II. Medizinische Klinik und Poliklinik (Onkologie, Hämatologie, Knochenmarktransplantation mit Sektion Pneumologie)

DGHO | Webinar 10. Mai 2024

Antiinfektive Prophylaxen nach allogener Stammzelltransplantation

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Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition	keine
2. Beratungs- bzw. Gutachtertätigkeit	Takeda, Gerichte in Bundesrepublik Deutschland
3. Besitz von Geschäftsanteilen, Aktien oder Fonds	keine
4. Patent, Urheberrecht, Verkaufslizenz	keine
5. Honorare	AstraZeneca, Takeda, Pfizer, Novartis, MSD, Daiichi Sankyo, JAZZ, Gilead, GSK
6. Finanzierung wissenschaftlicher Untersuchungen	keine
7. Andere finanzielle Beziehungen	keine
8. Immaterielle Interessenkonflikte	keine

Immunrekonstitution nach allogener Stammzelltransplantation

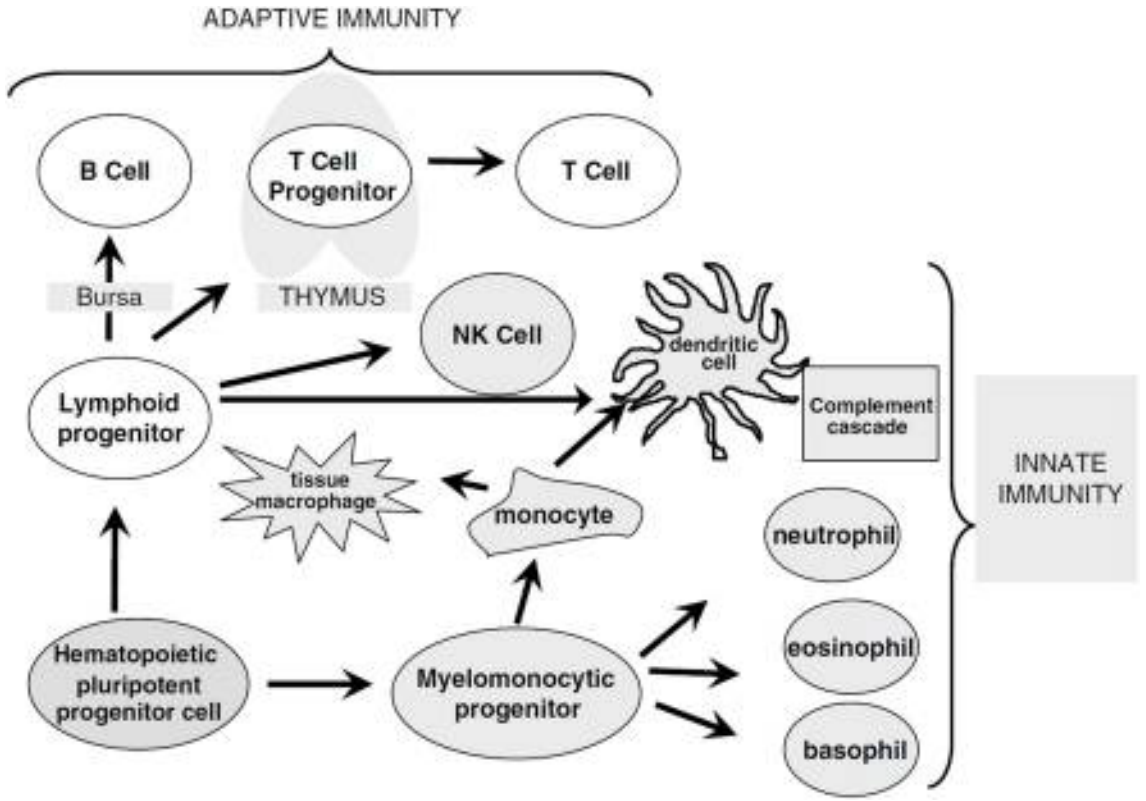
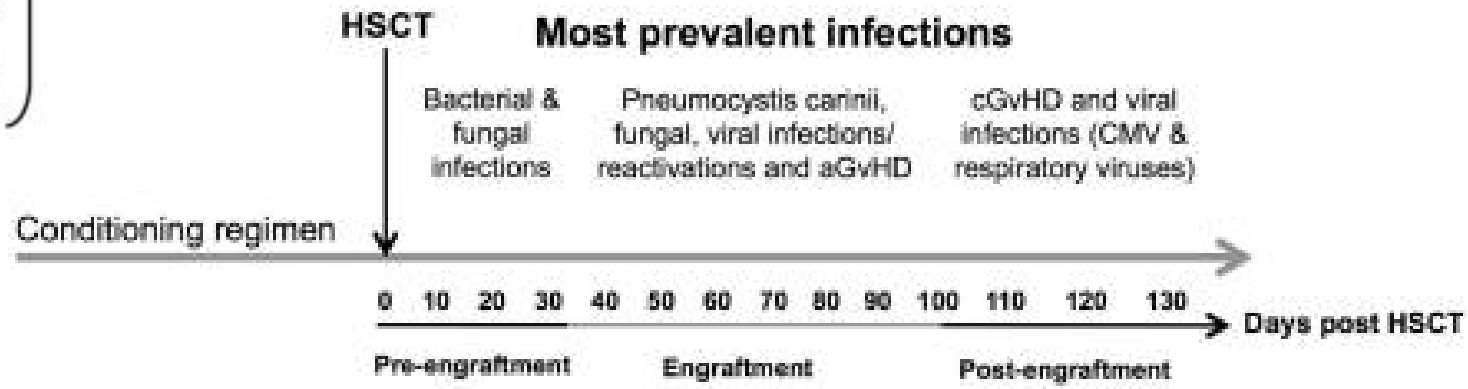


Table 1

Immune reconstitution after allogeneic HSCT.

Immune cells	Duration after allogeneic HSCT
Neutrophils >0.5 × 10^9/L	~14 days for PBSC, ~21 days for BM, and ~30 days for CB
NK cells	30–100 days
T cells	100 days
$CD19^+$ B cells	1–2 years



Ogonek J et al. Front Immunol 2016

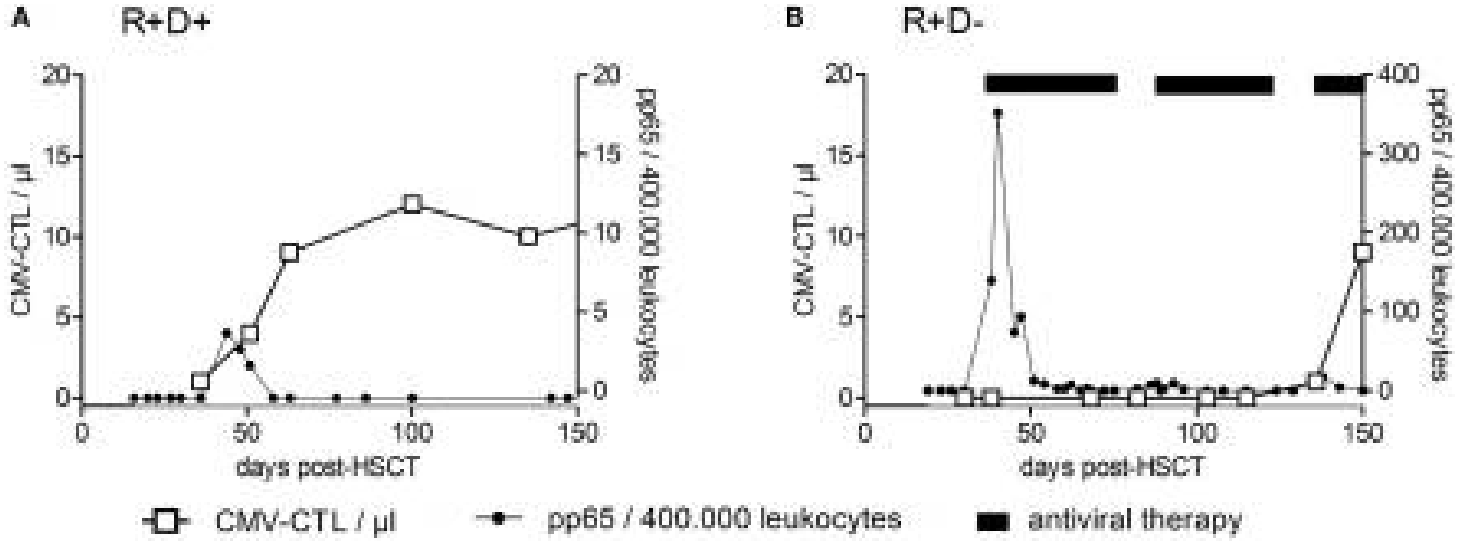
Einflussfaktoren

Table 2

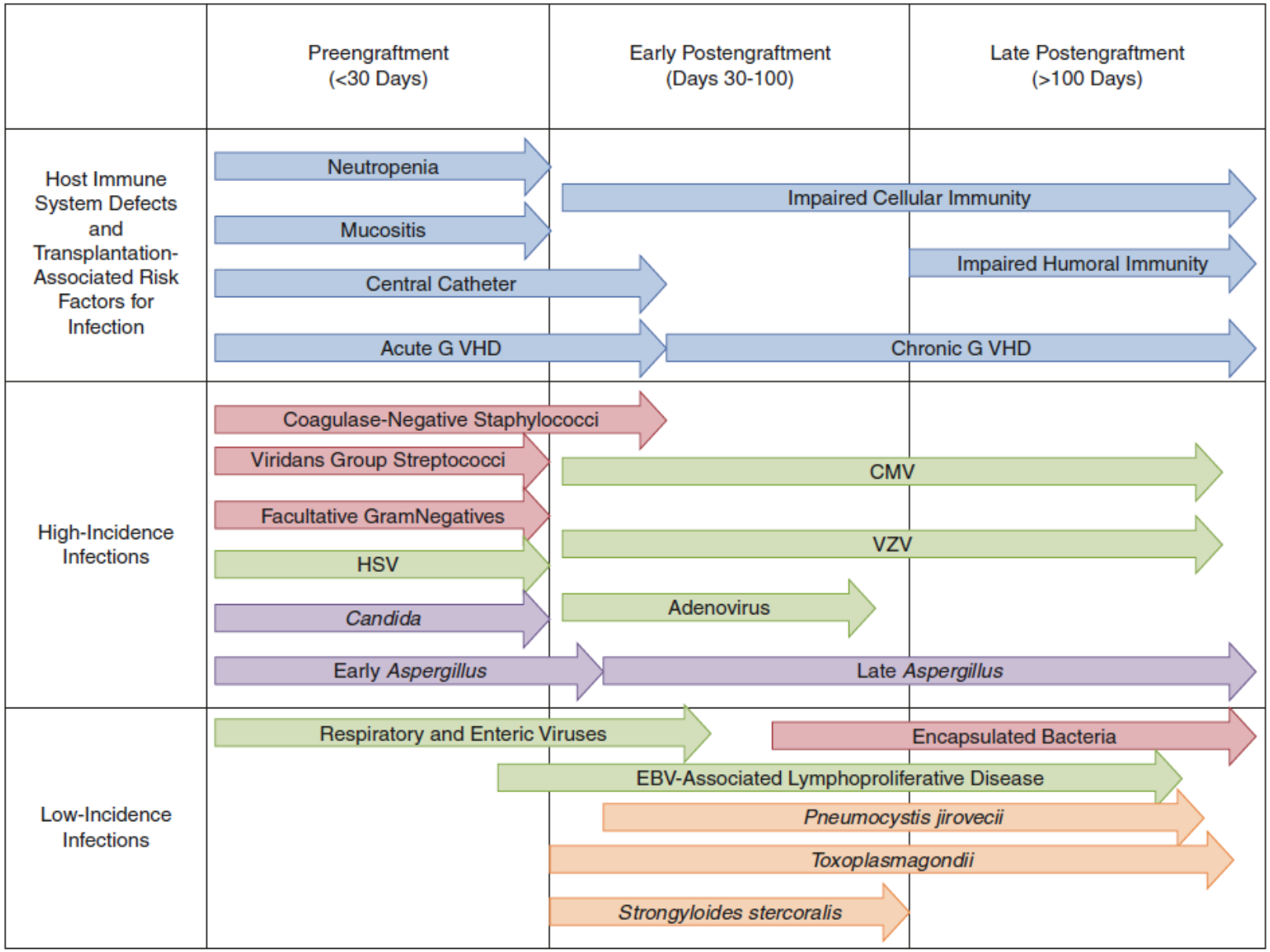
Stem cell source influences immune reconstitution and complications after HSCT.

Complication	PBSCs	BM	CB
aGvHD	++	+	+/−
Infections	+	+	++
Viral reactivations	++	++	+/−
Relapse	+/−	++	++

- Konditionierung
- Grunderkrankung
- Remissionsstatus
- Komorbiditäten
- CMV-Status Spender und Empfänger
- Transplantat
- HLA-Matching
- GvHD



Ogonek J et al. Front Immunol 2016



Bacterial pathogens	Predisposing risks	Clinical manifestations
Streptococcus viridans	Neutropenia, oral mucositis	Bacteremia
Streptococcus pneumoniae	Graft-versus-host disease (GVHD), lack of immunization	Pneumonia, meningitis, sepsis
Enterococcus species	Cephalosporin use, *C. difficile* infection	Bacteremia
Staphylococcus aureus	Central venous lines (CVL), colonization	Bacteremia, pneumonia, soft tissue infection
Coagulase-negative staphylococcus	CVL	Bacteremia
Escherichia coli	Neutropenia, mucositis	Bacteremia, pneumonia
Klebsiella pneumoniae	Neutropenia, mucositis	Bacteremia, pneumonia
Pseudomonas aeruginosa	Neutropenia, mucositis	Bacteremia, pneumonia, ecthyma
Stenotrophomonas maltophilia	CVL, prior broad-spectrum antibiotic exposure	Bacteremia
Acinetobacter species	CVL, prior broad-spectrum antibiotic exposure	Bacteremia, pneumonia
Achromobacter species	CVL, prior broad-spectrum antibiotic exposure	Bacteremia
Anaerobic bacteria (e.g., *Clostridium septicum*, *Bacteroides* species)	Neutropenia, mucositis	Bacteremia, necrotizing enterocolitis, typhlitis
Clostridium difficile	Antibiotic exposure, GVHD, local epidemiology, previous *C. difficile* infection	Colitis, megacolon, secondary bacteremia

Pereira, Pouch and Scully in: A. Safdar (ed.), Principles and Practice of Transplant Infectious Diseases, Springer Nature 2019

Category, grade	Definition
Strength of recommendation	
A	AGIHO strongly supports a recommendation for use
B	AGIHO moderately supports a recommendation for use
C	AGIHO marginally supports a recommendation for use
D	AGIHO supports a recommendation against use
Quality of evidence	
I	Evidence from at least 1 properly designed randomized, controlled trial
II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
IIr	meta-analysis or systematic review of RCT
IIt	transferred evidence, i.e. results from different patient cohorts or similar immune status situation
IIh	comparator group historical control
IIu	uncontrolled trials
IIa	published abstract, presented at an international symposium or meeting
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

Diagnostics	
Screening for • HBV (anti-HBc antibodies, HBs antigen, nucleic acid testing) • HCV (anti-HCV, nucleic acid testing) • HEV (nucleic acid testing) • HIV (HIV1/2 antibodies, nucleic acid testing) • Anti-delta if HBsAg positive	Yes • it is the law by the way
HBsAg and/or anti-HBc positive: HBV nucleic acid testing for ≥ 6 months after SCT	Yes, or virustatic
Elevated liver enzymes: HEV nucleic acid testing	Yes
Routine screening for CMV viremia	Yes
Routine screening for HSV, VZV, EBV, HHV6, serum galactomannan antigen, serum 1,3-β-D-glucan, blood cultures in asymptomatic afebrile patients	No

Antibiotikaprophylaxe?

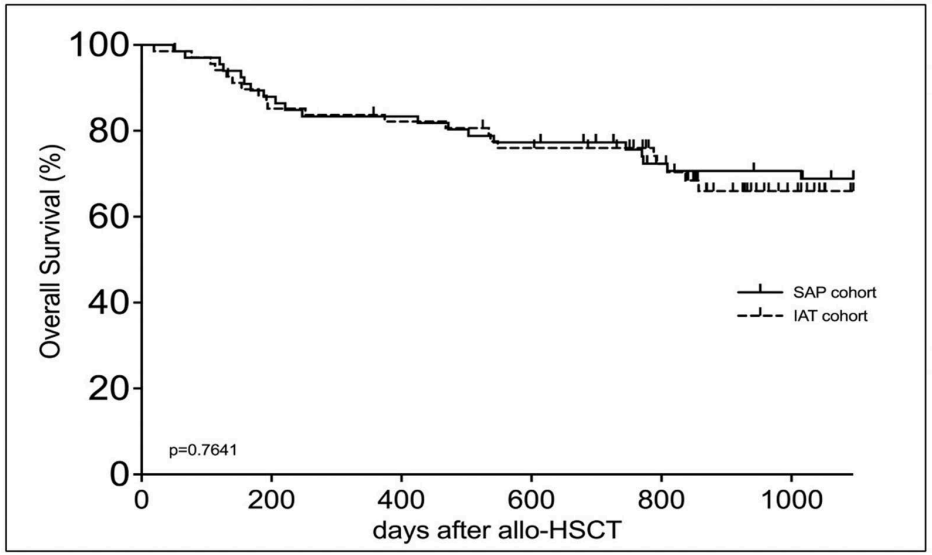
- Kein Überlebensvorteil in prospektiven Prüfungen
- Interaktionen
- Rote Hand Briefe zu ZNS-UAW
- Auswirkung auf Mikrobiom
- Neutropenie nach allogener Stammzelltransplantation nicht immer sooo langdauernd
- Daten zu Vorteil antibiotischer Prophylaxe sehr alt
  - Geringere Awareness damals
  - Schnellere Reaktionen, kleinere Zimmer etc. bessere Versorgungssituation heute
- Reduzierte Inzidenz bakterieller Infektionen bei prolongierter Neutropenie
- Fieberfreiheit bei prolongierter Neutropenie

Antibiotikaprophylaxe im historischen Vergleich

Table 1: Summary of patient characteristics transplanted in 2017 (SAP cohort) and 2019 (IAT cohort)

Patient Characteristics	all patients n=135	SAP n=67	IAT n=68	p-value
Type of underlying disease: No. (%)				0.061
Acute Leukemia	100 (74)	58 (87)	42 (63)	
Myelodysplastic syndromes	10 (7)	3 (5)	7 (10)	
Lymphomas	9 (7)	1 (1)	8 (12)	
Myeloproliferative neoplasms	12 (9)	3 (4)	9 (13)	
Aplastic Anemia	3 (2)	1 (1)	2 (3)	
Multiple myeloma	1 (1)	1 (1)	0 (0)	
Age at HSCT: median [range], y	56 [18-78]	56 [18-78]	55 [19-77]	0.143
Remission status at HSCT: No. (%)				0.117
Complete remission	79 (59)	44 (66)	35 (51)	
Active disease	56 (41)	23 (34)	33 (49)	
Myeloablative conditioning: No. (%)	66 (50)	40 (60)	26 (38)	0.025
Graft Type PBSC: No. (%)	111 (82)	56 (84)	55 (80)	0.822
Donor Type: No. (%)				0.178
MRD 10/10	23 (17)	16 (24)	7 (10)	
MUD 10/10	83 (61)	38 (57)	45 (66)	
MMUD (9/10 or 8/10)	11 (8)	4 (6)	7 (10)	
Haploidentical donor	18 (13)	9 (13)	9 (13)	
GvHD prophylaxis, including antithymocyte globulin (ATG): No. (%)	89 (66)	41 (61)	48 (71)	0.279
HCT-CI: No. (%)				0.032
0 (low risk)	15 (11)	10 (15)	5 (7)	
1-2 (intermediate risk)	58 (43)	33 (49)	25 (37)	
≥ 3 (high risk)	62 (45)	24 (35)	38 (56)	

Figure 1. Kaplan-Meier curve illustrates the tree years overall survival after allogeneic stem cell transplantation for patient with systemic antibiotic prophylaxis (SAP, solid line) versus patients with an interventional antibiotic treatment (AIT, dotted line)



Toenges et al. ASH 2022

Virustatika

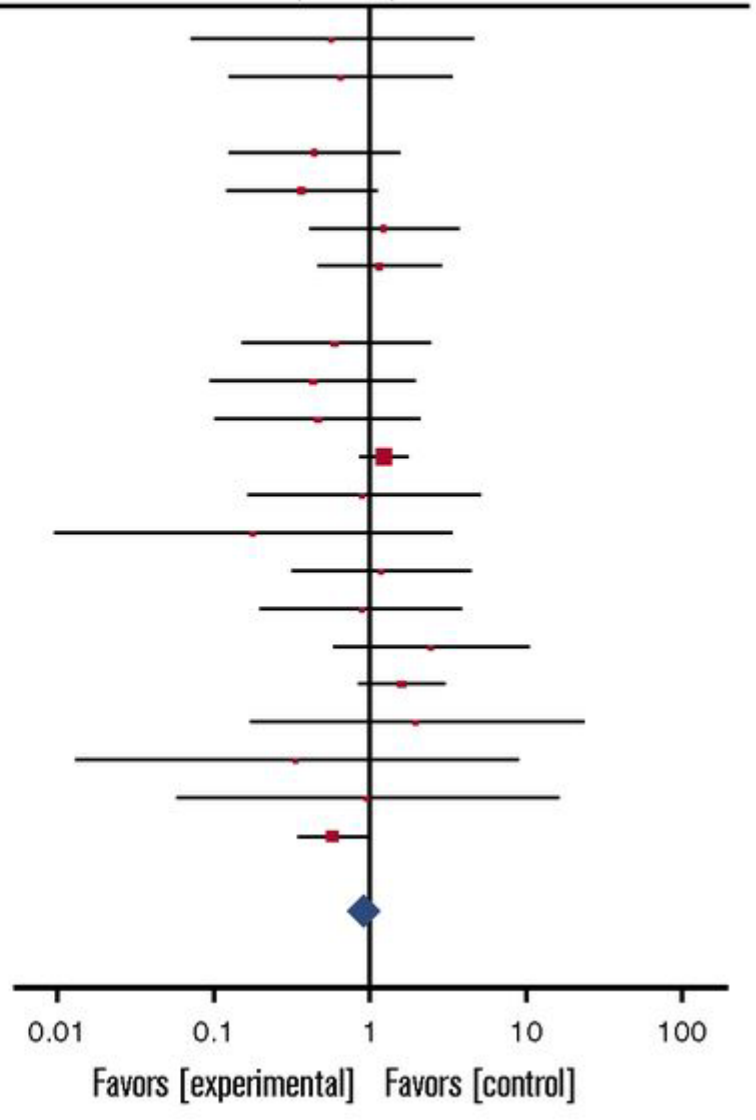
- Aciclovir für „365 Tage“
- CMV?

All Cause Mortality

A

Study or Subgroup	Prophylaxis Events	Prophylaxis Total	Placebo Events	Placebo Total	Odds Ratio M-H, Fixed, 95% CI
Saral 1981 - IV acyclovir 250 mg/m^2	7	10	8	10	0.58 [0.07, 4.56]
Gluckman 1983 - oral acyclovir 200 mg	3	20	4	19	0.66 [0.13, 3.45]
Hann 1983 - IV acyclovir 5 mg/kg	0	0	0	0	Not estimable
Ljungman 1986 - acyclovir 250 mg/m^2	10	22	13	20	0.45 [0.13, 1.56]
Boeckh 2006 - oral acyclovir 800 mg	6	38	13	39	0.38 [0.13, 1.12]
Goodrich 1993 - IV ganciclovir 6 mg/kg	10	33	8	31	1.25 [0.42, 3.74]
Winston 1993 - IV ganciclovir 5 mg/kg	14	40	14	45	1.19 [0.48, 2.95]
Boeckh 1996 - IV ganciclovir 5 mg/kg	0	0	0	0	Not estimable
Winston 2008 - oral maribavir 100 mg BID	4	28	6	28	0.61 [0.15, 2.46]
Winston 2008 - oral maribavir 400 mg daily	3	28	6	28	0.44 [0.10, 1.97]
Winston 2008 - oral maribaivr 400 mg BID	3	26	6	28	0.48 [0.11, 2.15]
Marty 2011 - oral maribavir 100 mg BID	139	454	59	227	1.26 [0.88, 1.80]
Marty 2013 - brincidofovir 40 mg weekly	2	25	5	59	0.94 [0.17, 5.20]
Marty 2013 - brincidofovir 100mg weekly	0	27	5	59	0.18 [0.01, 3.38]
Marty 2013 - brincidofovir 100mg twice weekly	5	50	5	59	1.20 [0.33, 4.41]
Marty 2013 - brincidofovir 200mg weekly	3	39	5	59	0.90 [0.20, 4.00]
Marty 2013 - brincidofovir 200mg twice weekly	4	21	5	59	2.54 [0.61, 10.55]
Marty 2016 - brincidofovir 100 mg twice weekly	47	303	15	149	1.64 [0.88, 3.04]
Chemaly 2014 - letermovir 60mg daily	2	33	1	33	2.06 [0.18, 23.94]
Chemaly 2014 - letermovir 120mg daily	0	31	1	33	0.34 [0.01, 8.76]
Chemaly 2014 - letermovir 240mg daily	1	34	1	33	0.97 [0.06, 16.17]
Marty 2017 - 480 mg letermovir daily	38	376	31	194	0.59 [0.36, 0.98]
Total (95% CI)		**1638**		**1212**	**0.96 [0.78, 1.18]**
Total events	301		211		

Heterogeneity: $Chi^2 = 19.86$, df = 19 (P = 0.40); $I^2 = 4\%$
Test for overall effect: Z = 0.37 (P = 0.71)



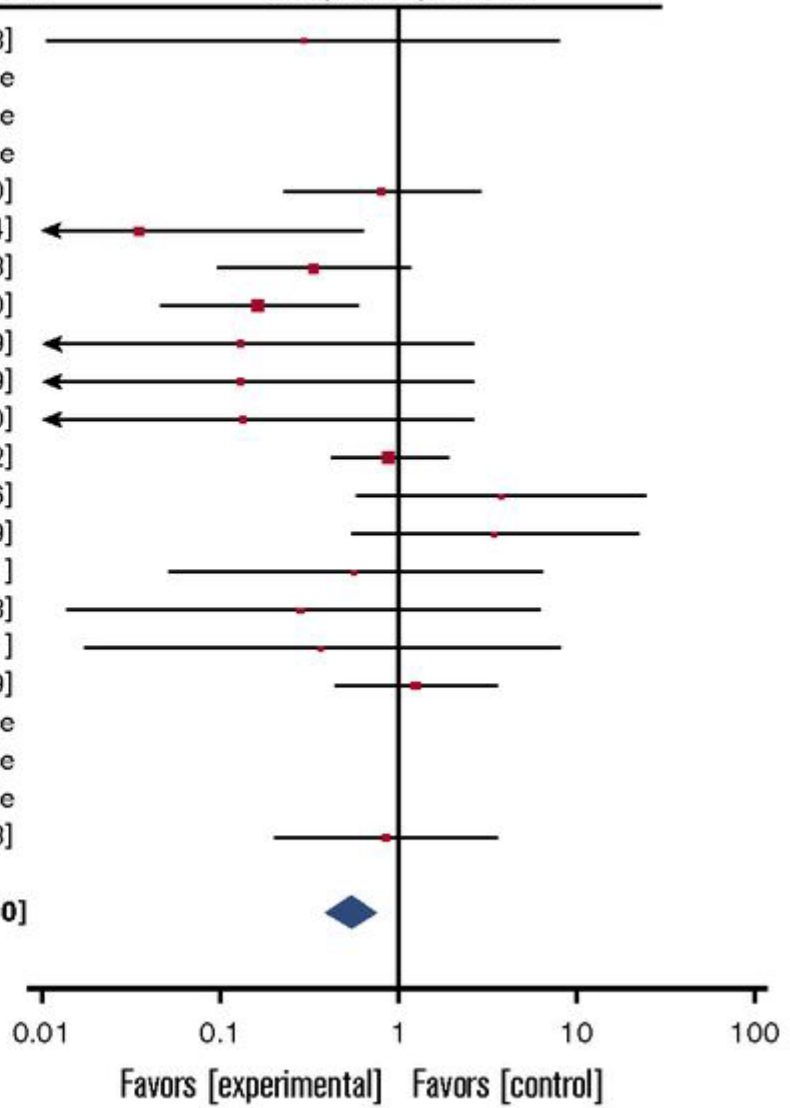
Chen et al. Blood 2018

CMV Disease

B

Study or Subgroup	Prophylaxis Events	Prophylaxis Total	Placebo Events	Placebo Total	Odds Ratio M-H, Fixed, 95% CI
Saral 1981 - IV acyclovir 250 mg/m^2	0	10	1	10	0.30 [0.01, 8.33]
Gluckman 1983 - oral acyclovir 200 mg	0	0	0	0	Not estimable
Hann 1983 - IV acyclovir 5 mg/kg	0	0	0	0	Not estimable
Ljungman 1986 - acyclovir 250 mg/m^2	0	0	0	0	Not estimable
Boeckh 2006 - oral acyclovir 800 mg	5	38	6	39	0.83 [0.23, 3.00]
Goodrich 1993 - IV ganciclovir 6 mg/kg	0	33	9	31	0.04 [0.00, 0.64]
Winston 1993 - IV ganciclovir 5 mg/kg	4	40	11	45	0.34 [0.10, 1.18]
Boeckh 1996 - IV ganciclovir 5 mg/kg	3	112	16	114	0.17 [0.05, 0.60]
Winston 2008 - oral maribavir 100 mg BID	0	27	3	28	0.13 [0.01, 2.69]
Winston 2008 - oral maribavir 400 mg daily	0	27	3	28	0.13 [0.01, 2.69]
Winston 2008 - oral maribaivr 400 mg BID	0	26	3	28	0.14 [0.01, 2.80]
Marty 2011 - oral maribavir 100 mg BID	20	454	11	227	0.90 [0.43, 1.92]
Marty 2013 - brincidofovir 40 mg weekly	3	25	2	59	3.89 [0.61, 24.86]
Marty 2013 - brincidofovir 100mg weekly	3	27	2	59	3.56 [0.56, 22.69]
Marty 2013 - brincidofovir 100mg twice weekly	1	50	2	59	0.58 [0.05, 6.61]
Marty 2013 - brincidofovir 200mg weekly	0	39	2	59	0.29 [0.01, 6.23]
Marty 2013 - brincidofovir 200mg twice weekly	0	30	2	59	0.38 [0.02, 8.11]
Marty 2016 - brincidofovir 100 mg twice weekly	13	303	5	149	1.29 [0.45, 3.69]
Chemaly 2014 - letermovir 60mg daily	0	33	0	33	Not estimable
Chemaly 2014 - letermovir 120mg daily	0	31	0	33	Not estimable
Chemaly 2014 - letermovir 240mg daily	0	34	0	33	Not estimable
Marty 2017 - 480 mg letermovir daily	5	325	3	170	0.87 [0.21, 3.68]
Total (95% CI)		**1664**		**1263**	**0.56 [0.40, 0.80]**
Total events	57		81		

Heterogeneity: $Chi^2 = 23.21$, df = 15 (P = 0.08); $I^2 = 35\%$
Test for overall effect: Z = 3.18 (P = 0.001)



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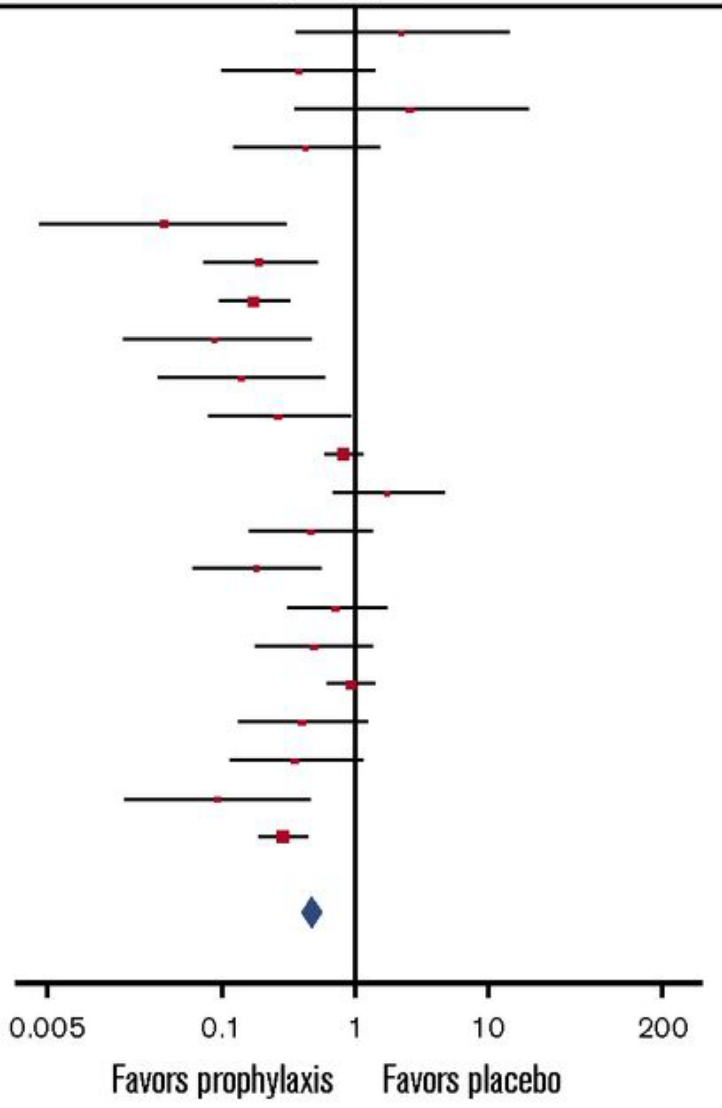
CMV Reactivation

C

Study or Subgroup	Prophylaxis Events	Prophylaxis Total	Placebo Events	Placebo Total	Odds Ratio M-H, Fixed, 95% CI
Saral 1981 - IV acyclovir 250 mg/m^2	5	10	3	10	2.33 [0.37, 14.61]
Gluckman 1983 - oral acyclovir 200 mg	7	20	11	19	0.39 [0.11, 1.43]
Hann 1983 - IV acyclovir 5 mg/kg	4	10	2	10	2.67 [0.36, 19.71]
Ljungman 1986 - acyclovir 250 mg/m^2	10	22	13	20	0.45 [0.13, 1.56]
Boeckh 2006 - oral acyclovir 800 mg	0	0	0	0	Not estimable
Goodrich 1993 - IV ganciclovir 6 mg/kg	1	33	14	31	0.04 [0.00, 0.31]
Winston 1993 - IV ganciclovir 5 mg/kg	8	40	25	45	0.20 [0.08, 0.53]
Boeckh 1996 - IV ganciclovir 5 mg/kg	46	114	90	114	0.18 [0.10, 0.32]
Winston 2008 - oral maribavir 100 mg BID	2	27	13	28	0.09 [0.02, 0.47]
Winston 2008 - oral maribavir 400 mg daily	3	27	13	28	0.14 [0.04, 0.59]
Winston 2008 - oral maribaivr 400 mg BID	5	26	13	28	0.27 [0.08, 0.94]
Marty 2011 - oral maribavir 100 mg BID	183	454	101	227	0.84 [0.61, 1.16]
Marty 2013 - brincidofovir 40 mg weekly	13	25	22	59	1.82 [0.71, 4.69]
Marty 2013 - brincidofovir 100mg weekly	6	27	22	59	0.48 [0.17, 1.37]
Marty 2013 - brincidofovir 100mg twice weekly	5	50	22	59	0.19 [0.06, 0.54]
Marty 2013 - brincidofovir 200mg weekly	12	39	22	59	0.75 [0.32, 1.77]
Marty 2013 - brincidofovir 200mg twice weekly	7	30	22	59	0.51 [0.19, 1.39]
Marty 2016 - brincidofovir 100 mg twice weekly	155	303	78	149	0.95 [0.64, 1.41]
Chemaly 2014 - letermovir 60mg daily	7	33	13	33	0.41 [0.14, 1.23]
Chemaly 2014 - letermovir 120mg daily	6	31	13	33	0.37 [0.12, 1.15]
Chemaly 2014 - letermovir 240mg daily	2	34	13	33	0.10 [0.02, 0.47]
Marty 2017 - 480 mg letermovir daily	57	325	71	170	0.30 [0.20, 0.45]
Total (95% CI)		**1680**		**1273**	**0.49 [0.42, 0.58]**
Total events	544		596		

Heterogeneity: $Chi^2 = 76.82$, $df = 20$ ($P < 0.00001$); $I^2 = 74\%$
Test for overall effect: $Z = 8.73$ ($P < 0.00001$)



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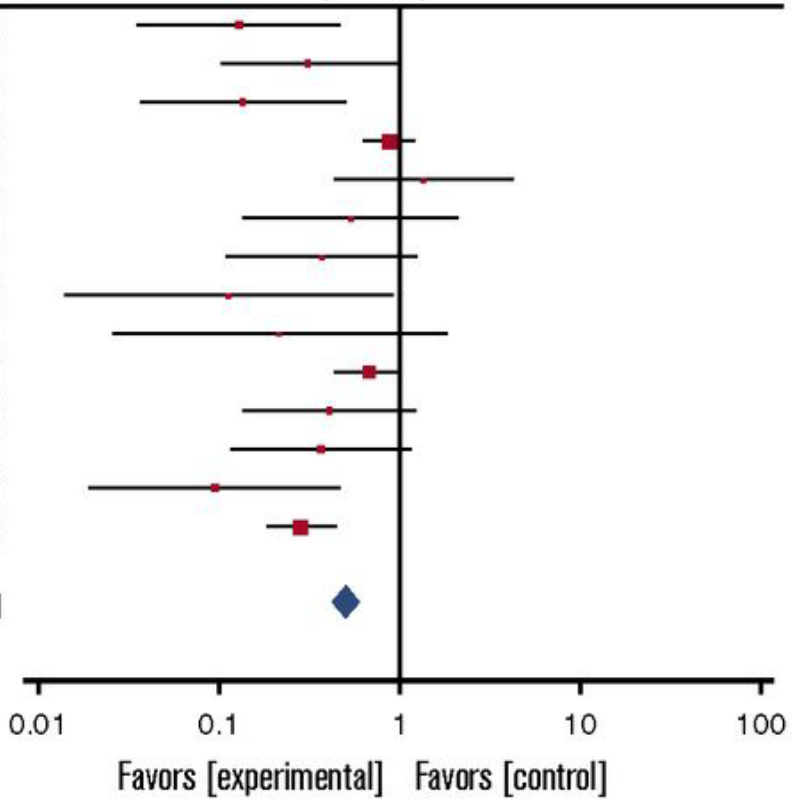
Preemptive Therapy

D

Study or Subgroup	Prophylaxis Events	Prophylaxis Total	Placebo Events	Placebo Total	Odds Ratio M-H, Fixed, 95% CI
Winston 2008 - oral maribavir 100 mg BID	4	27	16	28	0.13 [0.04, 0.48]
Winston 2008 - oral maribavir 400 mg daily	8	27	16	28	0.32 [0.10, 0.96]
Winston 2008 - oral maribavir 400 mg BID	4	26	16	28	0.14 [0.04, 0.50]
Marty 2011 - oral maribavir 100 mg BID	172	454	92	227	0.90 [0.65, 1.24]
Marty 2013 - brincidofovir 40 mg weekly	6	25	11	59	1.38 [0.45, 4.26]
Marty 2013 - brincidofovir 100mg weekly	3	27	11	59	0.55 [0.14, 2.14]
Marty 2013 - brincidofovir 100mg twice weekly	4	50	11	59	0.38 [0.11, 1.28]
Marty 2013 - brincidofovir 200mg weekly	1	39	11	59	0.11 [0.01, 0.93]
Marty 2013 - brincidofovir 200mg twice weekly	1	21	11	59	0.22 [0.03, 1.80]
Marty 2016 - brincidofovir 100 mg twice weekly	88	303	56	149	0.68 [0.45, 1.03]
Chemaly 2014 - letermovir 60mg daily	7	33	13	33	0.41 [0.14, 1.23]
Chemaly 2014 - letermovir 120mg daily	6	31	13	33	0.37 [0.12, 1.15]
Chemaly 2014 - letermovir 240mg daily	2	34	13	33	0.10 [0.02, 0.47]
Marty 2017 - 480 mg letermovir daily	52	325	68	170	0.29 [0.19, 0.44]
Total (95% CI)		**1422**		**1024**	**0.51 [0.42, 0.62]**
Total events	358		358		

Heterogeneity: $Chi^2 = 39.73$, $df = 13$ ($P = 0.0002$); $I^2 = 67\%$

Test for overall effect: $Z = 7.08$ ($P < 0.00001$)



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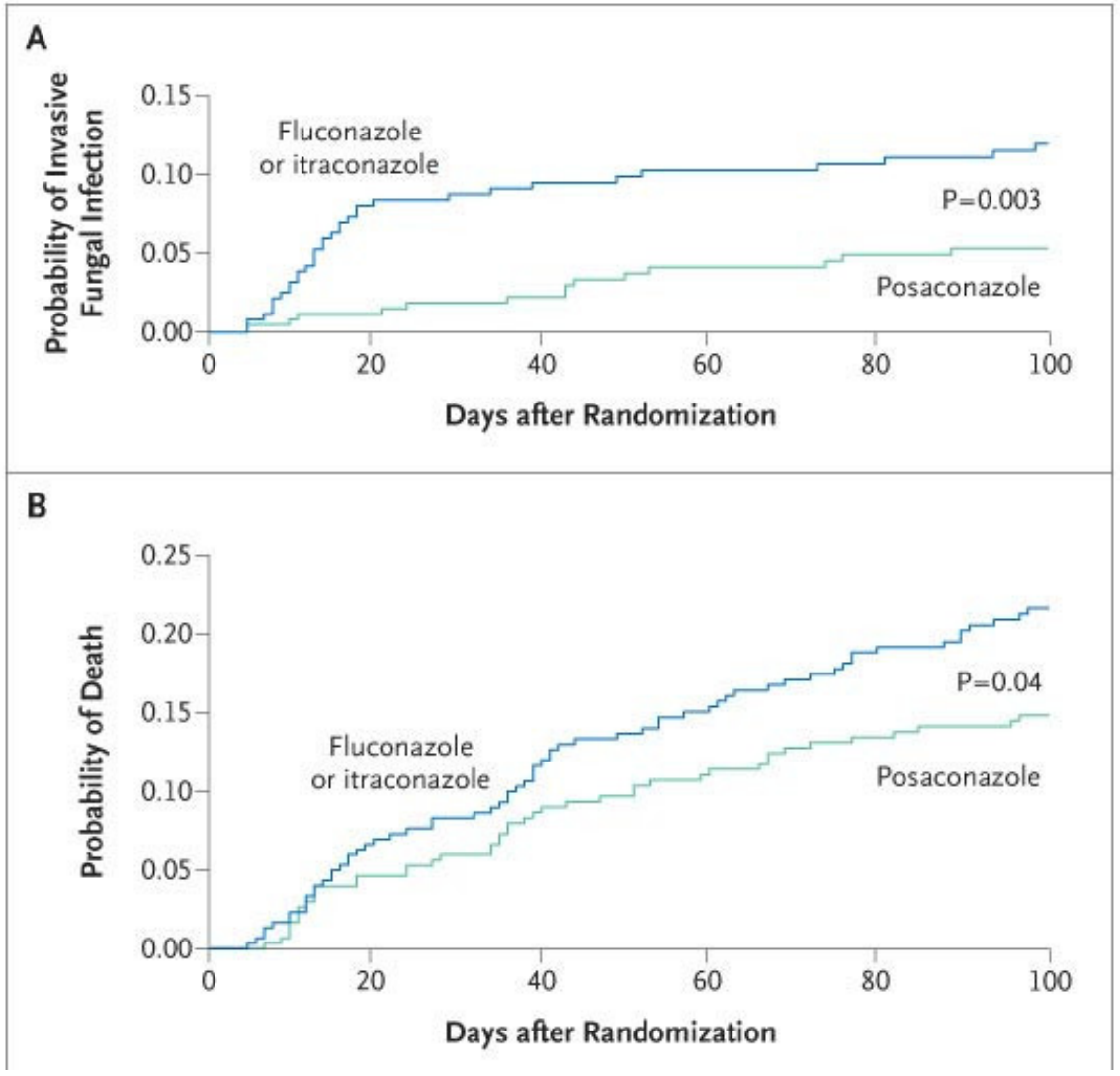
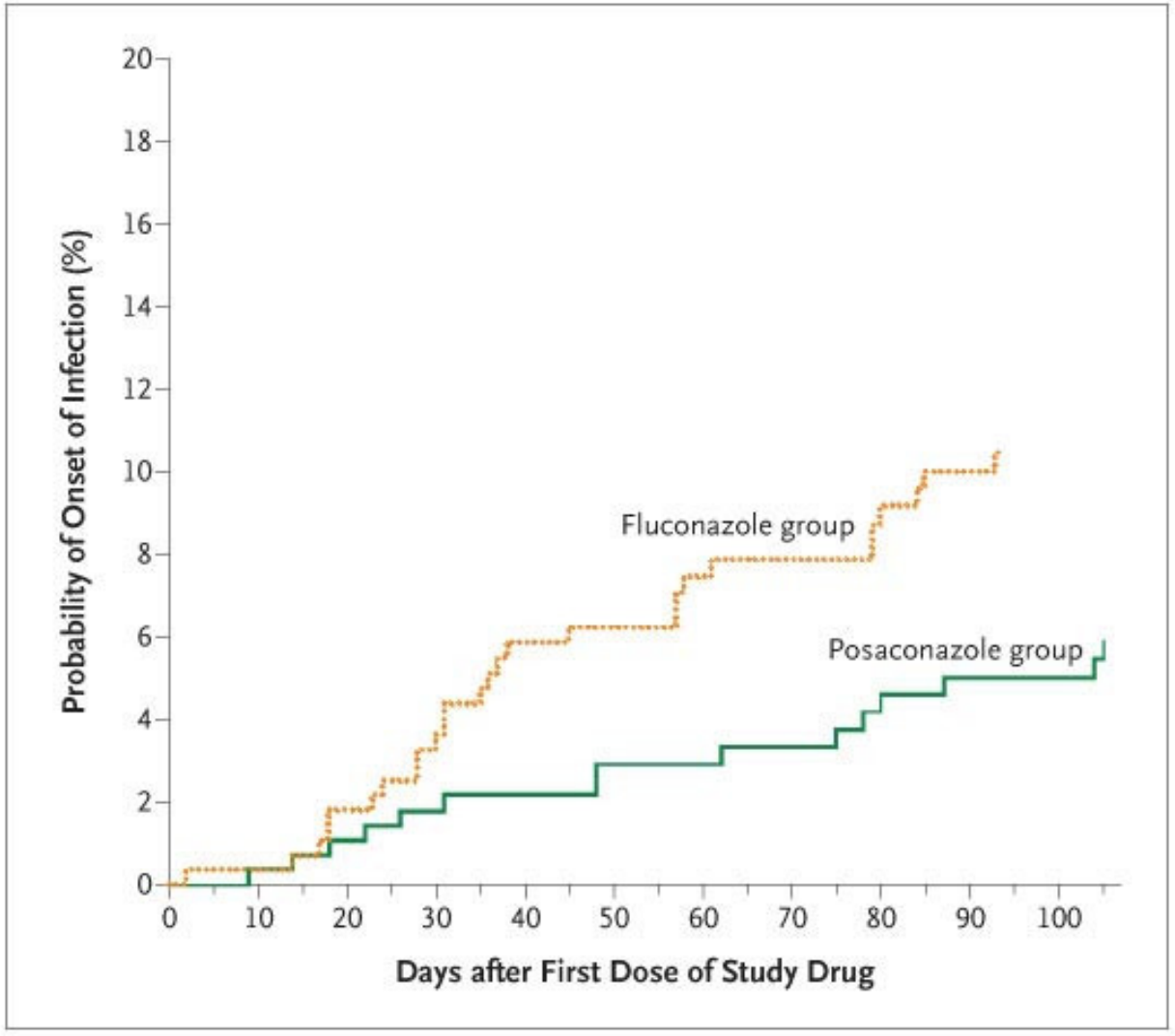
Letermovir

- Zulassung Prophylaxe Erwachsene seropositive Empfänger einer allogenen Stammzelltransplantation
- Zulassung Tag 0 (spätestens Tag 28) bis Tag 100, bei hohem Risiko länger
- Dosierung 240 mg bei Immunsuppression mit Ciclosporin A, 480 mg sonst

Aspergilluswirksame Antimykose prolongierte Neutropenie/ schwere GvHD





Cornely OA et al NEJM 2007
Ullmann AJ et al. NEJM 2007

Antimykotische Prophylaxe gegen Aspergillus und gegen Candida

empfohlen

Zusammenfassung

- Lokale Gegebenheiten respektieren
- Surveillance
- Antibiotische Prophylaxe
- Prophylaxe mit Aciclovir und Letermovir
- Aspergilluswirksame antimykotische Prophylaxe
- Pneumocystisprophylaxe mit Cotrimoxazol oder Pentamidin oder Atovaquon

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