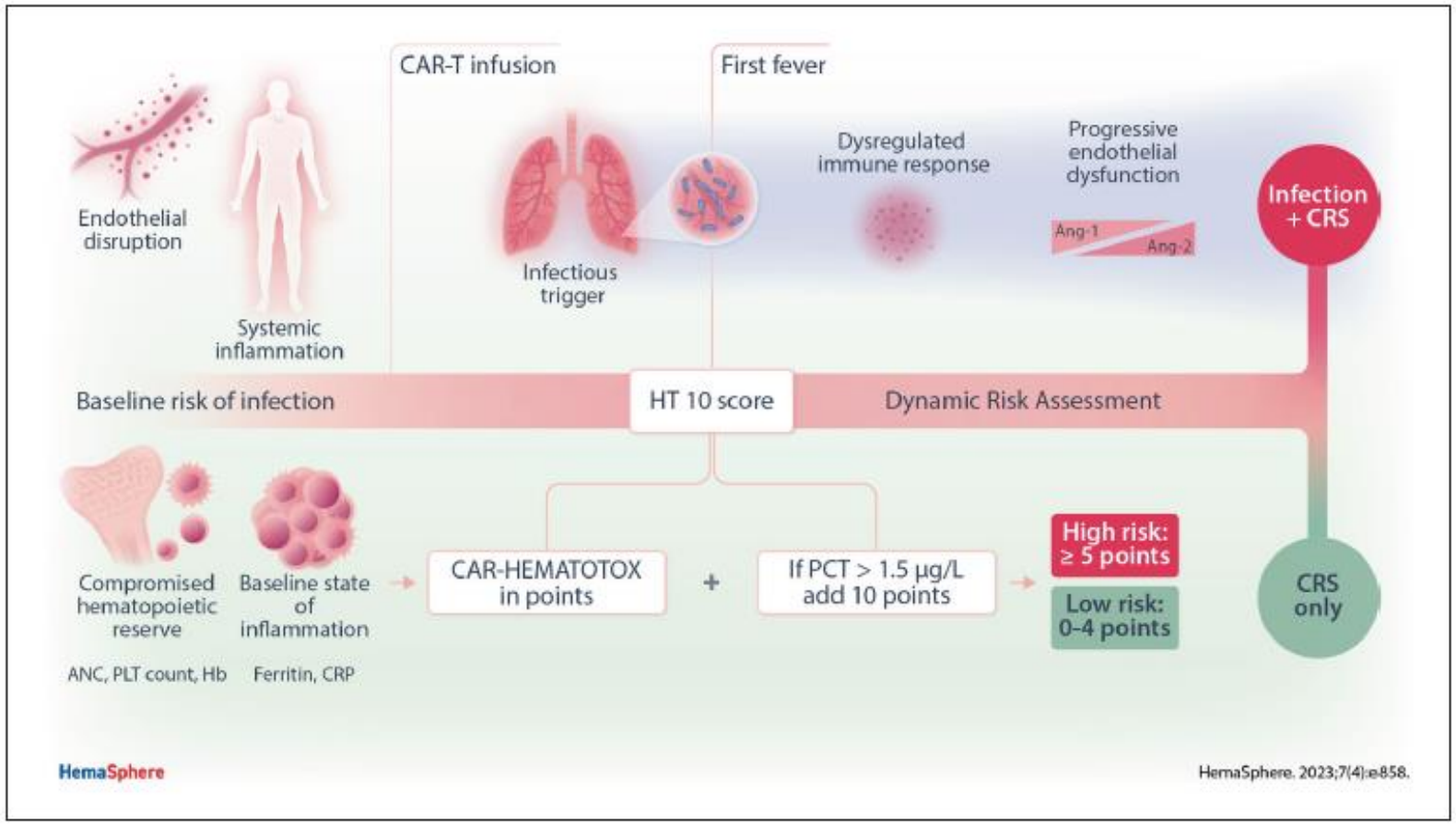
- **3-cytokines model**
  - IL-8
  - IFN-γ
  - IL-1β
- **Double Peak of IL-6**

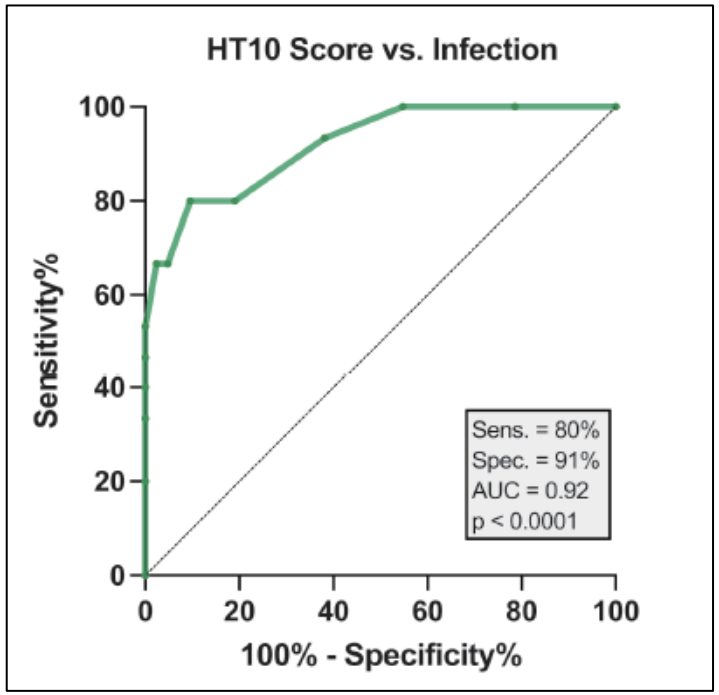


Luo et al. J ImmunoTher Cancer 2019; 7:271.

Identifying Early Infections in the Setting of CRS With Routine and Exploratory Serum Proteomics and the HT10 Score Following CD19 CAR-T for Relapsed/Refractory B-NHL

Kai Rejeski[1,2,3,4], Viktoria Blumenberg[1,2,3,4], Gloria Iacoboni[5,6], Lucia Lopez-Corral[7,8], Soraya Kharboutli[4,9], Rafael Hernani[10], Agnese Petrera[11], Niklas Müller[1], Friederike Hildebrand[1], Lisa Frölich[1,3], Philipp Karschnia[12], Christian Schmidt[1], David M. Cordas dos Santos[1,3], José Luis Piñana[10], Fabian Müller[4,9], Ana Africa Martin[7,8], Martin Dreyling[1], Michael von Bergwelt-Baildon[1,3,4], Pere Barba[5,6], Marion Subklewe[1,2,3,4], Veit L. Bücklein[1,2,3,4]





Rejeski et al. HemaSphere 2023: 7:e858.

Agenda

Infectious complications after CAR T-cell therapies

- Incidence
- Risk factors
- Diagnosis
- Preventive strategies

SPECIAL ARTICLE

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)

P. J. Hayden[1†], C. Roddie[2,3*†], P. Bader[4], G. W. Basak[5], H. Bonig[6], C. Bonini[7], C. Chabannon[8], F. Ciceri[9], S. Corbacioglu[10], R. Ellard[11], F. Sanchez-Guijo[12], U. Jäger[13], M. Hildebrandt[14], M. Hudecek[15], M. J. Kersten[16], U. Köhl[17,18], J. Kuball[19], S. Mielke[20], M. Mohty[21], J. Murray[22], A. Nagler[23], J. Rees[3,24], C. Rioufol[25], R. Saccardi[26], J. A. Snowden[27], J. Styczynski[28], M. Subklewe[29], C. Thieblemont[30], M. Topp[15], Á. U. Ispizua[31], D. Chen[3,32], R. Vrhovac[33], J. G. Gribben[32], N. Kröger[34], H. Einsele[15] & I. Yakoub-Agha[35]

Table 12. Infection prophylaxis post-CAR-T

	EBMT/EHA recommendation	Comments
Neutropenia	G-CSF to shorten duration of neutropenia from day +14 or after resolution of CRS or ICANS Can consider starting earlier, e.g. day 5,[a] if patient is at high risk of infection, e.g. ALL, post-allo-HCT, high-dose steroids. For persistent neutropenia ($<0.5 \times 10^9$/l) following day +28, consider G-CSF	Avoid if patient has CRS or ICANS
Antibacterial prophylaxis	Not routinely recommended[b]	Can be considered in case of prolonged neutropenia and should be based on local guidelines, e.g. with levofloxacin or ciprofloxacin
Anti-viral	Valaciclovir 500 mg bid or aciclovir 800 mg bid	Start from LD conditioning until 1-year post-CAR T-cell infusion AND until $CD4^+$ count $>0.2 \times 10^9$/l
Anti-pneumocystis	Co-trimoxazole 480 mg once daily or 960 mg three times each week To start from LD conditioning until 1-year post-CAR-T cell infusion AND until $CD4^+$count $>0.2 \times 10^9$/l Where there is prolonged myelosuppression, postpone start after ANC $>0.5 \times 10^9$/l	Can be started later depending on centre guidelines In case of co-trimoxazole allergy (or cytopenias precluding use of co-trimoxazole), pentamidine inhalation (300 mg once every month), dapsone 100 mg daily or atovaquone 1500 mg once daily can be considered
Systemic anti-fungal prophylaxis	Not recommended routinely; consider posaconazole (300 mg/day) or fluconazole (200 mg/day) or micafungin (50 mg i.v./day) in patients with severe (ANC $<0.5 \times 10^9$/l) or prolonged (>14 days) neutropenia and/or in patients on long-term or high-dose (>72 h) corticosteroids or in patients post-allo-HCT	In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids, posaconazole prophylaxis should be considered
i.v. Immunoglobulin	Routine in children. Consider in adults with serious/ recurrent infections with encapsulated organisms and hypogammaglobulinemia (<4 g/l)	Clinical evidence does not support routine use in adults following allo-HCT

ANNALS OF ONCOLOGY
driving innovation in oncology

Hayden et al. Annals Oncol 2022

SPECIAL ARTICLE

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)

P. J. Hayden[1†], C. Roddie[2,3*†], P. Bader[4], G. W. Basak[5], H. Bonig[6], C. Bonini[7], C. Chabannon[8], F. Ciceri[9], S. Corbacioglu[10], R. Ellard[11], F. Sanchez-Guijo[12], U. Jäger[13], M. Hildebrandt[14], M. Hudecek[15], M. J. Kersten[16], U. Köhl[17,18], J. Kuball[19], S. Mielke[20], M. Mohty[21], J. Murray[22], A. Nagler[23], J. Rees[3,24], C. Rioufol[25], R. Saccardi[26], J. A. Snowden[27], J. Styczynski[28], M. Subklewe[29], C. Thieblemont[30], M. Topp[15], Á. U. Ispizua[31], D. Chen[3,32], R. Vrhovac[33], J. G. Gribben[32], N. Kröger[34], H. Einsele[15] & I. Yakoub-Agha[35]

ANNALS OF ONCOLOGY
driving innovation in oncology

Table 13. Eligibility criteria for vaccination in patients receiving CD19-targeted CAR T-cell therapy

Agent	EBMT/EHA recommendations		Comments
	Pre-CAR-T	Post-CAR-T	
Influenza vaccine	Preferably vaccinate 2 weeks before LD In B-cell aplasia low likelihood of serological response	>3 months after CAR-T patients should be vaccinated irrespective of immunological reconstitution	Where there is incomplete immune reconstitution[a] or ongoing immunosuppression, there is a high likelihood of lower vaccine responses. Consensus view is that vaccination may still be beneficial to reduce rates of infection and improve clinical course. Consider boost upon B-cell recovery
SARS-CoV-19	Preferably vaccinate before CAR-T therapy In B-cell aplasia low likelihood of serological response	>3 months after CAR T-cell infusion	Limited data is available on vaccine response after CAR-T, and early reports suggest impaired serological responses.[84] However, SARS-CoV-19 vaccine-induced protection relies heavily on T-cell-mediated immunity, therefore B-cell aplasia does not seem to be a contraindication; no T-cell threshold has been defined. Post-vaccination response monitoring is desirable. Guidance on re-vaccination post-CAR-T and frequency/dosing of booster vaccines will vary between countries. National guidelines should be followed in this area of rapidly evolving clinical practice
Killed/inactivated vaccines		>6 months after CAR-T and >2 months after immunoglobulin replacement	Contraindications include concurrent immunosuppressive or cytotoxic therapy
Live and non-live adjuvant vaccines		1 year after CAR-T and fully immune reconstituted[a]	Contraindications include <2 years post-allo-HCT, <8 months after completion of immunoglobulin replacement

Hayden et al. Annals Oncol 2022

Vaccine schedule recommendations and updates for patients with hematologic malignancy post-hematopoietic cell transplant or CAR T-cell therapy

Gemma Reynolds[1,2,3] | Victoria G. Hall[1,2] | Benjamin W. Teh[1,2]

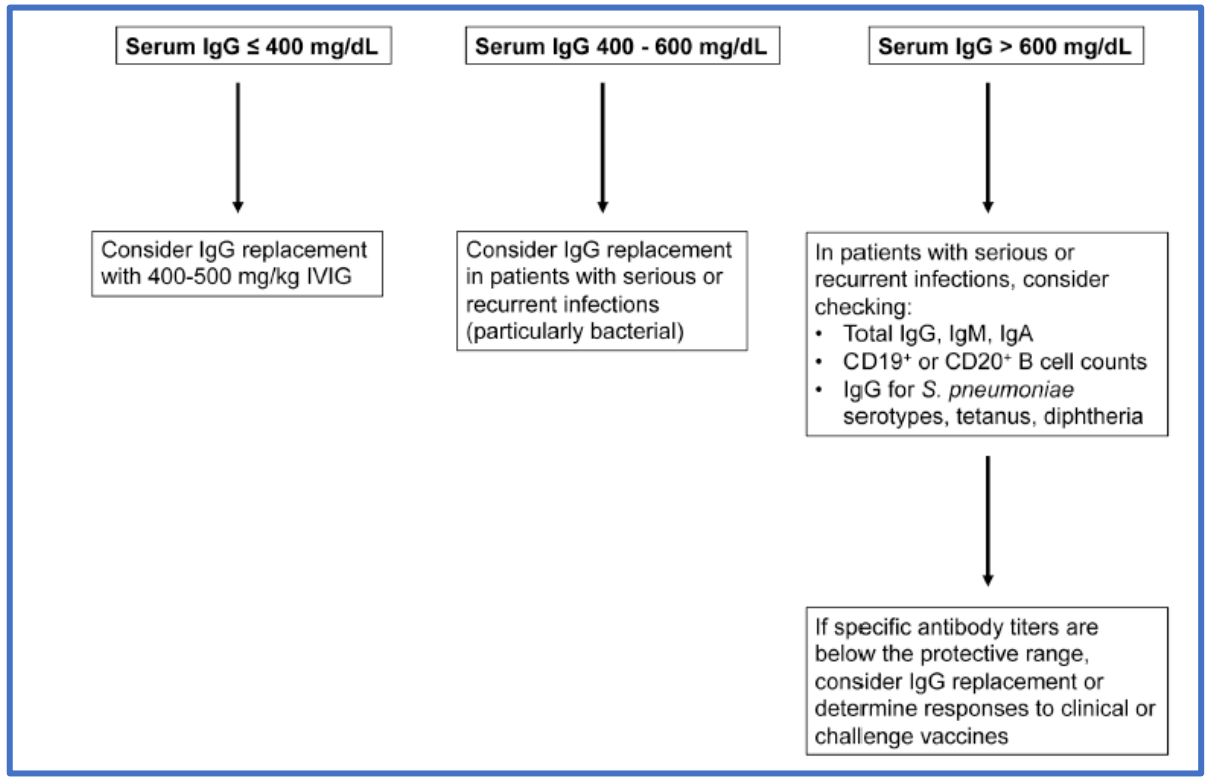
TABLE 4 Vaccination schedule[a] for adult patients treated with chimeric antigen receptor T-cell (CAR-T) therapy.[99]

Vaccines	Pre-CAR-T	≥6 months	≥8 months	≥10 months	≥12 months	≥18 months
IIV	Influenza	Influenza				
PCV		PCV13	PCV13	PCV13		
PPSV23						PPSV23
DTaP		DTaP	Td	Td		
HAV		HAV			HAV	
HBV		HBV	HBV		HBV	
Varicella zoster[b]					aRZV	aRZV

Reynolds et al. Transpl Infect Dis 2023; 25:e14109.

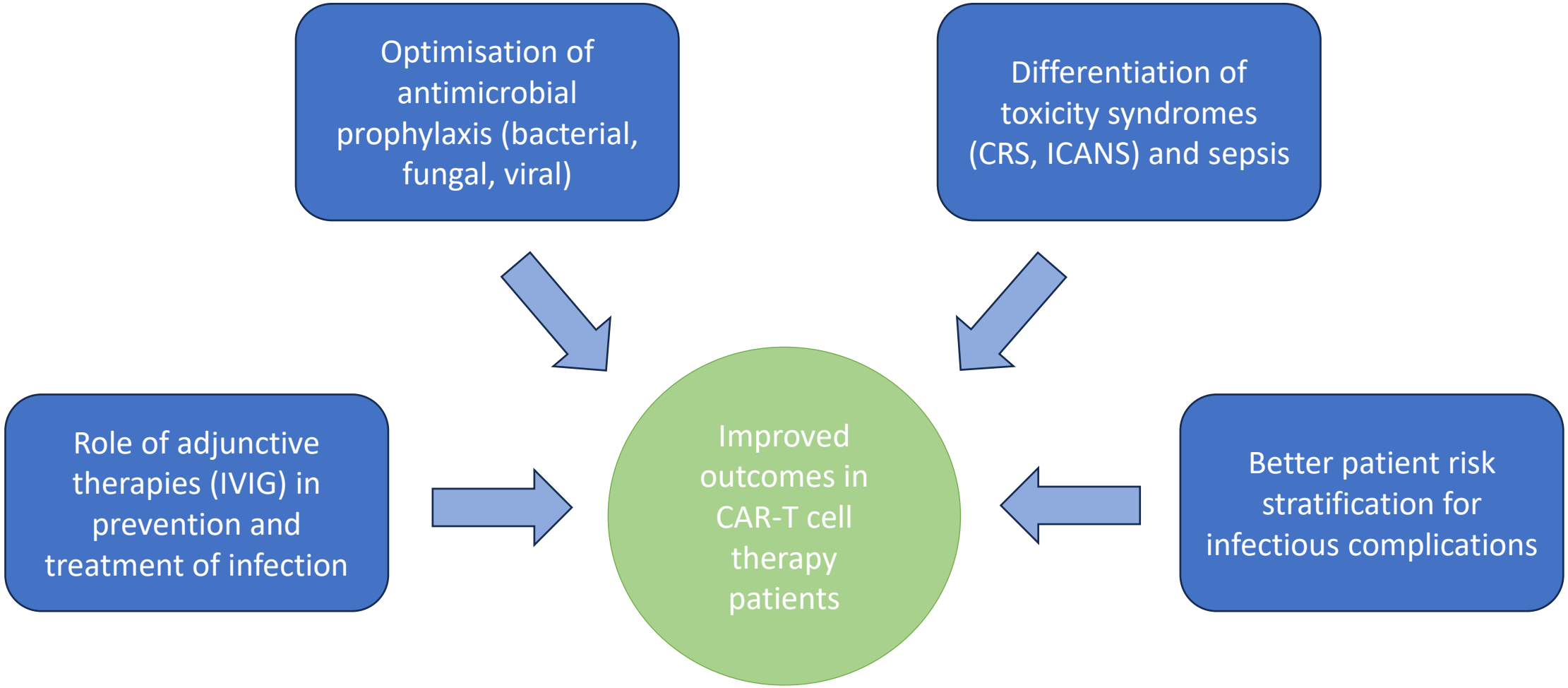
CAR-T– and a side order of IgG, to go? – Immunoglobulin Replacement in Patients Receiving CAR-T Cell Therapy

Joshua A. Hill[1,2], Sergio Giralt[3], Troy R. Torgerson[4,5], Hillard M. Lazarus[6]



Hill et al. Blood Rev 2019; 38:100596.

Research priorities



Take home messages

- Infections are common after CAR T-cell therapy:
  - Bacterial infections predominate in the early phase
  - Viral infections, mainly respiratory, occur late fater CAR T-cell infusion
  - The incidence of fungal infections remains low
- Infectious risk factors are multifactorial: CAR T-cell complications related treatment, prior lines of therapy, underlying disease
- Cytopenias and hypogammaglobulinemia are frequent and can last for months or years
- The CAR-HEMATOTOX score may help identifying patients at high risk of infections
- Preventive strategies are crucial but further studies are warranted to optimize antimicrobial prophylaxis and vaccination.