Uniklinikum Würzburg

Infektionsprävention bei BiSpec-Therapie

PD Dr. med. habil. Daniel Teschner, Universitätsklinikum Würzburg

Zentrum für allogene Stammzelltherapien
Medizinische Klinik und Poliklinik II

Potentielle Interessenskonflikte

Uniklinikum Würzburg

Anstellungsverhältnis oder Führungsposition
- Universitätsklinikum Würzburg

Beratungs- bzw. Gutachtertätigkeit
- Abbvie, ACI Clinical, Astra Zeneca, BioNTech, DGHO, Gilead, iQone, MSD, Noscendo, Octapharma, Pfizer, Takeda, Tillotts, GBA, DGHO, ESCMID

Besitz von Geschäftsanteilen, Aktien oder Fonds
- keine

Patent, Urheberrecht, Verkaufslizenz
- keine

Honorare
- Abbvie, ACI Clinical, AstraZeneca, BioNTech, F2G, Gilead, iQone, Jazz, MSD, Noscendo, New Concepts Oncology, Octapharma, Pfizer, Sanofi, Takeda, Tillotts, LAEK Hessen, AAEF Rheinland-Pfalz, Akad. für Infektionsmedizin, GBA

Finanzierung wissenschaftlicher Untersuchungen
- Stiftung Deutsche Krebshilfe, Gilead, JOGU Mainz, Wilhelm Sander-Stiftung, Stiftung Forschung-hilft

Andere finanzielle Beziehungen
- AbbVie, Astellas, Celgene, Gilead, Jazz, Medac, MSD, Tillotts (alle Kongress-/Reisekostenunterstützung)

Immaterielle Interessenkonflikte
- keine

Agenda

Uniklinikum Würzburg

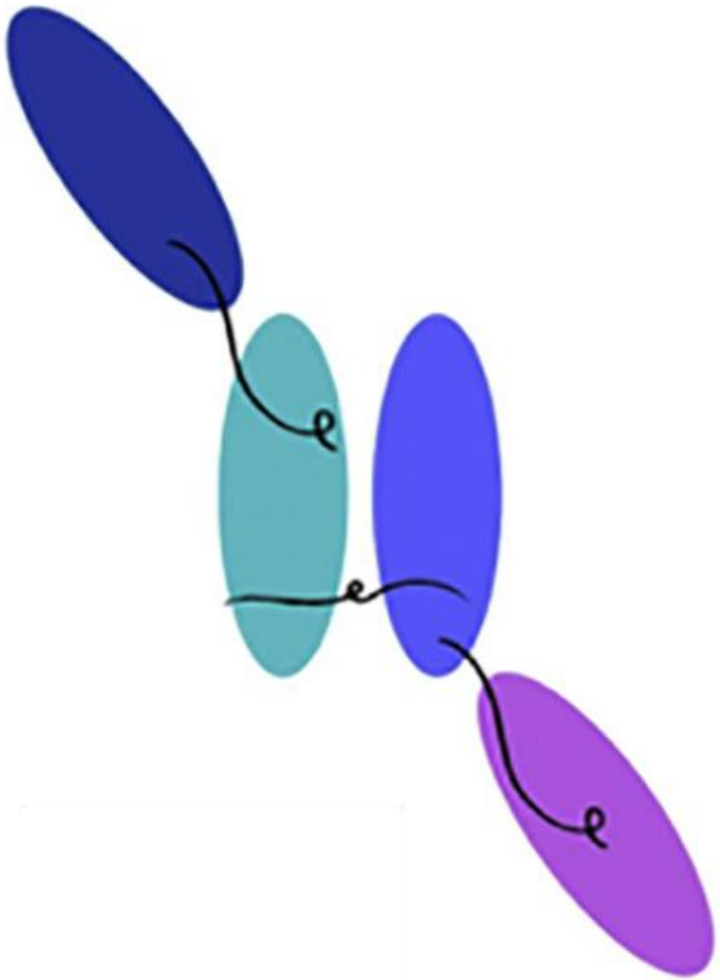
Infektionsprävention nach Therapie mit bispezifischen Antikörpern (BiSpecs)

- Grundlagen / „Mechanismen“
- Infektionen nach/unter Therapie mit BiSpecs
- Infektionsmonitoring nach/unter Therapie mit BiSpecs
- Infektionsprävention nach/unter Therapie mit BiSpecs
- Zusammenfassung

Stellungnahme der Arbeitsgemeinschaft für Infektionen in der Hämatologie und Onkologie (AGIHO)

Infektionen unter/nach Therapie mit bispezifischen Antikörpern (BiSpecs)

A. Ruckdeschel, J. v. Herder, N. Giesen, M. Sandherr, C. Rieger, D. Teschner

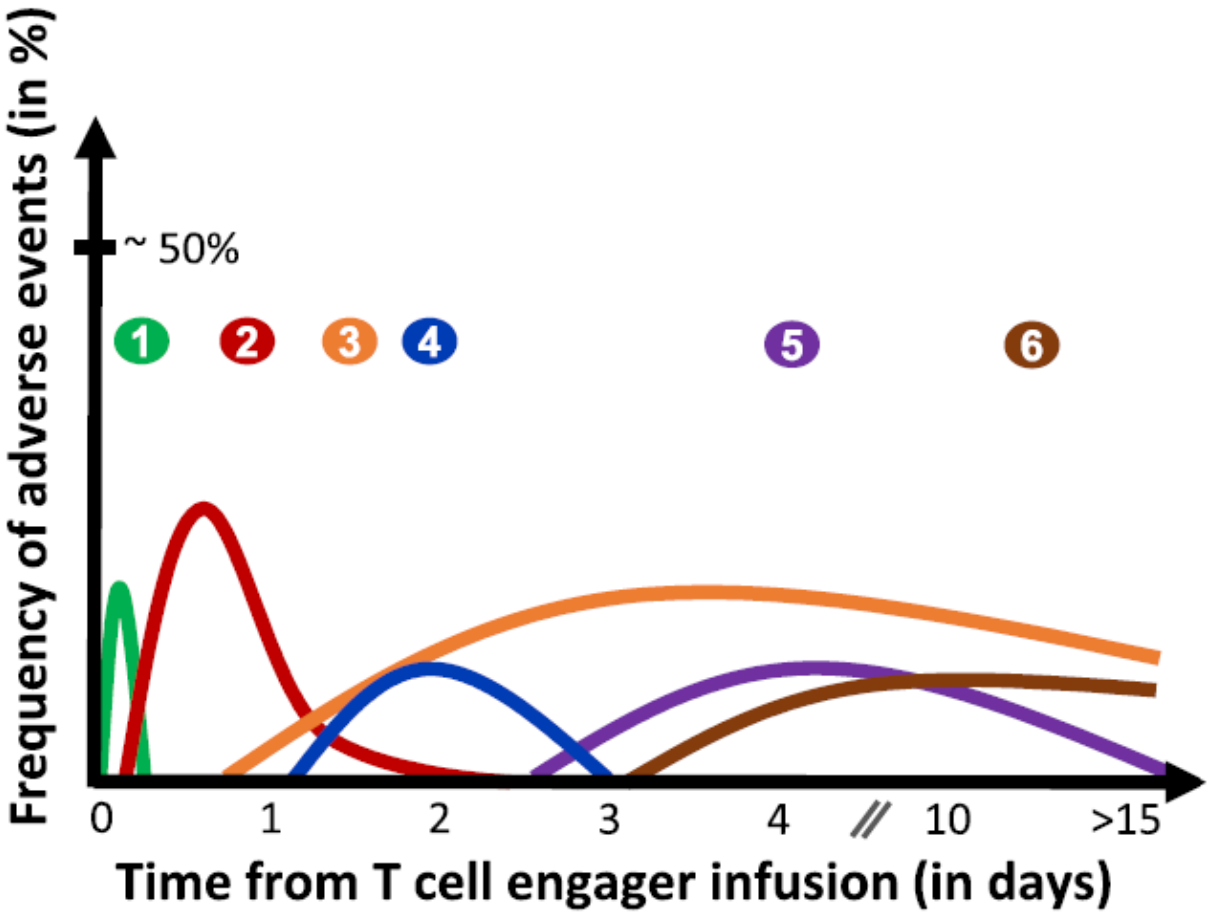


Entität	Präparat (Wirkstoff)
MM	Teclistamab
	Elranatamab
	Talquetamab
NHL	Mosunetuzumab
	Glofitamab
	Epcoritamab
ALL	Blinatumomab

Longhitano *et al*., Blood Rev 2021

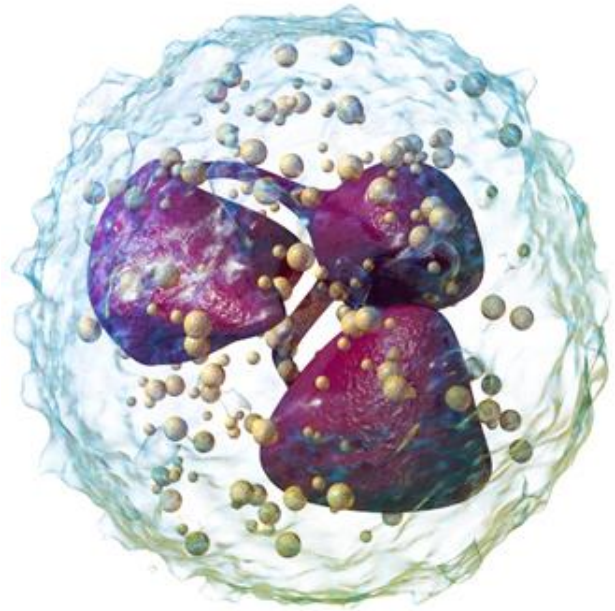
Infektionen unter Therapie mit BiSpecs

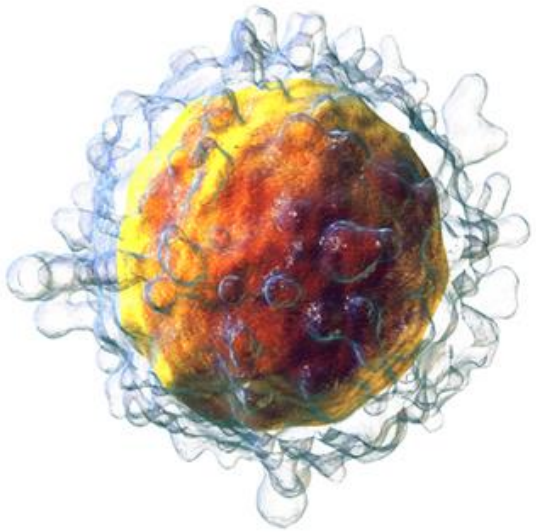
1. IRR
2. CRS
3. Infections
4. Tumor flare reaction
5. ICANS
6. Cytopenia

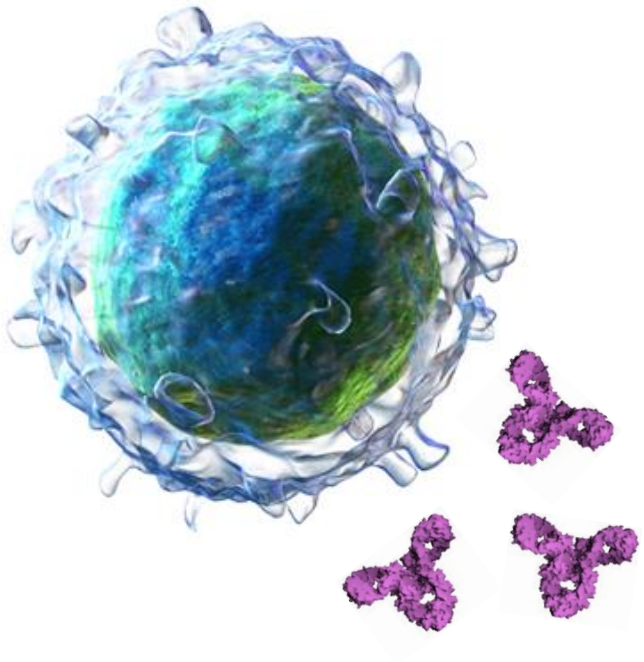


Géraud *et al.*, Eur J Cancer 2024

Zelluläre (und humorale) **Immunität…**







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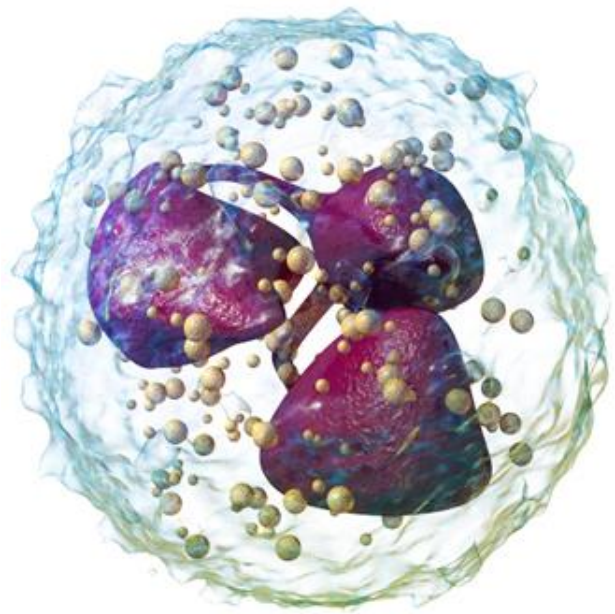
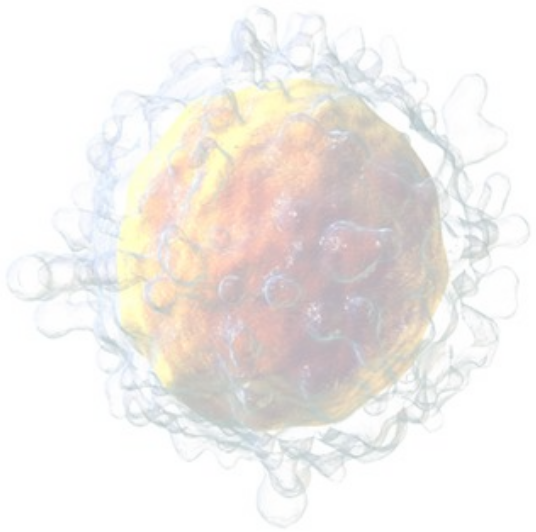
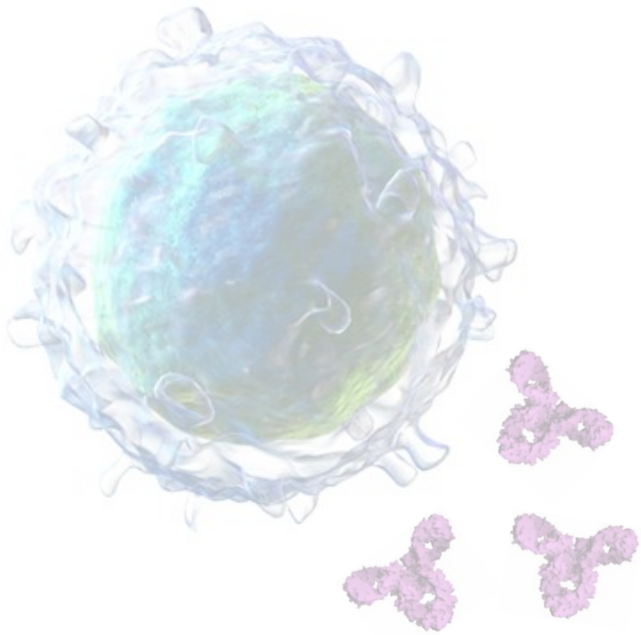
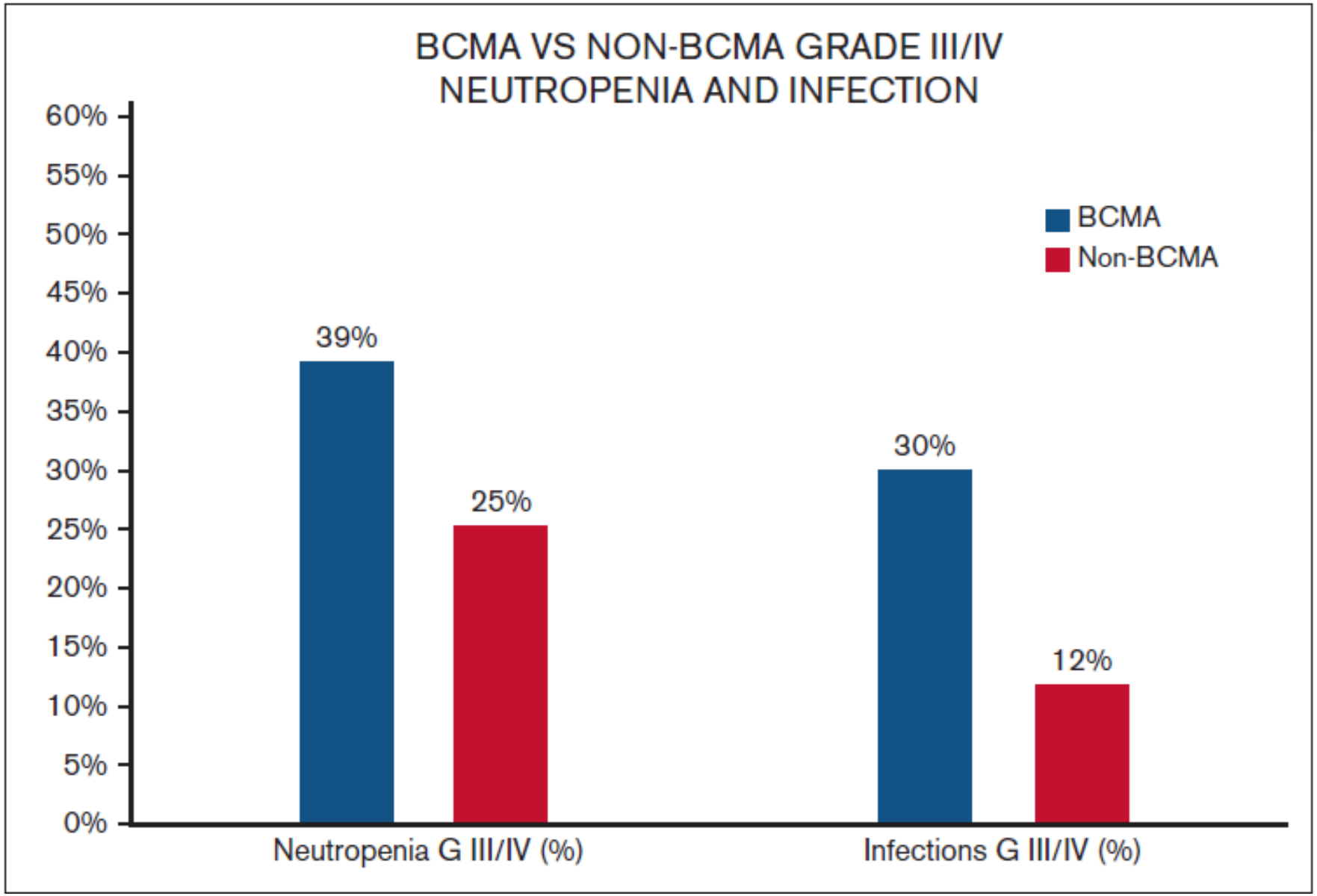


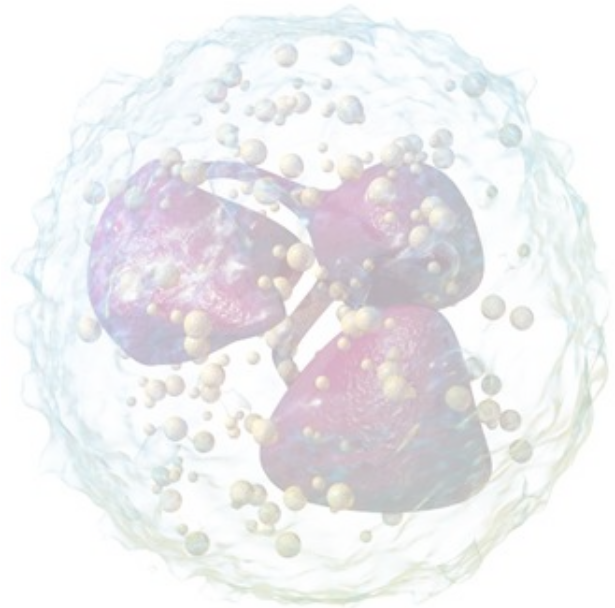


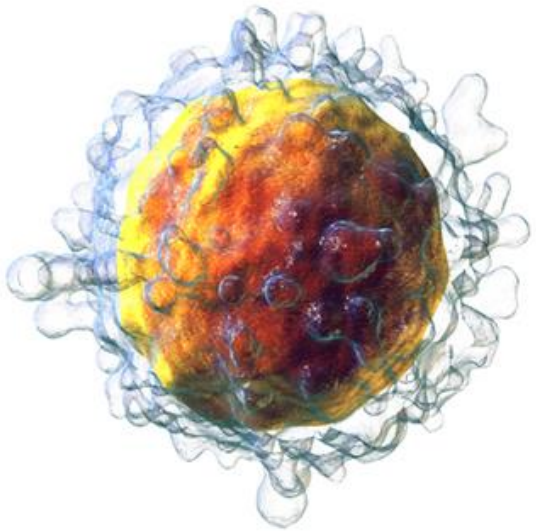


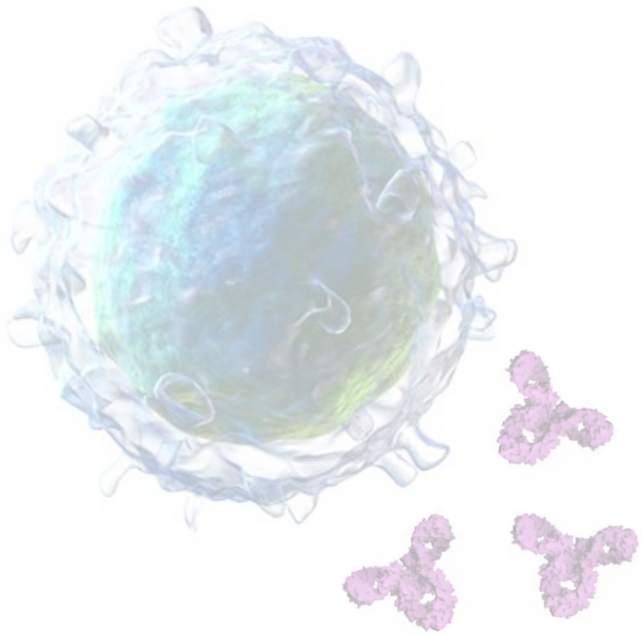


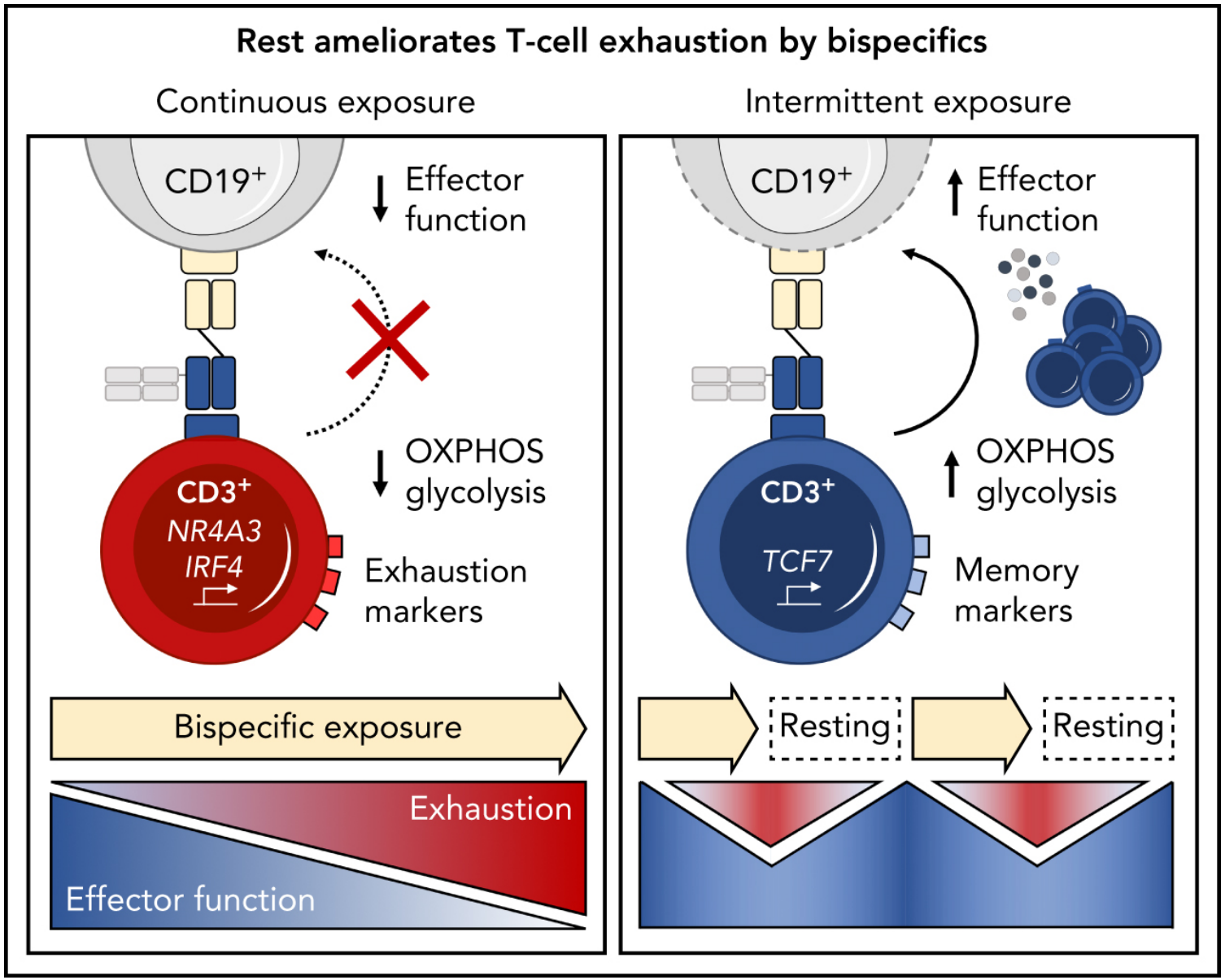
Mazahreh *et al.*, Blood Adv 2022 *(modified)*

Zelluläre (und humorale) **Immunität…**



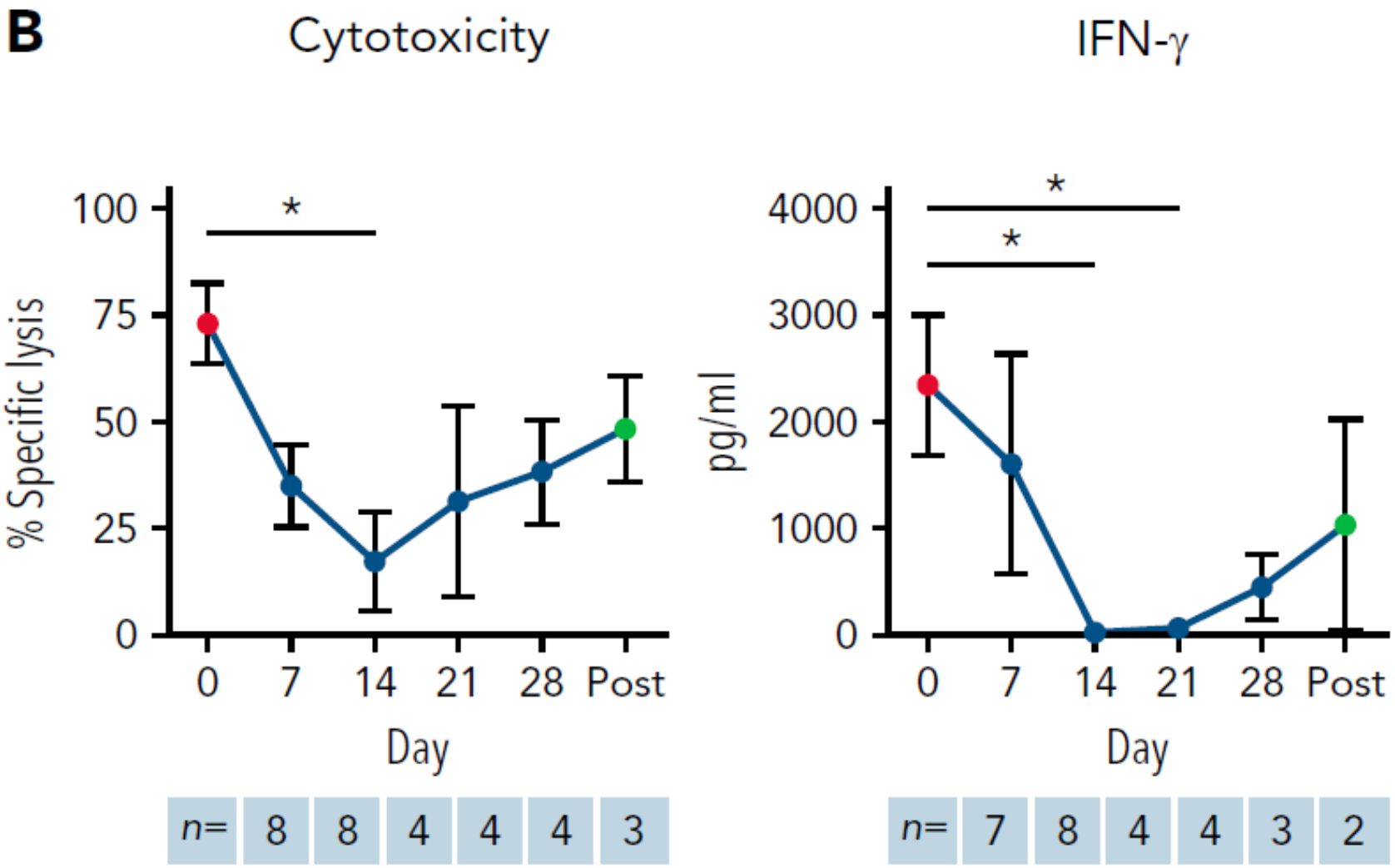






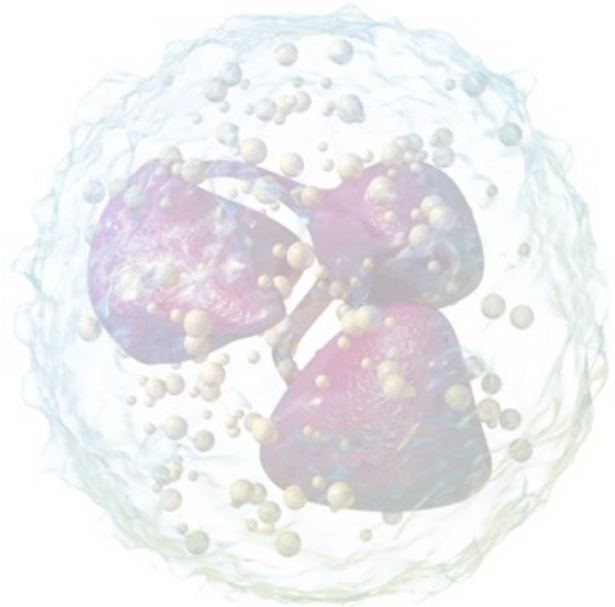
Philipp *et al.*, Blood 2022

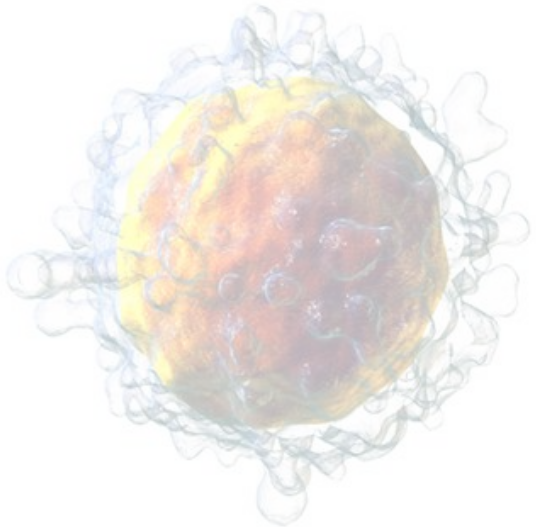
T-Zell-Funktionalität unter Blinatumomab

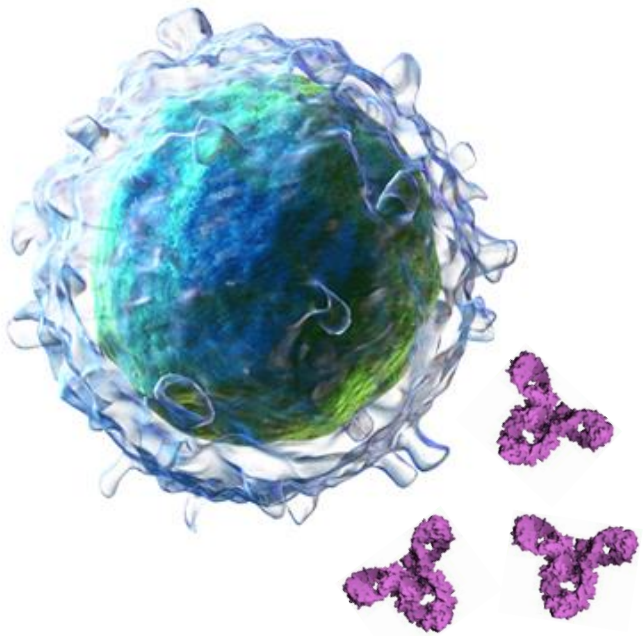


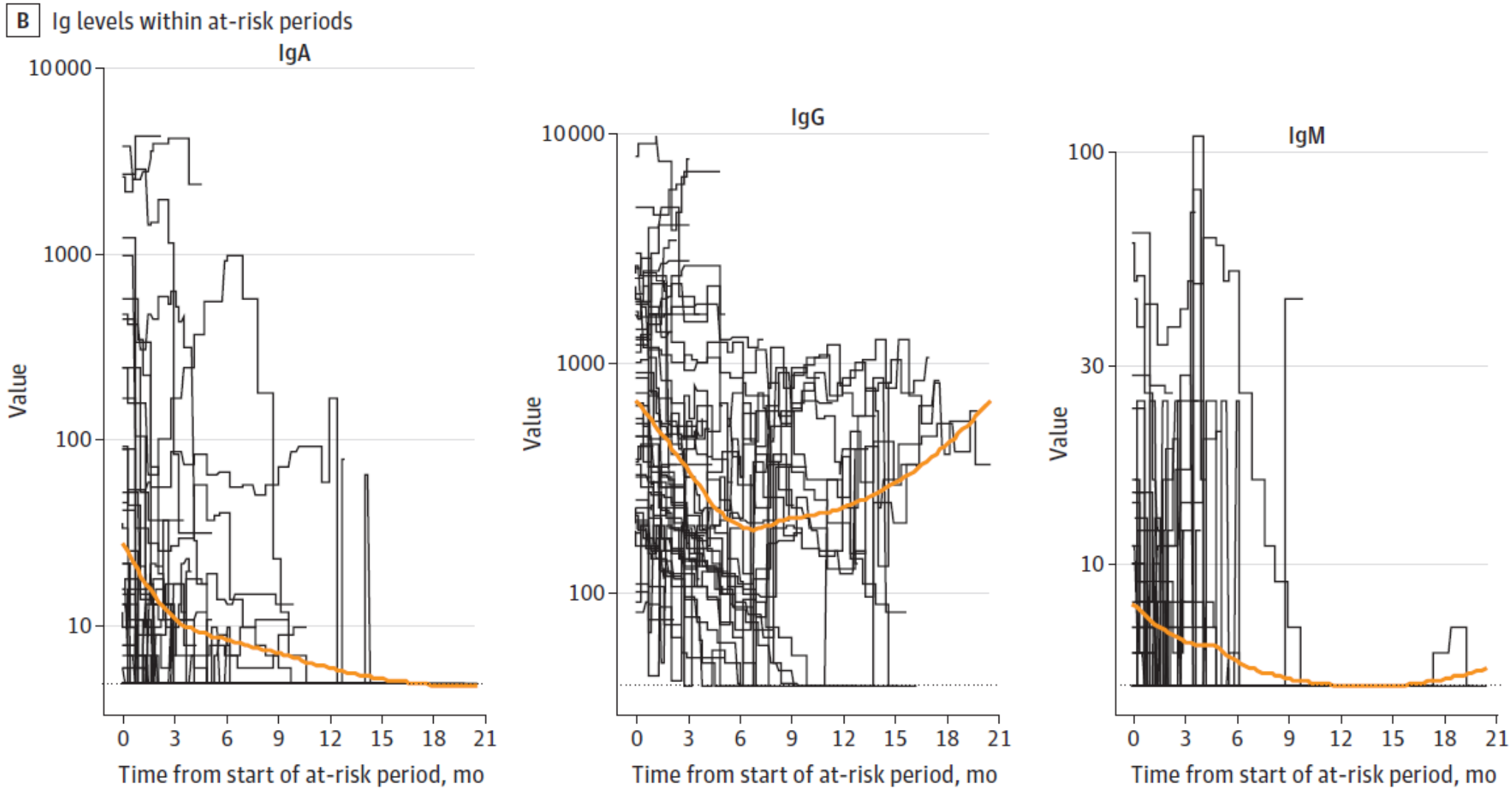
Philipp *et al.*, Blood 2022

Zelluläre (und humorale) **Immunität…**









Hammons *et al.*, Jama Network Open 2022

Infektionen und Immunstatus

endogene Infektionen
- bakterielle Infektionen (Haut/Darm)
- fungale Infektionen (Hefen)
- Virusreaktivierungen (CMV, HSV, EBV…)

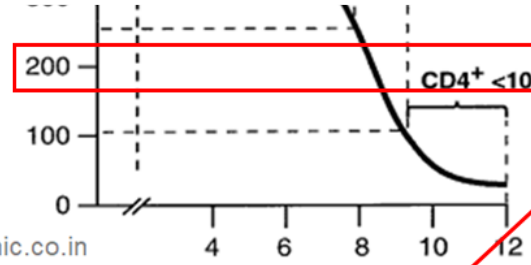
exogene Infektionen
- fungale Infektionen (Schimmel)
- respiratorische Virusinfektionen

endogene Infektionen
- Virusreaktivierungen (VZV, Hepatitiden…)

exogene Infektionen
- respiratorische Virusinf.
- bekapselte Erreger (Bakterien, Schlauchpilze)
- virale GI-Infektionen

Mittleres Plättchenvolumen	12.4	fl
Neutrophile	0.94	n*1000/µl
Lymphozyten	0.06	n*1000/µl
Monozyten	0.57	n*1000/µl
Eosinophile	0	n*1000/µl
Basophile	0.0	n*1000/µl

< 500/µl



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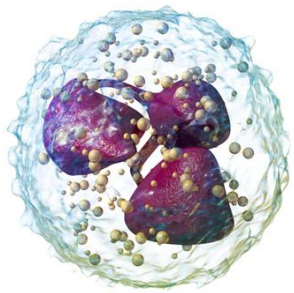
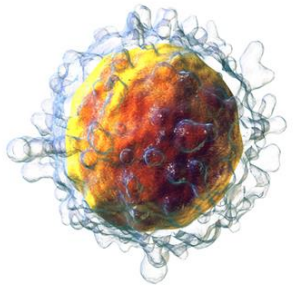
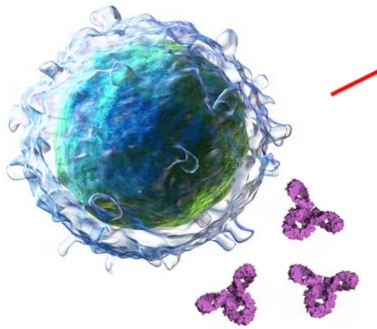
< 200/µl

Serumproteine			
Immunglobulin G	1246	mg/dl	< 400mg/dl







Infektionen unter Therapie mit BiSpecs

Predominance of bacterial respiratory tract and line-related infections and febrile neutropenia
Most common: URTI and BSI Less common: LRTI, UTI, meningitis, cellulitis, infections with C. diff, HSV and mould (mucormycosis, aspergillosis) Risks: previous lines therapy, higher CAR-T dose, severe CRS and underlying disease. Fungal infection associated HCT and severe CRS. Timing: early after infusion due to impaired immune function.

Longhitano *et al*., Blood Rev 2021

Table 1. A summary of significant ≥ CTCAE grade 3 AEs from selected key clinical trials of T-cell engagers in haematological malignancies

Trial phase	Trial context	≥ CTCAE [6] Grade 3 toxicities
CD20-CD3 TCE		
Phase 1/2	Epicoritamab treatment in adults with relapsed-refractory B-cell NHL [9]	CRS: 0% Neurologic: 3% TLS: 1%
Phase 1	Glofitamab treatment in adults with relapsed-refractory B-cell NHL [10]	CRS: 27.4% Neurologic: 0% Neutropenia:25.1% Infection: 17.5%
Phase 1	Odronextamab treatment in adults with relapsed-refractory B-cell NHL [11]	CRS: 7% Neurologic: 3% Neutropenia: 19% Infection: 23%
Phase 1	Mosunetuzumab treatment in adults with relapsed-refractory B-cell NHL [12]	CRS: 1% Neurologic: 4.1% Neutropenia: 25.4% Pneumonia: 2.5% UTI: 2.5%

Reynolds *et al.*, Blood Adv 2024

Table 1. Summary of included c

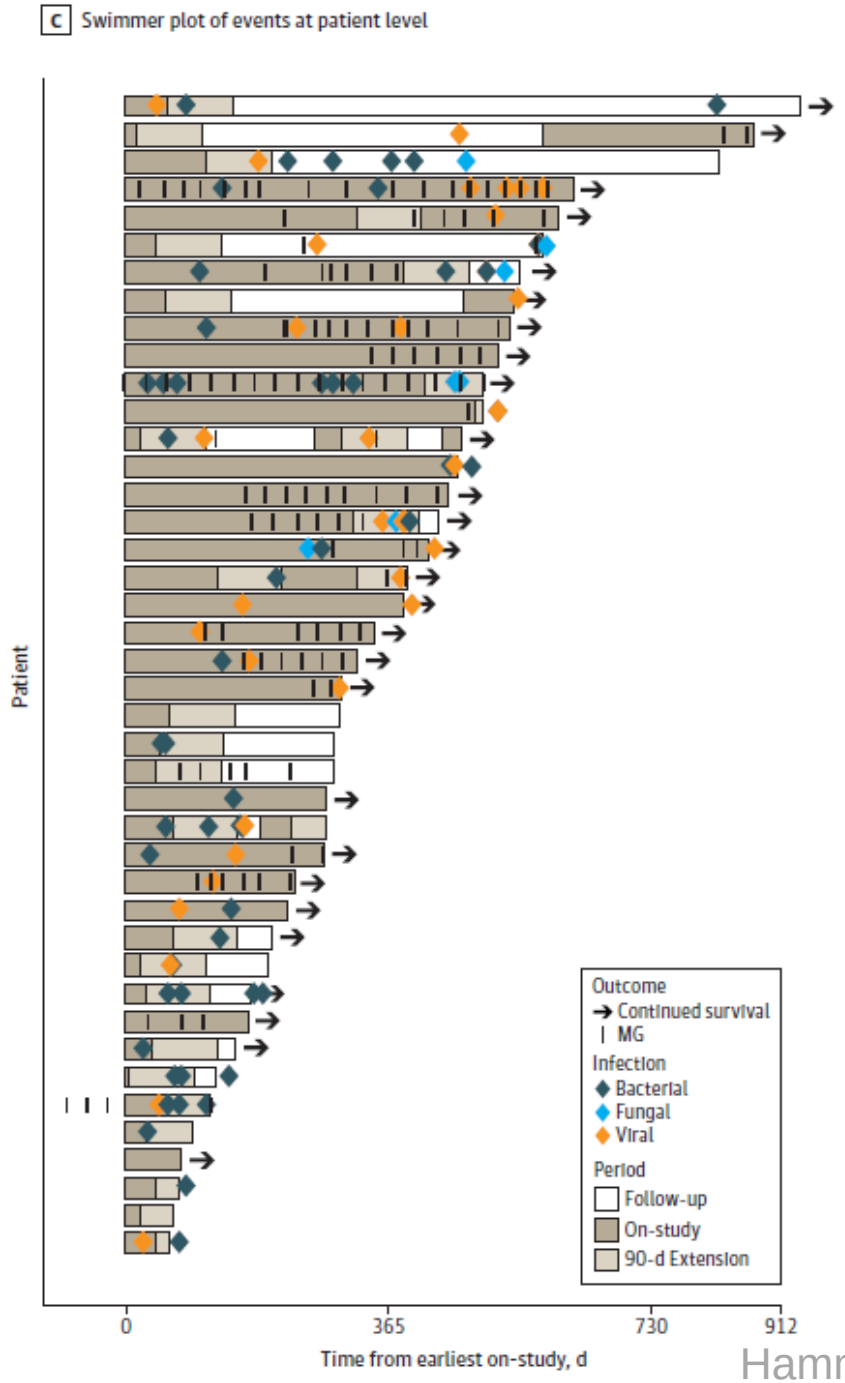
Malignant target	BsAb	l-grade infection, % (95% CI)	Median length of follow-up, mo (IQR)
CD20	Epcoritamab	39 (29-47)	11.4 (6.1-17.1)
	Glofitamab	42 (30-53)	10.6 (6-15)
	Mosunetuzumab	43 (47-50)	12.5 (8-28.5)
	Odronextamab	59 (48-69)	21 (NR)

NR, not reported; NHL, non-Hodgkin ly

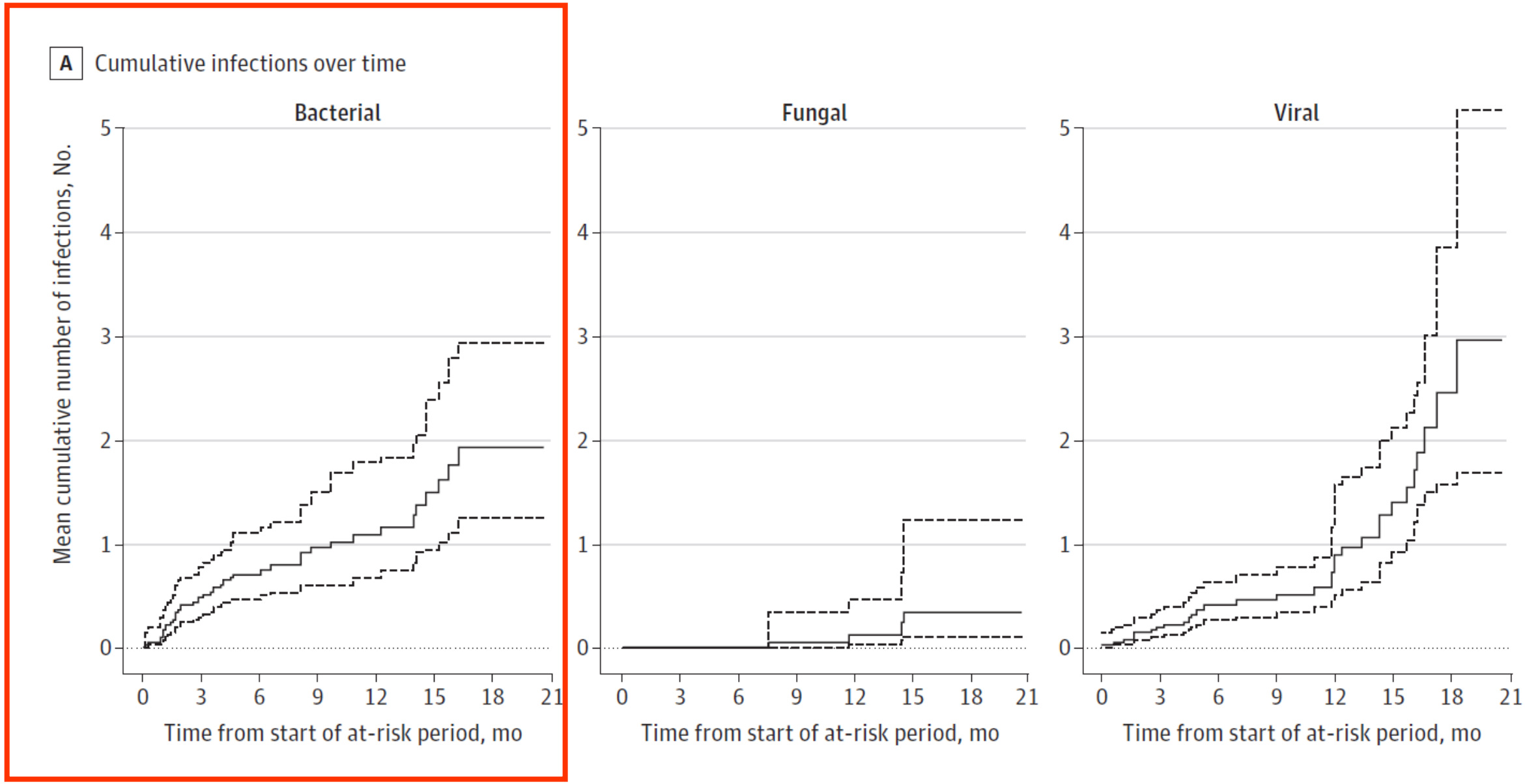
Table 2. Etiology of fatal infections

	n
Fatal infections	79
Microbiologically confirmed	**42 (53% of fatal infections)**
Viral	32 (41% of fatal infections)
SARS-CoV-2	>29*
EBV	1
CMV	1†
PML	1
Bacterial	4 (5% of fatal infections)
Gram-negative bacteremia	4
Fungal	5 (6% of fatal infections)
Candidemia	1
Pneumocystis jirovecii pneumonia	3
Systemic mycoses	1
Protozoan	
Toxoplasmosis	1
Clinically diagnosed	**12 (15% of fatal infections)**
Sepsis	4
Pneumonia	8
Etiology not reported	25 (32% of total infections)

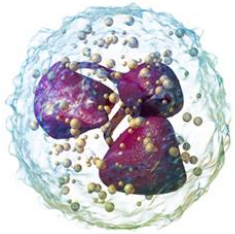
Reynolds *et al.*, Blood Adv 2024



Hammons *et al.*, Jama Network Open 2022



Hammons *et al.*, Jama Network Open 2022



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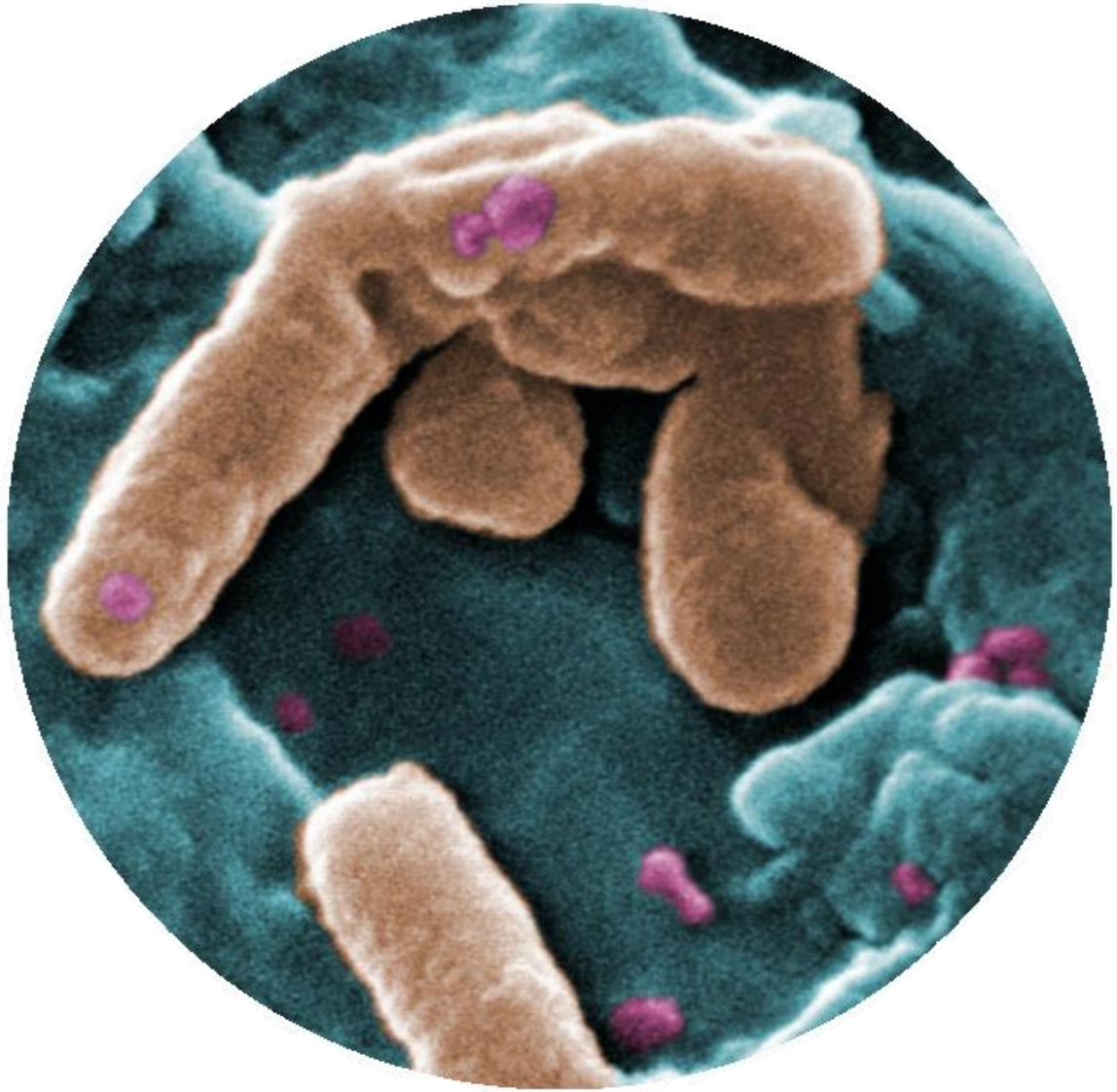

Source: hhttps://upload.wikimedia.org/wikipedia/commons/b/b3/Pseudomonas.jpg - license CC0 public domain

Ann Hematol (2017) 96:1775–1792
DOI 10.1007/s00277-017-3098-3

REVIEW ARTICLE

Diagnosis and empirical treatment of fever of unknown origin (FUO) in adult neutropenic patients: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO)

W. J. Heinz[1] · D. Buchheidt[2] · M. Christopeit[3] · M. von Lilienfeld-Toal[4] · O. A. Cornely[5,6,7,8,9] · H. Einsele[1] · M. Karthaus[10,18] · H. Link[11] · R. Mahlberg[12] · S. Neumann[13] · H. Ostermann[14] · O. Penack[15] · M. Ruhnke[16] · M. Sandherr[17] · X. Schiel[18] · J. J. Vehreschild[5,6] · F. Weissinger[19] · G. Maschmeyer[20]

Annals of Hematology (2021) 100:239–259
https://doi.org/10.1007/s00277-020-04286-x

ORIGINAL ARTICLE

Central venous catheter–related infections in hematology and oncology: 2020 updated guidelines on diagnosis, management, and prevention by the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO)

Boris Böll[1] · Enrico Schalk[2] · Dieter Buchheidt[3] · Justin Hasenkamp[4] · Michael Kiehl[5] · Til Ramon Kiderlen[6] · Matthias Kochanek[1] · Michael Koldehoff[7] · Philippe Kostrewa[8] · Annika Y. Claßen[1] · Sibylle C. Mellinghoff[1] · Bernd Metzner[9] · Olaf Penack[10] · Markus Ruhnke[11] · Maria J. G. T. Vehreschild[12] · Florian Weissinger[13] · Hans-Heinrich Wolf[14] · Meinolf Karthaus[15] · Marcus Hentrich[16]

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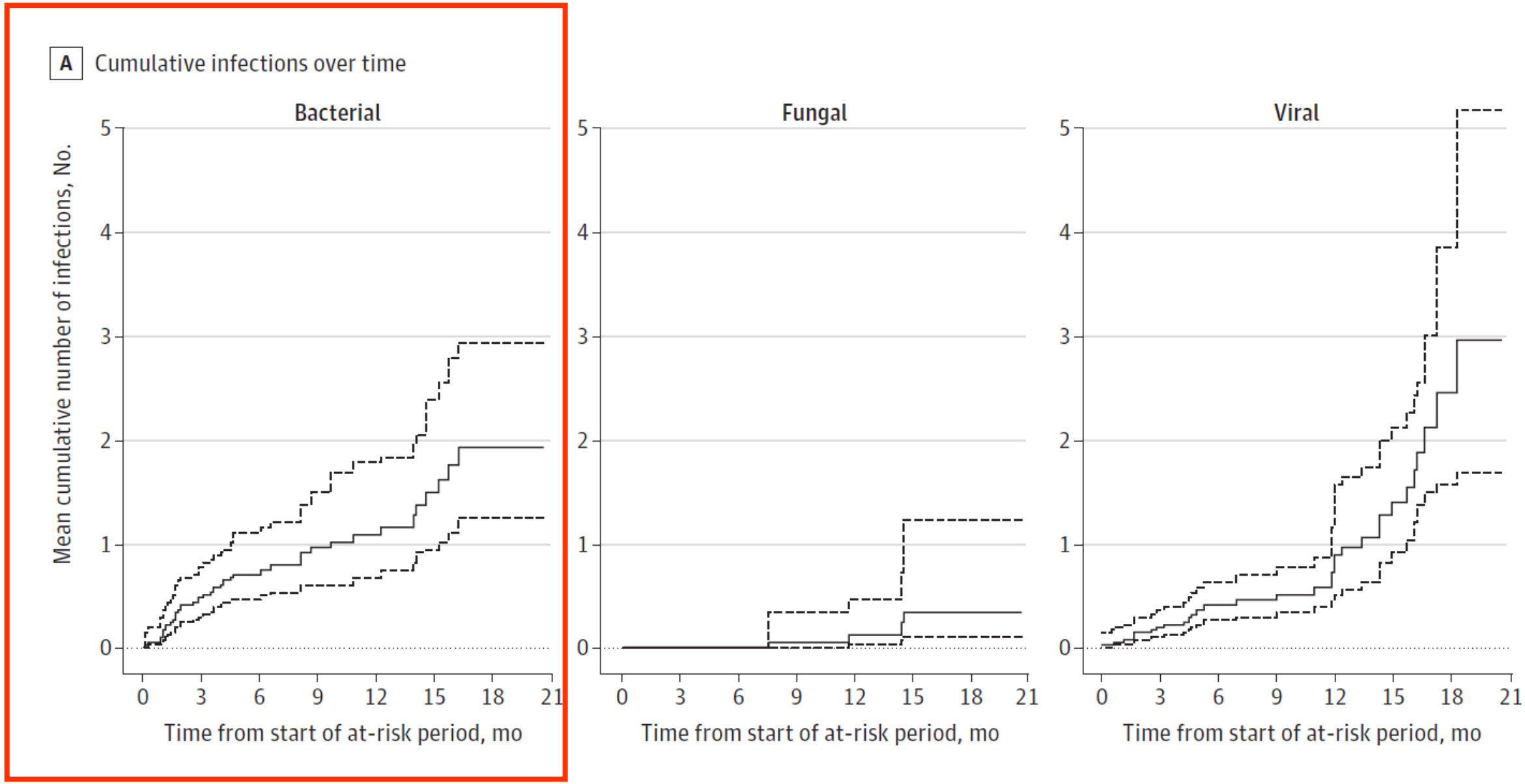
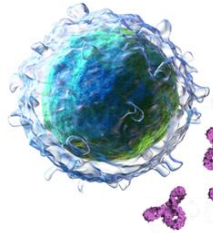


Hammons *et al.*, Jama Network Open 2022



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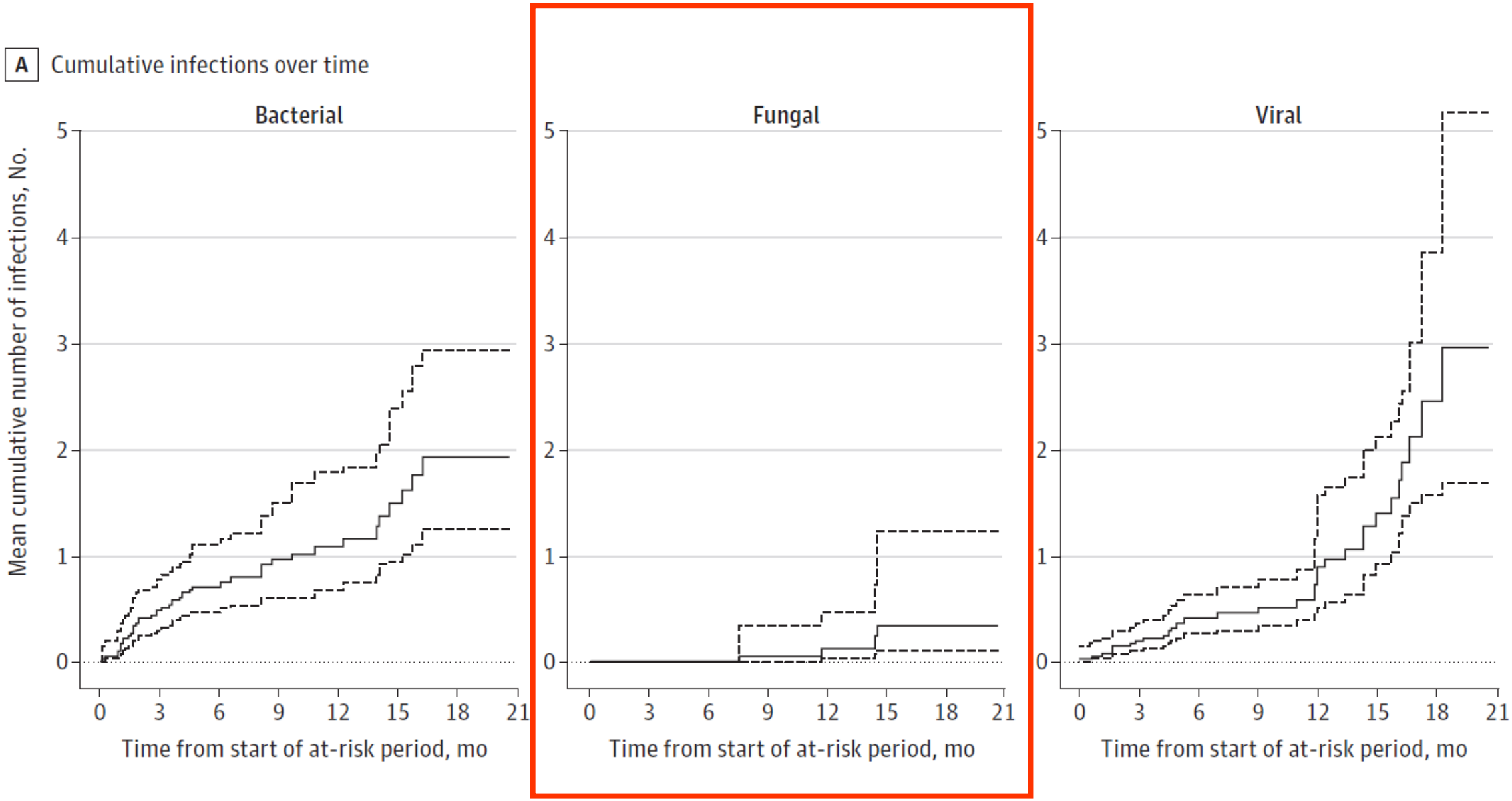
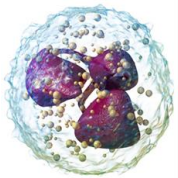


Hammons *et al.*, Jama Network Open 2022



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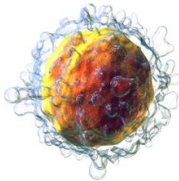

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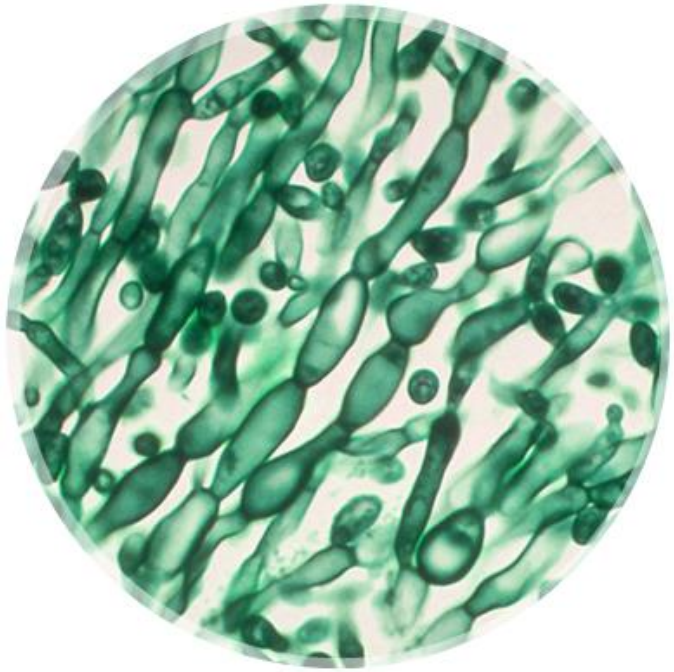

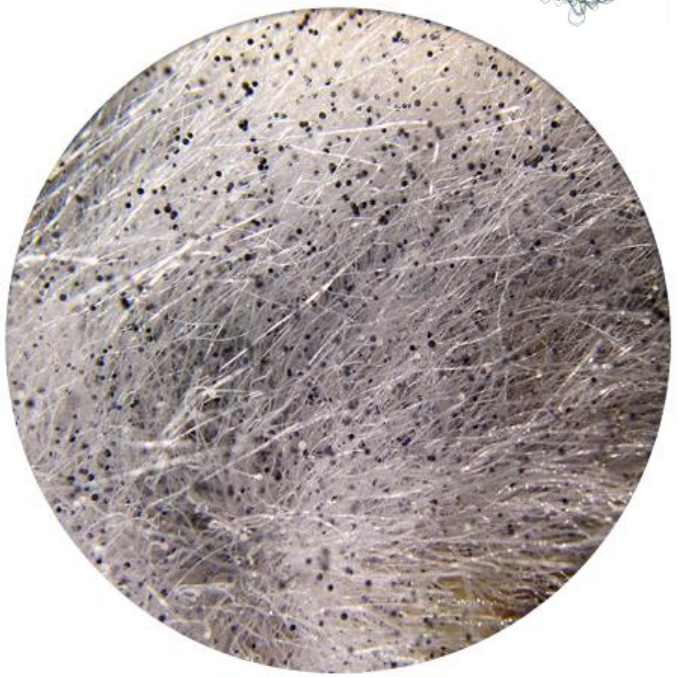

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Received: 20 February 2020 | Revised: 5 March 2020 | Accepted: 10 March 2020

DOI: 10.1111/myc.13082

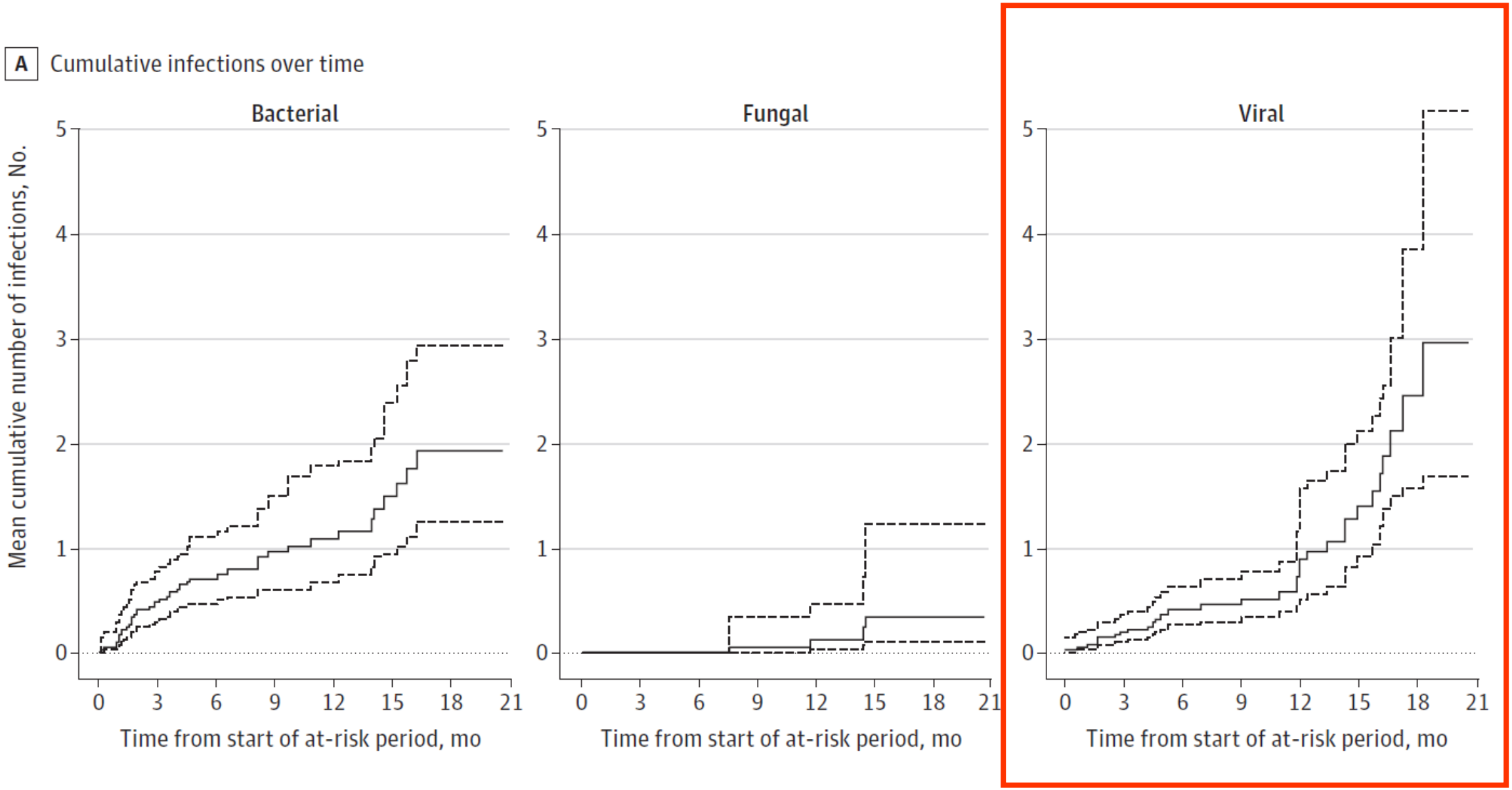
mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases

WILEY

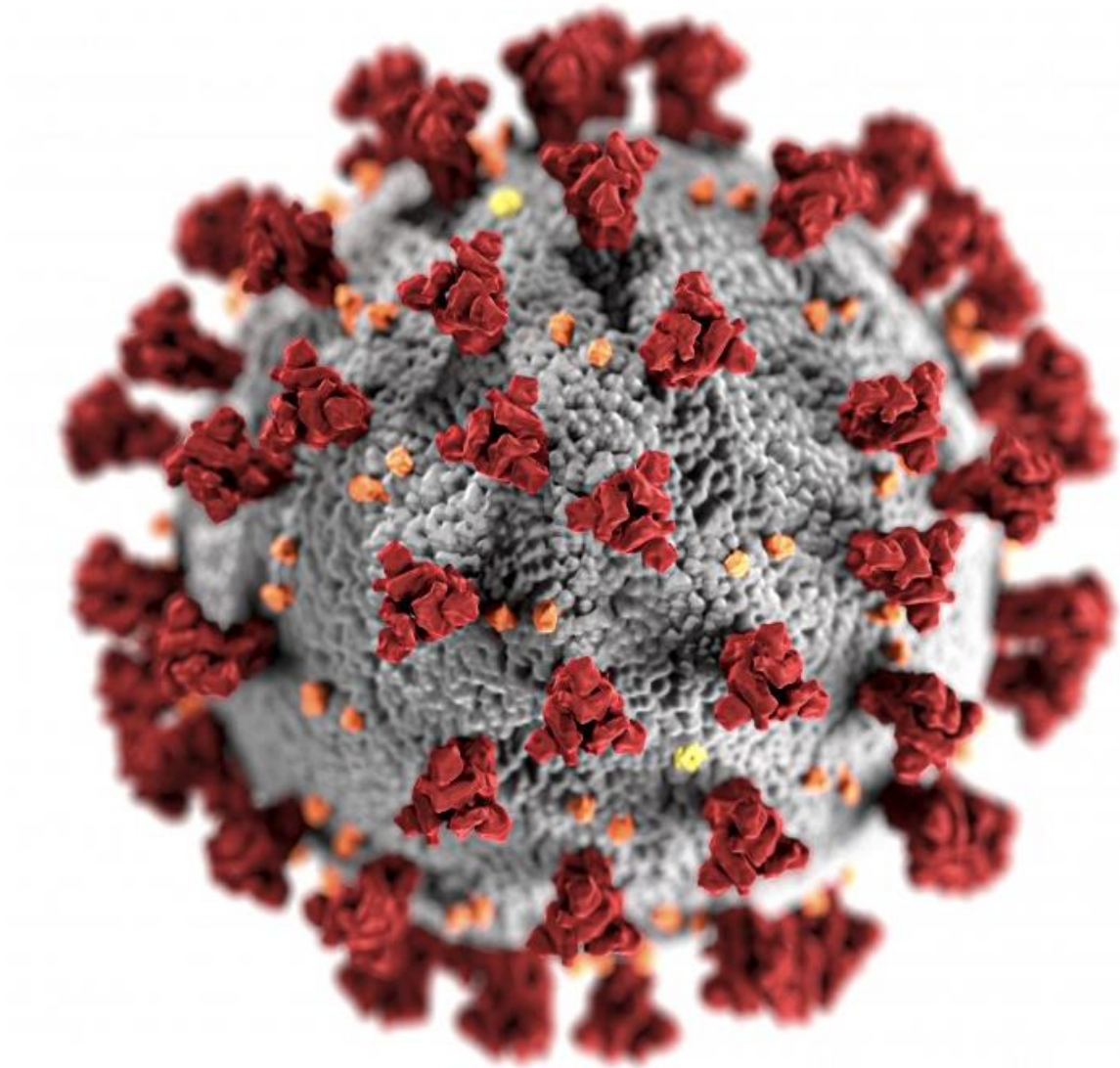
ORIGINAL ARTICLE

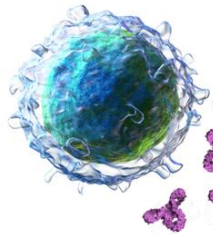
Treatment of invasive fungal diseases in cancer patients—Revised 2019 Recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

Markus Ruhnke[1] | Oliver A. Cornely[2,3,4,5] | Martin Schmidt-Hieber[6] | Nael Alakel[7] | Boris Boell[2] | Dieter Buchheidt[8] | Maximilian Christopeit[9] | Justin Hasenkamp[10] | Werner J. Heinz[11] | Marcus Hentrich[12] | Meinolf Karthaus[13] | Michael Koldehoff[14] | Georg Maschmeyer[15] | Jens Panse[16] | Olaf Penack[17] | Jan Schleicher[18] | Daniel Teschner[19] | Andrew John Ullmann[20] | Maria Vehreschild[2,3,21,22] | Marie von Lilienfeld-Toal[23] | Florian Weissinger[1] | Stefan Schwartz[24]



Hammons *et al.*, Jama Network Open 2022





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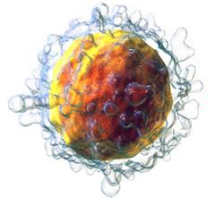

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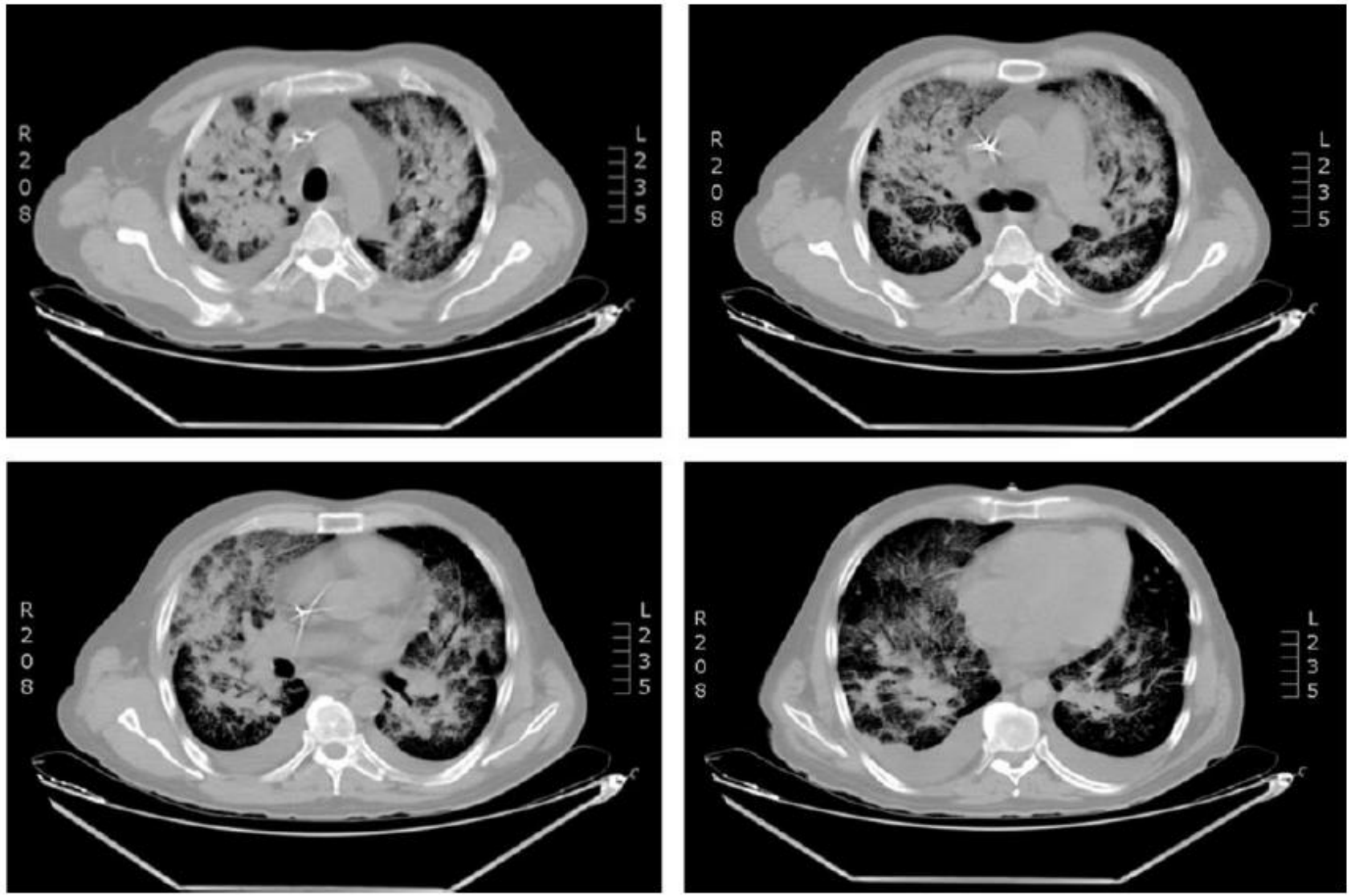

Figure 2. Computed tomography (CT) scan of the chest revealing bilateral bronchopneumonia

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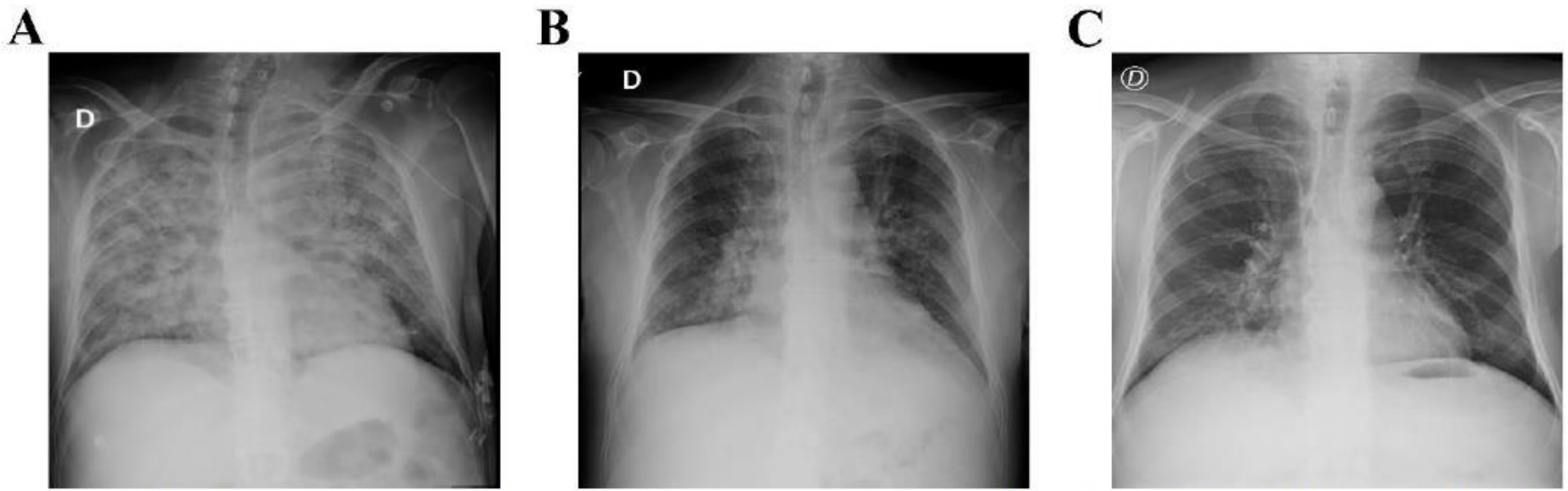

Figure 1. Chest X-ray before and after intravenous immunoglobulin substitution (IVIG). A) Chest X-ray with signs of bilateral pneumonia before starting IVIG treatment. Chest X-ray after 3 days (B) and 5 days (C) of IVIG replacement showing improvement of the pneumonia

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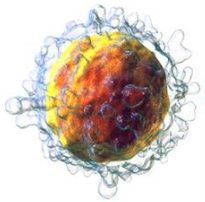

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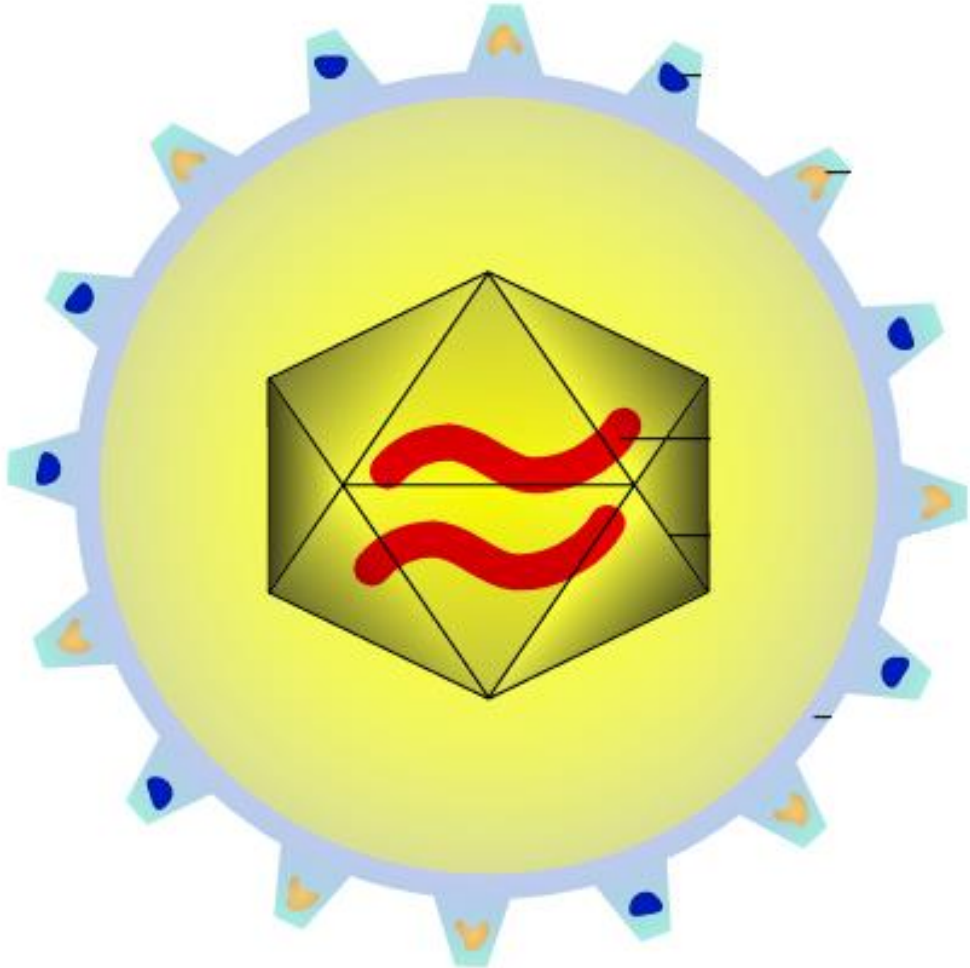

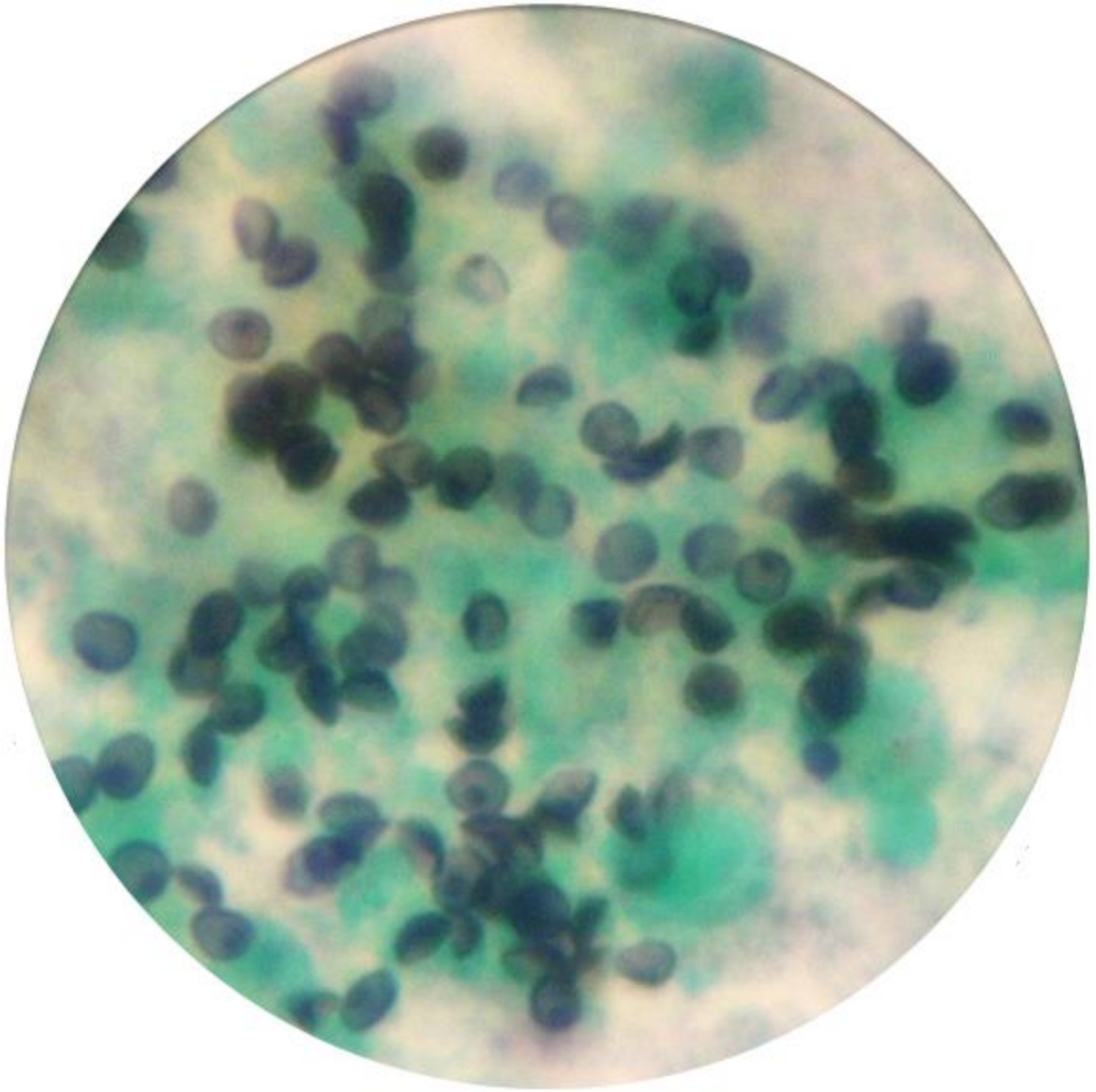

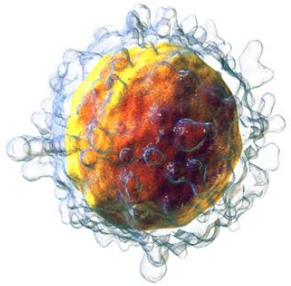

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Pneumocystis jirovecii Pneumonia Secondary to Blinatumomab Therapy: A Case Report

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Infektions- & Immunmonitoring unter Therapie mit BiSpecs

prä-BiSpec/vor der Therapie

- Hepatitis-, HIV-, CMV-Serologie; ggf. IGRA (TBC); Screening auf MRSA und MRGN

post-BiSpec - während der Neutropenie

- Galactomannan-AG 1x/Woche bei Neutropenie >14 Tage

post-BiSpec - während der Neutropenie und CD4<200/µl

- CD4-T-Zellzahl 1x/Monat
- Gesamt-IgG 1-2x/Monat
- CMV-PCR 1-2x/Monat (falls vorliegend / CMV+)
- HBV-PCR 1x/Monat (falls vorliegend / HBV+)

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Common Bacterial Infections	
Interventions & Prophylaxis	**Indications & Duration**
Levofloxacin 500 mg PO daily. Alternatives: Cefdinir 300 mg PO twice a day or augmentin 875 mg PO twice a day.	• Newly diagnosed MM: Consider levofloxacin for 12 weeks after diagnosis[2] • CAR T-cell: Start when ANC <500 or per clinician discretion and continue until neutrophil recovery. • BsAb: Consider starting with therapy and administer throughout the first cycle.
IVIG: Suggested dose is 400 mg/kg once every 4 weeks.	• IVIG replacement is indicated for IgG <400 mg/dL and recurrent life-threatening infections.[a] Note: IVIG replacement during CAR T-cell and BsAb therapies is not guided by presence of infections. Duration: • Patients at high risk for infections[b]: At day +30 until end of therapy or serum IgG >400 mg/dL. • CAR T-cell[a]: Day +30 through 1 year. After 1 year continue until serum IgG >400 mg/dL. • BsAb[a]: Start at second cycle of therapy and continue until end of therapy or serum IgG >400 mg/dL (whichever is longer).
Pneumococcal vaccination	The CDC recommends 1 dose of PCV20 or 1 dose of PCV15 followed by 1 dose of PPSV23 at least 1 year later. CAR T-cell and/or autologous HCT: Revaccination starting 3–6 months after treatment. BsAb: Update vaccination status prior to starting BsAb treatment.

Common Viral and Fungal Infections	
Interventions & Prophylaxis	**Indication & Duration**
Herpes simplex virus or Varicella-zoster virus: Acyclovir 400–800 mg PO twice/day or valacyclovir 500 mg PO once or twice/day. Continue as clinically indicated	While recieving a regimen with PIs or monoclonal antibody and for at least 3 months beyond end of therapy or per institutional practice. CAR T-cell: A minimum of one year; indefinite (preferred), irrespective of vaccination status. BsAb: Indefinite, irrespective of vaccination status. Autologous HCT: for 1 year post-HCT or as clinically indicated
Hepatitis B virus and HIV: Screen for and treat as outlined in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections	CAR T-cell or BsAb: Patients HBsAg-positive or HBsAg-negative, HBcAb-IgG positive. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections for treatment duration.
Pneumocystis jiroveci pneumonia (PJP): Trimethoprim-sulfamethoxazole (TMP-SMX) therapy or pentamidine or atorvaquone	• CAR T-cell or BsAb: Start with therapy and continue until end of therapy or until CD4 ≥200/mm³ (whichever is longer). • For other myeloma therapy (Non CAR T-cell/BsAb: When equivalent dexamethasone dosing is >40 mg/day for 4 days per week or as clinically indicated per institutional practice.
SARS-CoV-2: COVID-19 vaccination	Autologous HCT and/or CAR T-cell: Revaccination 3–6 months after therapy. Per CDC for patients who are immunosuppressed.
Influenza virus: Vaccination	Per CDC for patients who are immunosuppressed.
RSV: Bivalent vaccine	Single dose of bivalent vaccine for MM patients aged ≥60 years. See CDC guidance for all other patient populations.
Adenovirus, CMV, EBV, JC virus, parvovirus: No prophylaxis	Routine monitoring of viral load is not recommended. Monitor viral load (by PCR) only in patients with suspected CMV-related disease (eg, colitis, pneumonitis, hepatitis) or otherwise unexplained fever and/or cytopenias or in patients with high risk of infections.[b]
Yeast: Fluconazole 400 mg PO daily	Start when ANC <500 or per clinician discretion and continue until neutrophil recovery.
Mold: Azole	In patients with high risk of infections[b]: Consider ongoing prophylaxis with anti-mold azole.

Infektionsprävention unter Therapie mit BiSpecs

prä-BiSpec/vor der Therapie

- möglichst Komplettierung des Impfschutzes (Auffrischungsimpfungen)

post-BiSpec - während der Neutropenie

- Im Regelfall keine antibakterielle medikamentöse Prophylaxe
- Ggf. antifungale medikamentöse Prophylaxe bei protrahierte Neutropenie >14 Tage
  - Posaconazol p.o.
- Ggf. GCSF bei protrahierte Neutropenie >14 Tage (CAVE: CRS)

Infektionsprävention unter Therapie mit BiSpecs

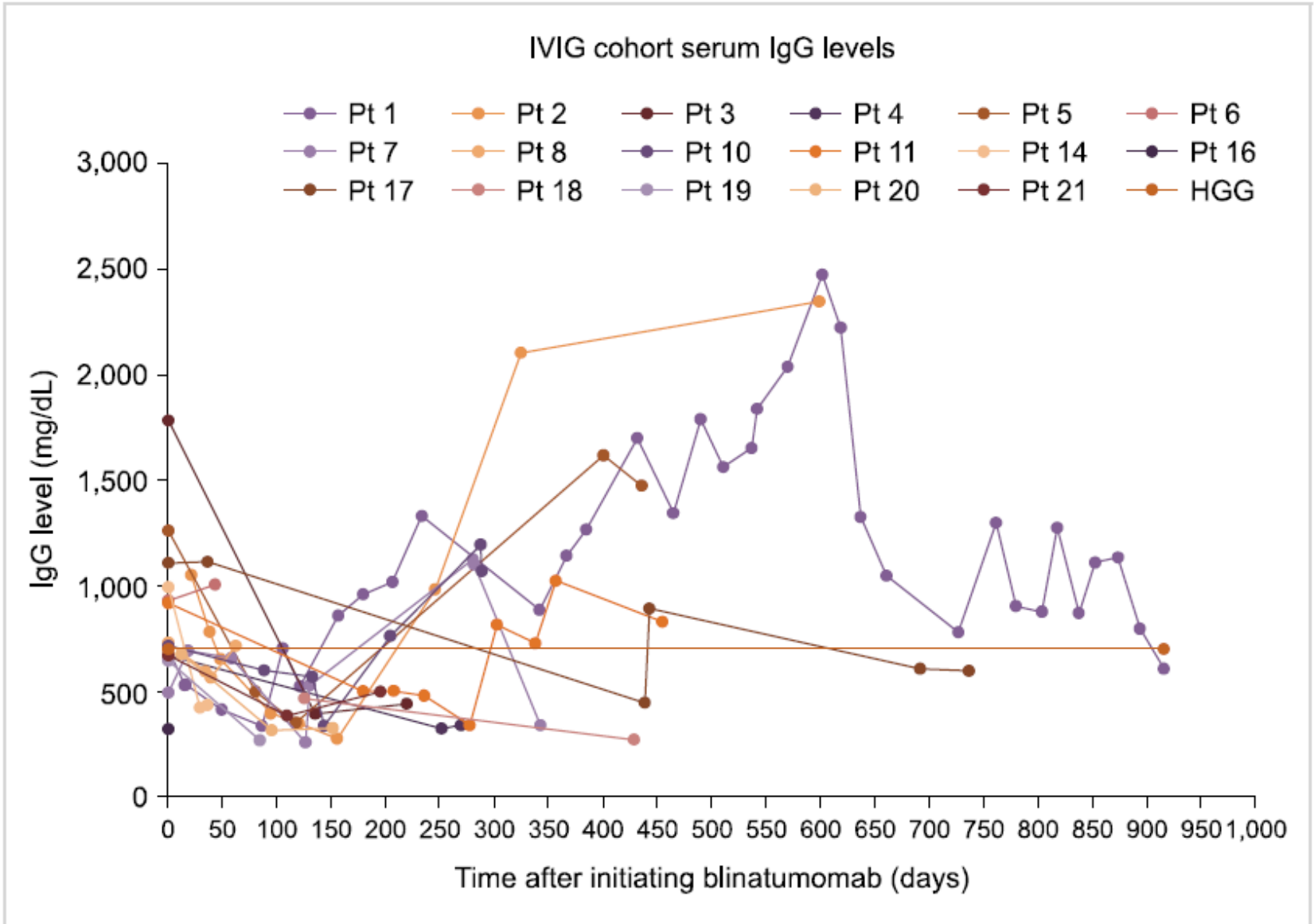
post-BiSpec – mindestens bis CD4<200/µl

- Medikamentöse Prophylaxe gegen *Pneumocystis jirovecii*
  - Trimetoprim/Sulfamethoxazol
- Medikamentöse Prophylaxe gegen *HSV* und *VZV*
  - Aciclovir
- Medikamentöse Prophylaxe gegen *HBV* (falls erforderlich)
  - Entecavir
- Medikamentöse Prophylaxe gegen *TBC* (falls erforderlich)
  - Isoniazid

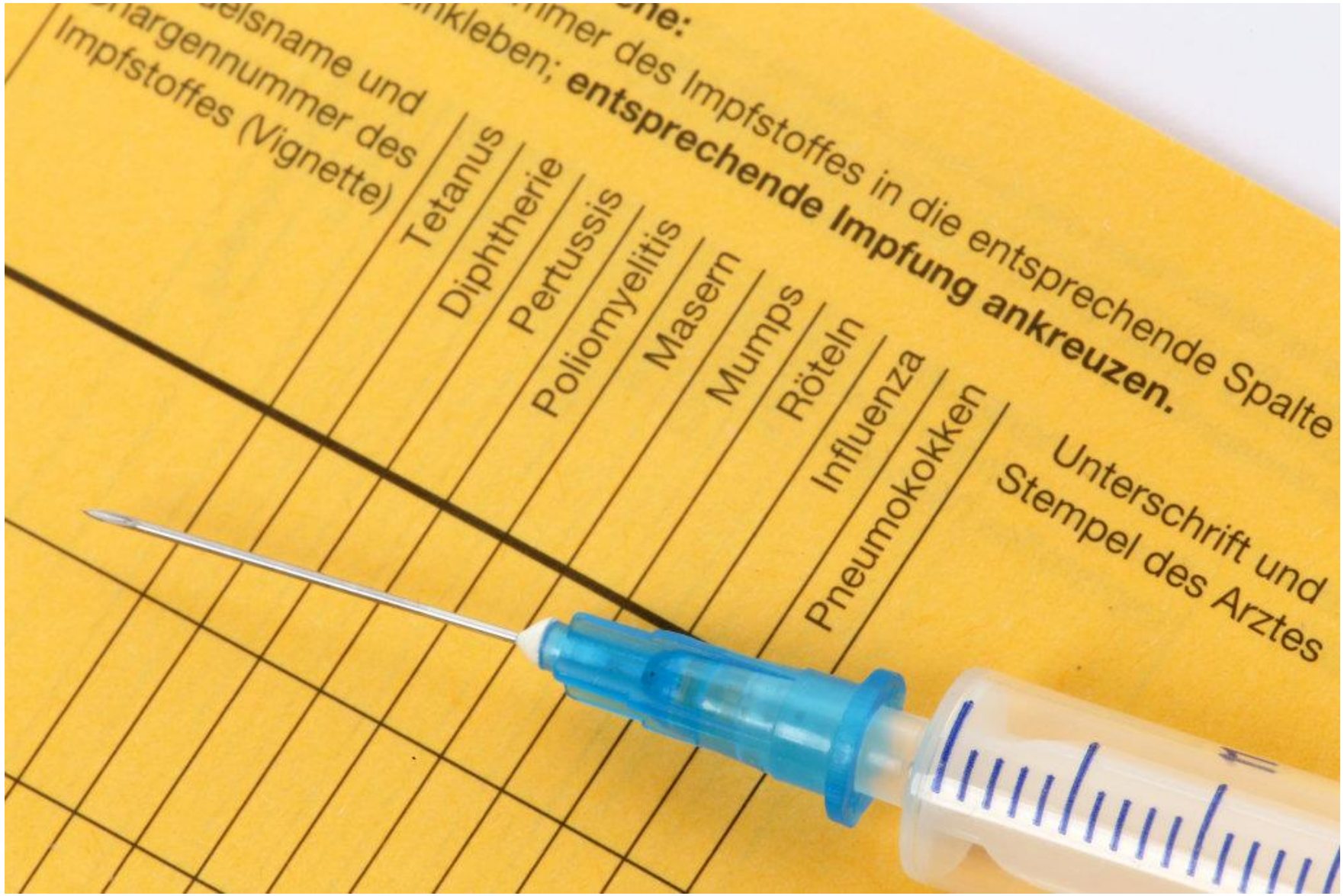
Infektionsprävention unter Therapie mit BiSpecs

post-BiSpec – grundsätzlich

- Substitution von IVIG 1x/Monat* bei Patienten
  - Gesamt-IgG <400mg/dl
  - rezidivierenden Infektionen ≥2x/Jahr



Wo *et al*., Blood Res 2022



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Infektionsprävention unter Therapie mit BiSpecs

post-BiSpec – grundsätzlich

- Substitution von IVIG 1x/Monat* bei Patienten
  - Gesamt-IgG <400mg/dl
  - rezidivierenden Infektionen ≥2x/Jahr

- Erneute Auffrischimpfungen
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae Typ B*
  - Respiratorische Viren (*SARS-CoV2, Influenza, RSV*)
  - *VZV* (Totimpfstoff)

Kernaussagen/persönliche Meinung

Uniklinikum Würzburg

- Infektionen nach/unter Therapie mit BiSpecs sind häufig und fokussieren sich auf zwei Phasen: eine frühere „neutropenische“ und eine späte „spezifisch-defiziente“ Phase
- In der neutropenischen Phase dominieren bakterielle Infektionen, im Verlauf „ergänzt“ durch virale Infektionen (CARV, Herpesviridae), seltener fungale Infektionen.
- Ein sorgfältiges infektiologisches Assessment vor Therapieeinleitung ist essentiell, um spezifische Risiken zu detektieren (Hepatitis, CMV, MRE, ggf. weitere)
- Ein regelm. Immunomonitoring (CD4, IgG) und ggf. Infektionsmonitoring (CMV, GM) sollte erfolgen, um das patientenindividuelle Infektionsrisiko zeitgerecht einschätzen zu können.
- Eine antiinfektive medikamentöse Primärprophylaxe sollte regelhaft gegen HSV/VZV und gegen PcP durchgeführt werden. Im Einzelfall auch gegen HBV, TBC und ggf. Pilze.
- Prophylaktisch sollte darüber hinaus regelhaft bei Hypogammaglobulinämie und Infektionen IVIG substituiert werden und Auffrischimpfungen erfolgen (resp. Erreger, VZV).

Vielen Dank für Ihre Aufmerksamkeit!

Kontakt:

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