Journal club

Kristina Nadrah

seminar KIBVS

Stress related disorders and subsequent risk of life threatening infections: population based sibling controlled cohort study

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BMJ 2019;367:l5784

- Psihološki stres bi lahko vplival na zvečano dovzetnost za okužbe zaradi zmanjšanja imunosti
- Eksperimentalne študije na ljudeh in živalih pokazale, da morda obstaja povezava med akutnimi okužbami dihal in psihološkim stresom

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- Švedska kohortna študija – populacija in sorojenci 1987-2013
- 144 919 oseb s stresnimi obolenji (PTSD, akutna stresna reakcija, prilagoditvena motnja, drugo) in 184 612 kontrol
- Izključili tiste s stresno dg pred 5.letom, z ogrožajočo infekcijo pred stresno dg
- Okužbe z visoko smrtnostjo: npr. sepsa, IE, okužbe CŽS

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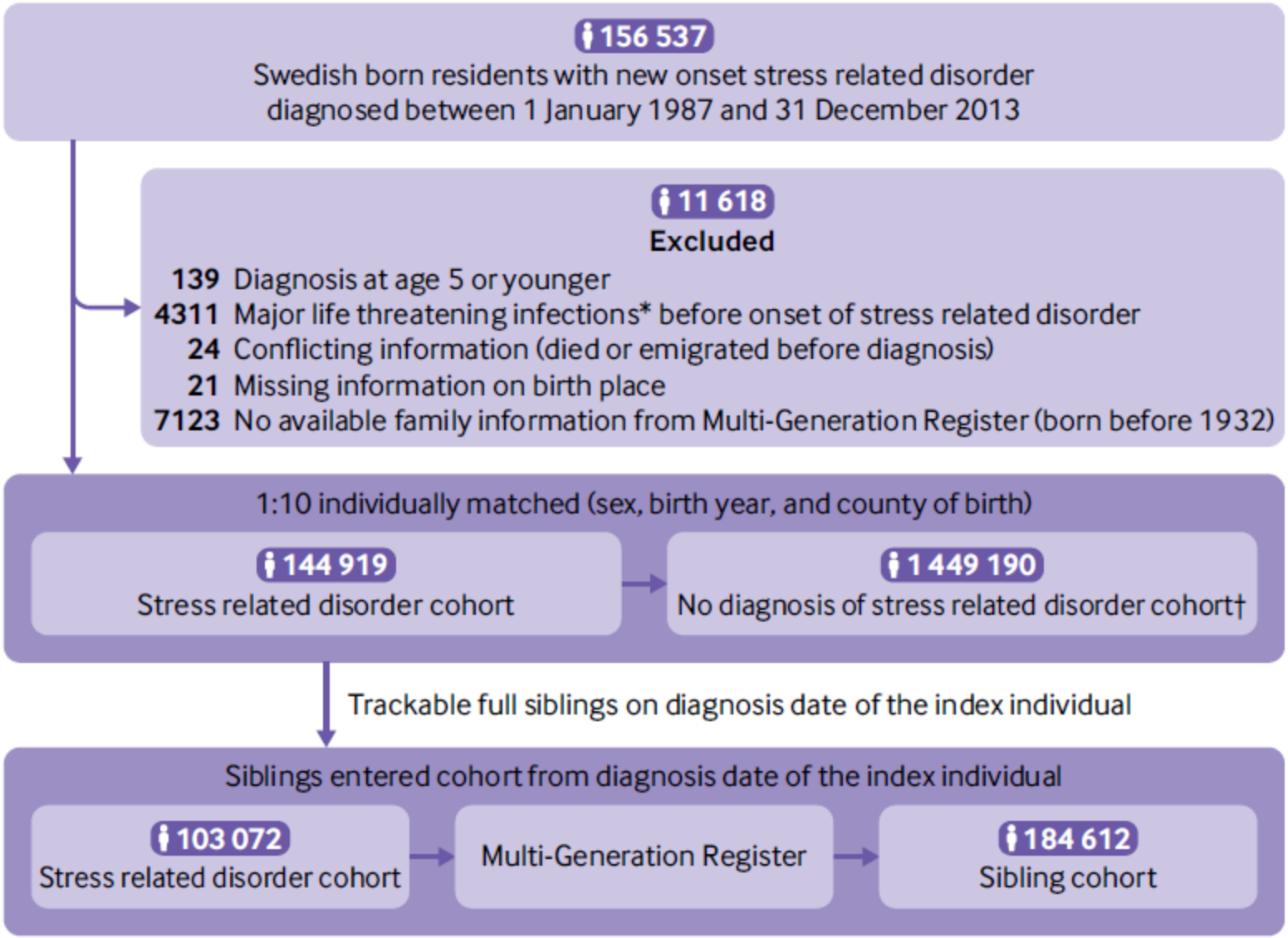

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- V povprečju stari 37 let ob diagnozi stresa (38,3%M)
- HR 1,47 (kateri koli stres), PTSD HR 1,92
- Največji riziko za meningitis HR 1,63 (vs. sorojenci)
- Uporaba SSRI je zmanjšala riziko
- Uporaba nedovoljenih substanc in stresnega obolenja zvečala riziko

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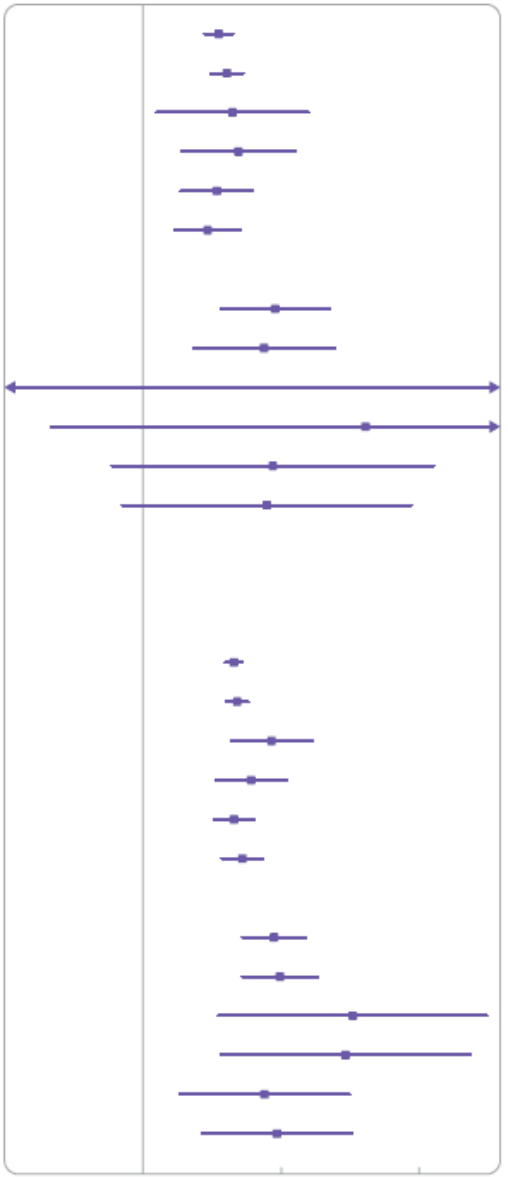
	No of cases (incidence rate per 1000 person years)	Hazard ratio (95% CI)
Sibling based analysis	**Exposed/sibling group**	
Any stress related disorder		
Life threatening infections	2197(2.7)/2646(1.69)	1.47 (1.37 to 1.58)
Sepsis	1384(1.7)/1651(1.05)	1.52 (1.39 to 1.66)
Endocarditis	103(0.12)/105(0.07)	1.57 (1.08 to 2.30)
Meningitis	120(0.15)/142(0.09)	1.63 (1.23 to 2.16)
Other CNS infections	296(0.36)/358(0.23)	1.45 (1.21 to 1.73)
Death due to other infections	445(0.54)/551(0.35)	1.39 (1.16 to 1.65)
Post-traumatic stress disorder		
Life threatening infections	170(2.94)/175(1.59)	1.92 (1.46 to 2.52)
Sepsis	111(1.91)/110(1)	1.84 (1.30 to 2.61)
Endocarditis	10(0.17)/8(0.07)	5.38 (0.46 to 62.9)
Meningitis	11(0.14)/8(0.07)	3.03 (0.63 to 14.6)
Other CNS infections	22(0.37)/27(0.24)	1.90 (0.85 to 4.24)
Death due to other infections	30(0.51)/36(0.33)	1.85 (0.89 to 3.83)
Population based analysis	**Exposed/unexposed group**	
Any stress related disorder		
Life threatening infections	3292(2.9)/15 684(1.34)	1.58 (1.51 to 1.65)
Sepsis	2044(1.8)/96 24(0.82)	1.61 (1.52 to 1.70)
Endocarditis	158(0.14)/591(0.05)	1.89 (1.55 to 2.32)
Meningitis	181(0.16)/962(0.08)	1.70 (1.43 to 2.02)
Other CNS infections	429(0.38)/2531(0.22)	1.58 (1.41 to 1.76)
Death due to other infections	711(0.62)/2769(0.24)	1.64 (1.48 to 1.81)
Post-traumatic stress disorder		
Life threatening infections	244(3.04)/1041(1.26)	1.95 (1.66 to 2.28)
Sepsis	156(1.94)/631(0.76)	2.01 (1.65 to 2.45)
Endocarditis	15(0.19)/40(0.05)	2.90 (1.46 to 5.76)
Meningitis	17(0.21)/58(0.07)	2.80 (1.49 to 5.26)
Other CNS infections	34(0.42)/169(0.2)	1.88 (1.23 to 2.87)
Death due to other infections	45(0.55)/196(0.24)	1.99 (1.37 to 2.90)



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PSYCHOLOGICAL STRESS AND SUSCEPTIBILITY TO THE COMMON COLD

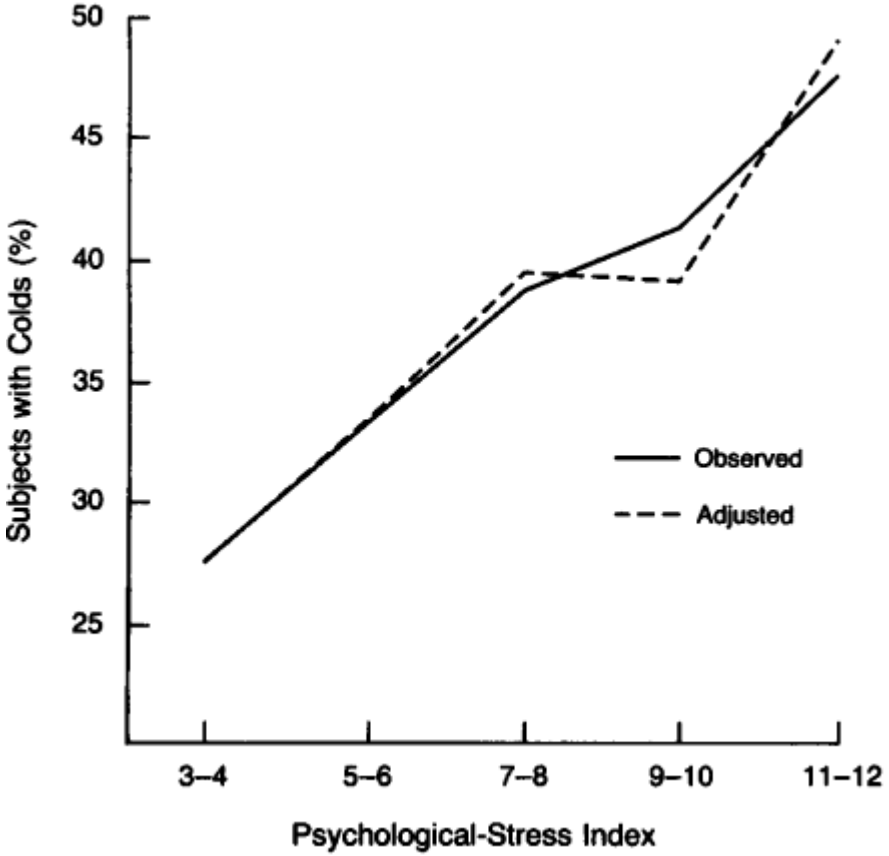
SHELDON COHEN, PH.D., DAVID A.J. TYRRELL, M.D., AND ANDREW P. SMITH, PH.D.

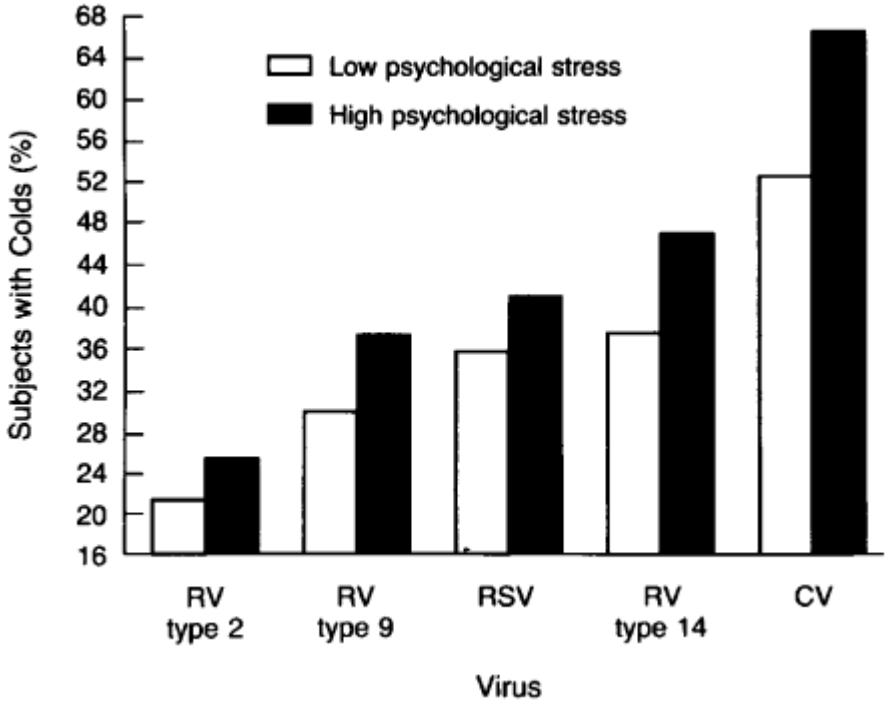
Abstract *Background.* It is not known whether psychological stress suppresses host resistance to infection. To investigate this issue, we prospectively studied the relation between psychological stress and the frequency of ... to levels of psychological stress, and the incidence of clinical colds ranged from approximately 27 percent to 47 percent. These effects were not altered when we controlled for age, sex, education, allergic status, weight

- 394 zdravih prostovoljcev izpolnilo vprašalnik o stresu in dobilo nosne kapljice z rinovirusi, RSV ali koronavirusom)
- 26 kontrol (FR)

- Število okužb dihal/prehladov se je povečalo v odvisnosti od velikosti psihološkega stresa
- Neodvisno od drugih dejavnikov (starost, spol, izobrazba, alergije, teža, letni čas, Pt proti virusom pred okužbo, tip virusa)

NEJM 1991, 325:606





NEJM 1991, 325:606

Vpliv stresa na odziv na cepljenje

- metaanaliza 13 študij, ki so preučevale vpliv stresa na odziv na cepljenje proti gripi
- 1158 pt
- stres je negativno vplival na odgovor na cepljenje

Brain, Behavior, and Immunity 23 (2009) 427–433

Vpliv stresa na odziv na cepljenje

Associations (ESR) between antibody levels and various types of stressors following influenza vaccination.

Stressor	Sample size		Heterogeneity[a]			Global effect sizes			Fail-safe *N*
	k	*n*	*Q*	df	*p*	ESR[b]	95% CI	*p*	
Chronic stress	6 (5) e	493	6.81	5	0.24	−0.18[c]	(−0.28 to −0.08)	0.001	13
Life events	6 (5) e	514	8.97	3	0.03	−0.18[d]	(−0.27 to −0.09)	0.0001	19
Perceived stress	3	151	9.21	2	0.01	−0.18[d]	(−0.33 to − 0.02)	0.02	0
Between groups[e]			0.13	2	0.94				

[a] *p*-Values of 0.1 or less were taken to suggest heterogeneity.
[b] A negative effect size correlation (ESR) indicates an effect size in the hypothesized direction, i.e. stress associated with lower level of antibodies.
[c] Fixed effects.
[d] Random effects.
[e] To assure independence, results for chronic stress in Glaser et al. (1998) and life events in Burns et al. (2003) were excluded in the between-groups analysis.

Associations (ESR) between stress and antibody response following vaccination—results for subtypes A/H1N1, A/H3N2, and B.

Subtype	Sample size		Heterogeneity[a]			Global effect sizes			Fail-safe *N*
	k	*n*	*Q*	df	*p*	ESR[b]	95% CI	*p*	
Old (overall ES)	6	568	0.9	5	0.97	−0.25[c]	(−0.34 to − 0.15)	0.0001	32
Younger (overall ES)	6	466	8.7	5	0.12	−0.17[c]	(−0.27 to −0.07)	0.001	8

ESR: effect size correlation.
[a] *p*-Values of 0.1 or less were taken to suggest heterogeneity.
[b] A negative effect size correlation (ESR) indicates an effect size in the hypothesized direction, i.e. stress associated with lower level of antibodies.
[c] Fixed effects.

Brain, Behavior, and Immunity 23 (2009) 427–433

SCIENCE IMMUNOLOGY | REPORT

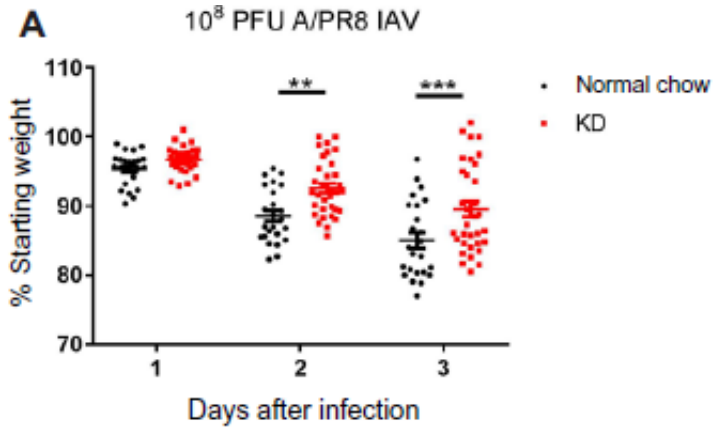
INFECTIOUS DISEASE

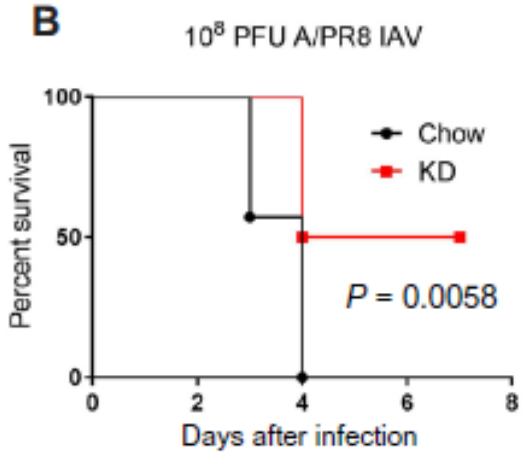
Ketogenic diet activates protective γδ T cell responses against influenza virus infection

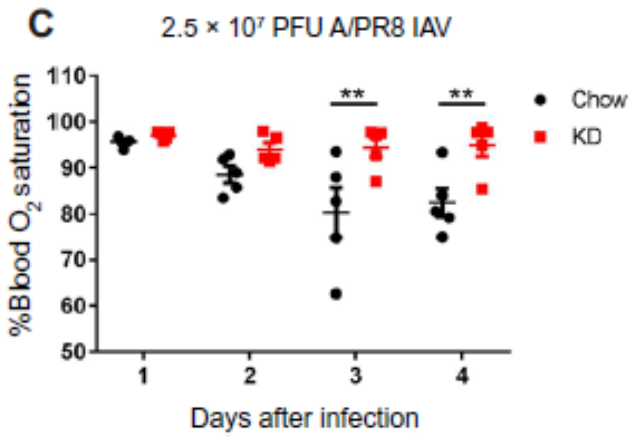
Emily L. Goldberg[1,2], Ryan D. Molony[2,3], Eriko Kudo[2], Sviatoslav Sidorov[1], Yong Kong[4], Vishwa Deep Dixit[1,2,5]*, Akiko Iwasaki[2,6,7]*

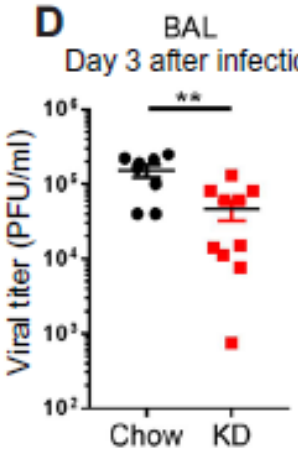
Influenza A virus (IAV) infection–associated morbidity and mortality are a key global health care concern, necessitating the identification of new therapies capable of reducing the severity of IAV infections. In this study, we show that the consumption of a low-carbohydrate, high-fat ketogenic diet (KD) protects mice from lethal IAV infection and disease. KD feeding resulted in an expansion of γδ T cells in the lung that improved barrier functions, thereby enhancing antiviral resistance. Expansion of these protective γδ T cells required metabolic adaptation to a ketogenic diet because neither feeding mice a high-fat, high-carbohydrate diet nor providing chemical ketone body substrate that bypasses hepatic ketogenesis protected against infection. Therefore, KD-mediated immune-metabolic integration represents a viable avenue toward preventing or alleviating influenza disease.

Ketogena dieta je miši zaščitila

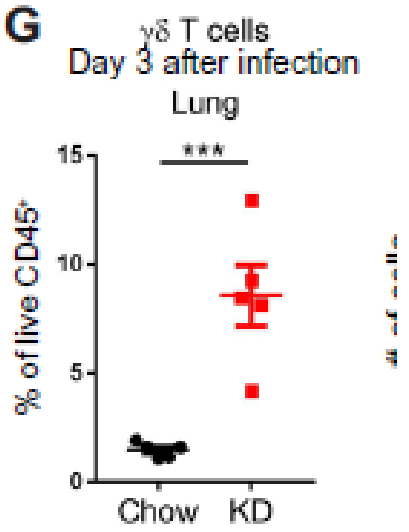


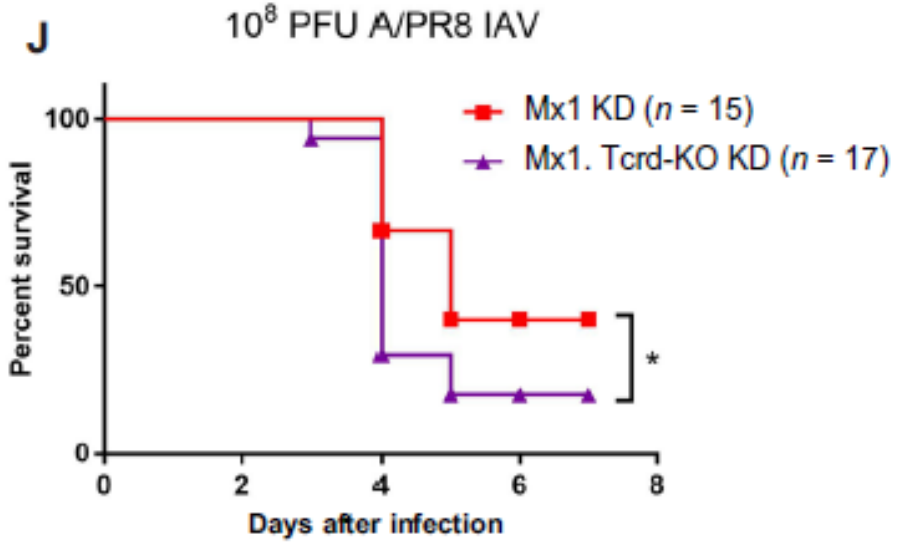




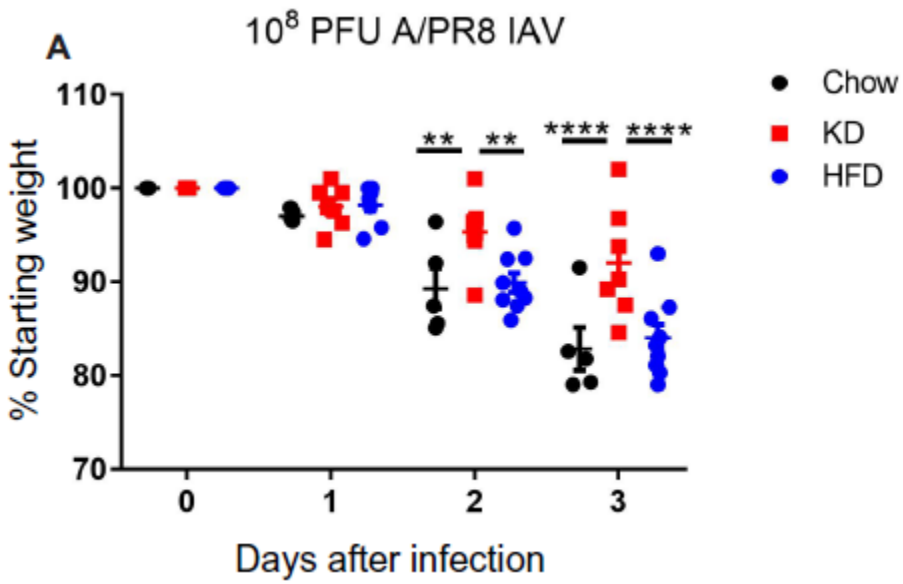


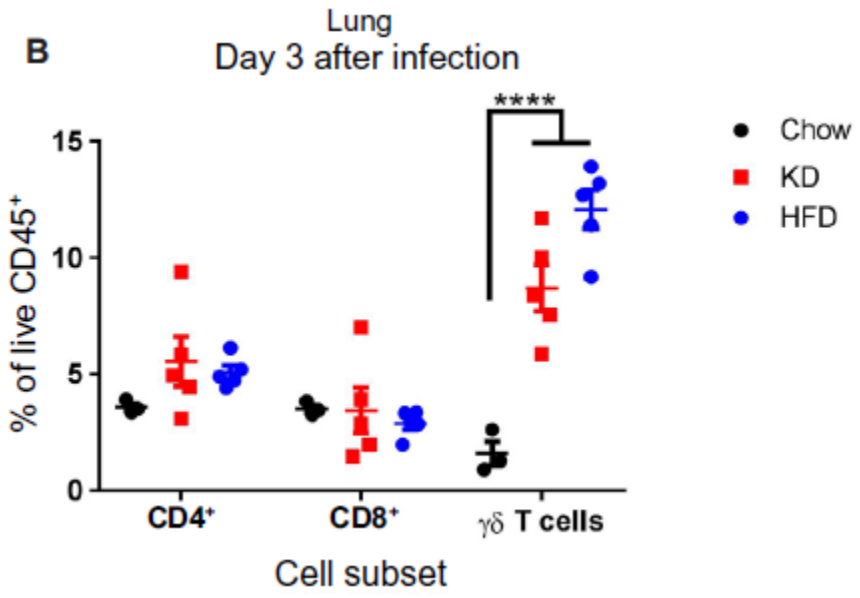
Zaščito posredujejo Tγδ IL-17 kompetentne celice





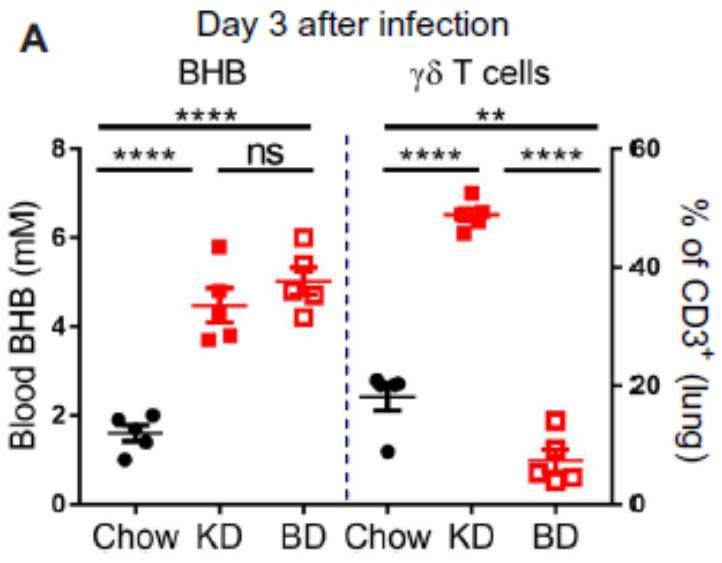
Ketogena ali le kalorična hrana?

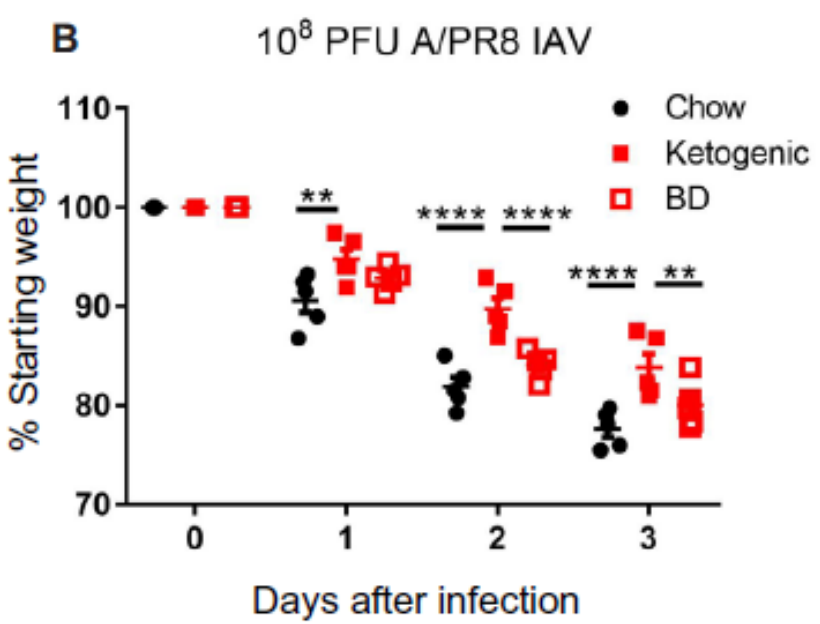




Beta-hidroksibutirat!

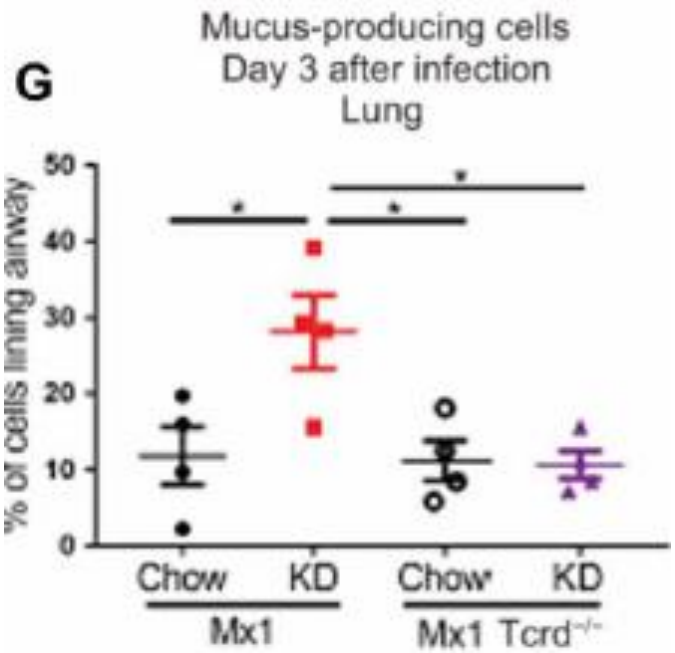
Pomembna je metabolna adaptacija

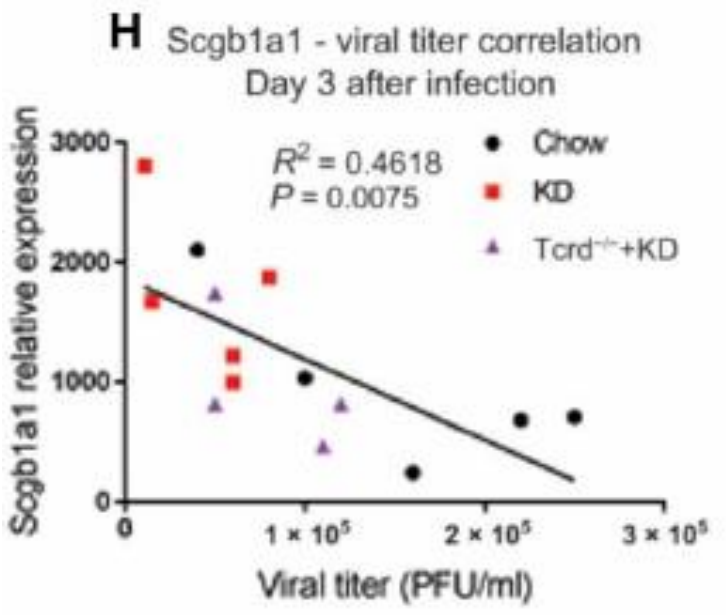




Premik oksidaciji maščobnih kislin

Boljša funkcija sekretornih celic





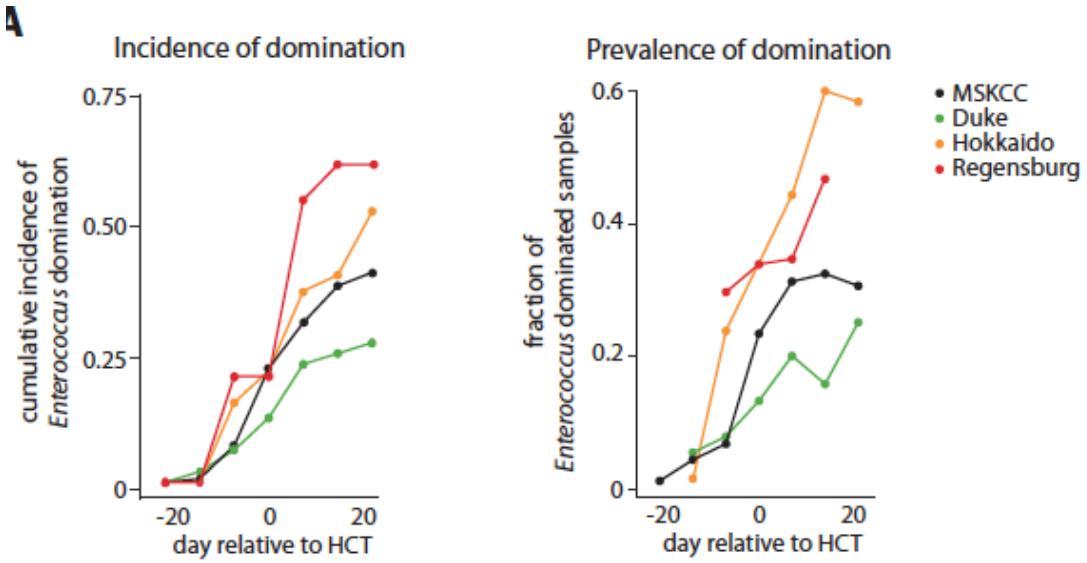
Zaključki študije

- ketogena dieta je miši zaščitila pred smrtno okužbo z infuenco A preko Tγδ IL-17 kompetentnih celic
- Proces je odvisen od metabolnega preklopa k oksidaciji maščobnih kislin
- V pljučih povišanje oksidativnega metabolizma in izboljšano redoks ravnotežje
- Hipoteza, da Tγδ modulirajo funkcijo in diferenciacijo epitelnih celic in s tem izboljšajo bariero pljuč

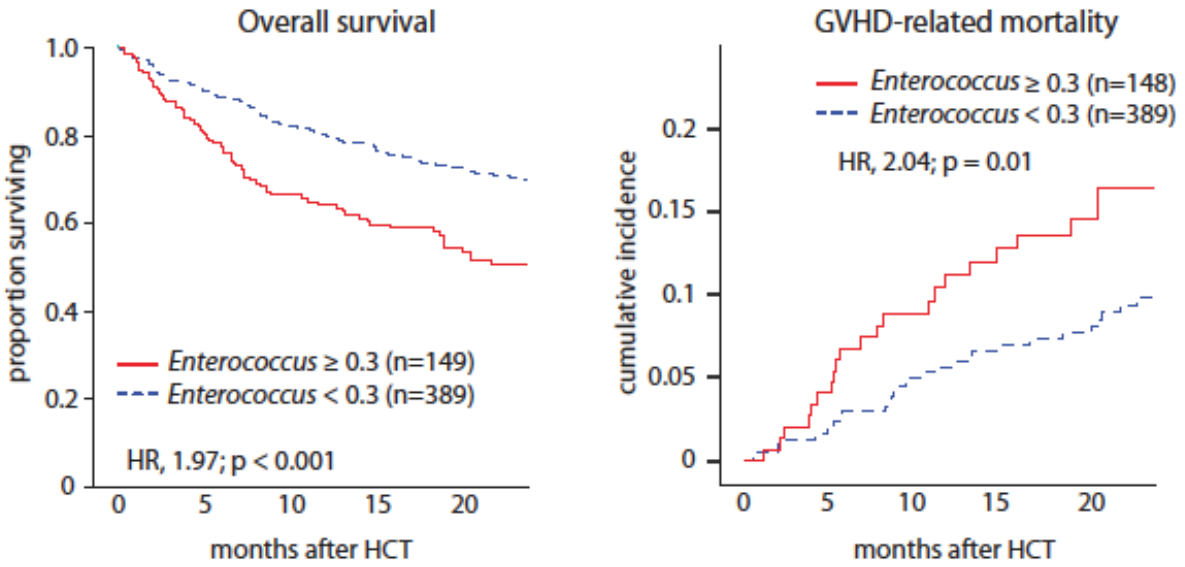
MICROBIOME

Lactose drives *Enterococcus* expansion to promote graft-versus-host disease

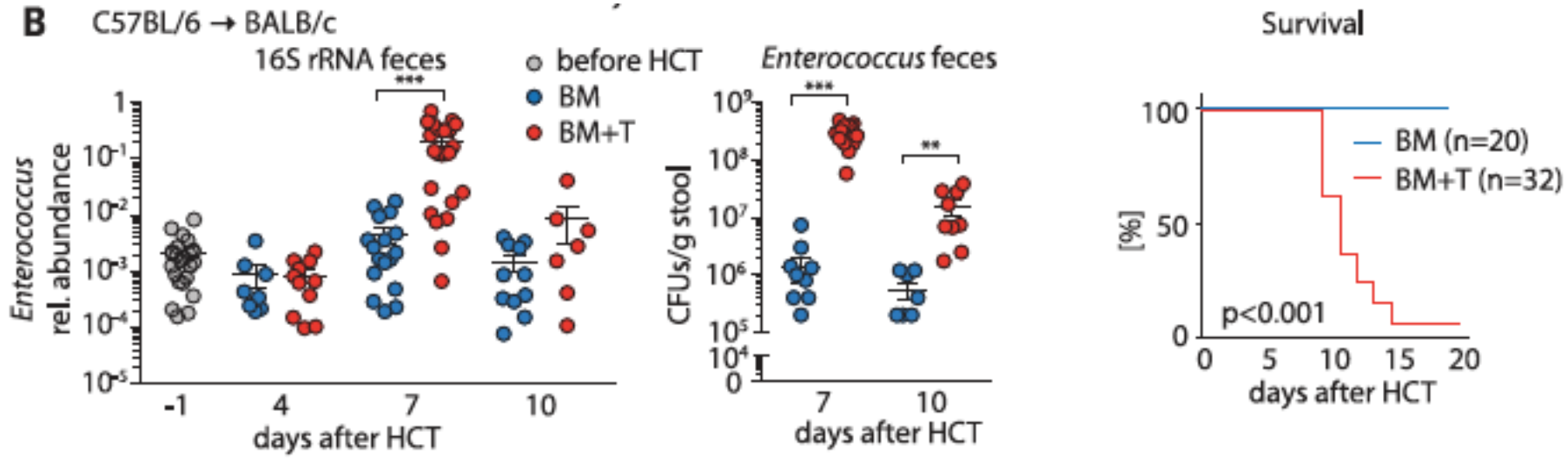
C. K. Stein-Thoeringer[1,2,3], K. B. Nichols[1,2], A. Lazrak[1,2], M. D. Docampo[1,2], A. E. Slingerland[1,2], J. B. Slingerland[1,2], A. G. Clurman[4], G. Armijo[1,2], A. L. C. Gomes[1,2], Y. Shono[1,2], A. Staffas[1,2], M. Burgos da Silva[1,2], S. M. Devlin[5], K. A. Markey[1,2,4], D. Bajic[6], R. Pinedo[7], A. Tsakmaklis[8,9], E. R. Littmann[1,10], A. Pastore[1], Y. Taur[11], S. Monette[12], M. E. Arcila[13], A. J. Pickard[14], M. Maloy[4], R. J. Wright[1], L. A. Amoretti[1], E. Fontana[1], D. Pham[15], M. A. Jamal[15], D. Weber[16], A. D. Sung[17], D. Hashimoto[18], C. Scheid[8], J. B. Xavier[19], J. A. Messina[20], K. Romero[21], M. Lew[17], A. Bush[17], L. Bohannon[17], K. Hayasaka[22], Y. Hasegawa[18], M. J. G. T. Vehreschild[8,9,23], J. R. Cross[14], D. M. Ponce[2,4], M. A. Perales[2,4], S. A. Giralt[2,4], R. R. Jenq[15], T. Teshima[18,22], E. Holler[16], N. J. Chao[17], E. G. Pamer[1,2,10], J. U. Peled[1,2,4]*†, M. R. M. van den Brink[1,2,4]*†



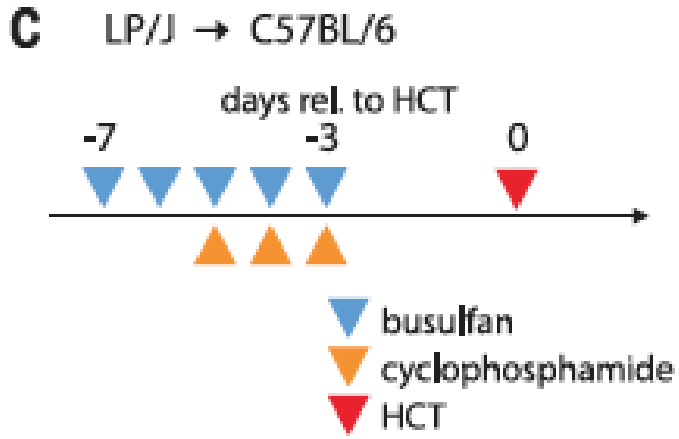
razrast enterokokov po PKMC

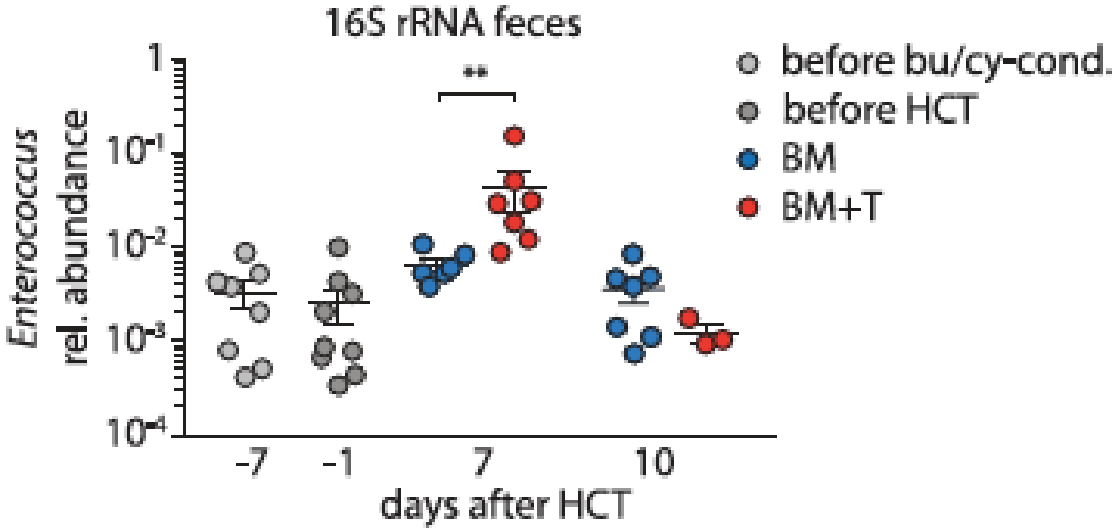


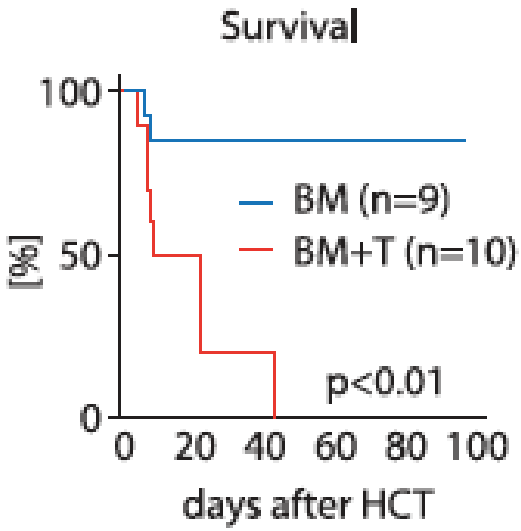
Razrast enterokokov pri GVHD



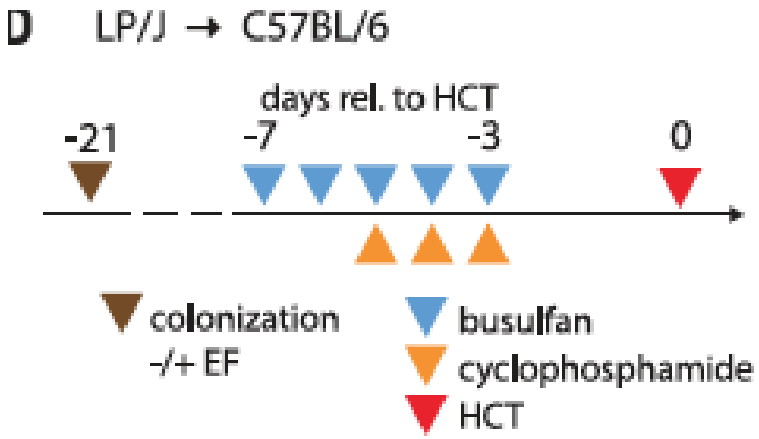
Enterokoki vs. GVHD

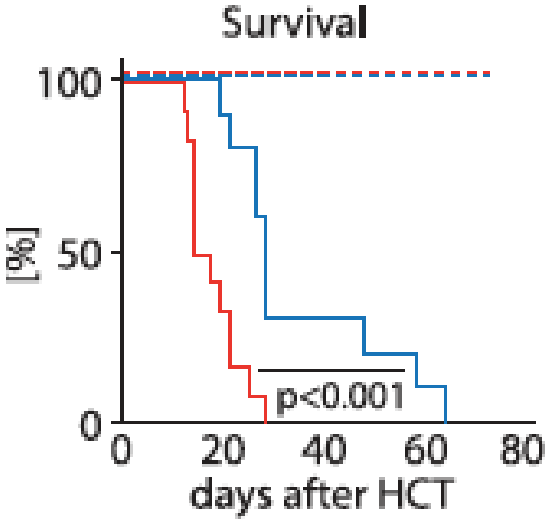




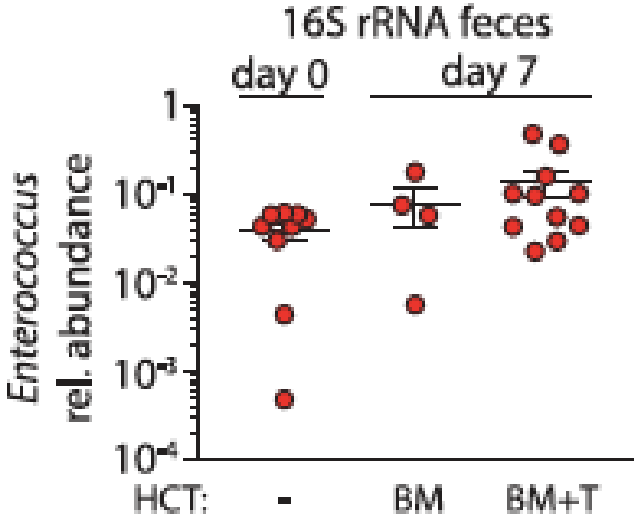


Enterokoki vs. GVHD

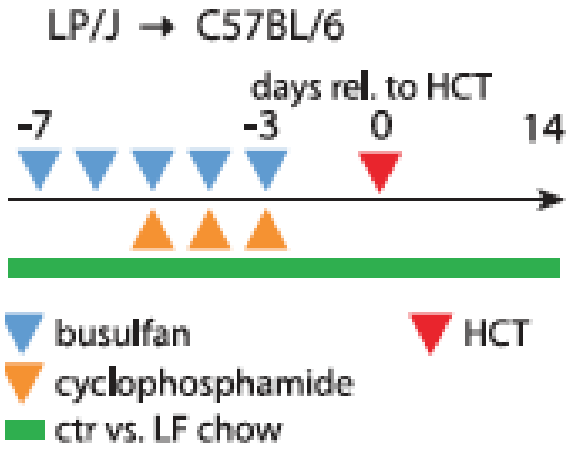


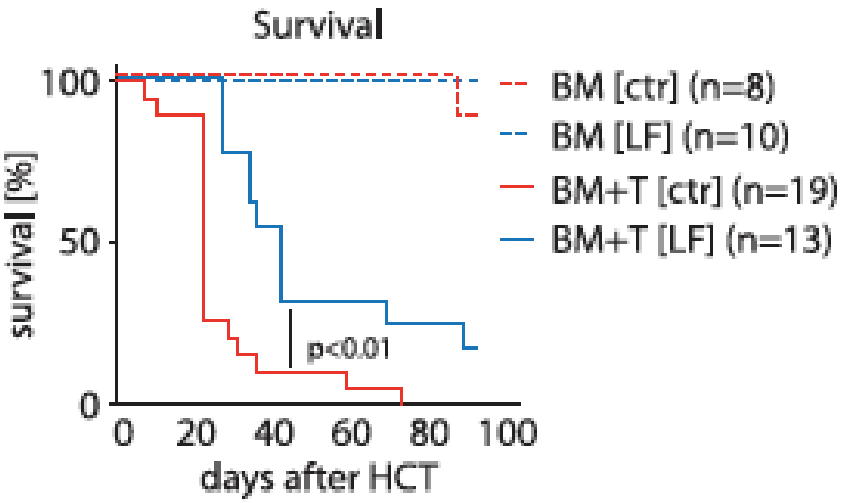


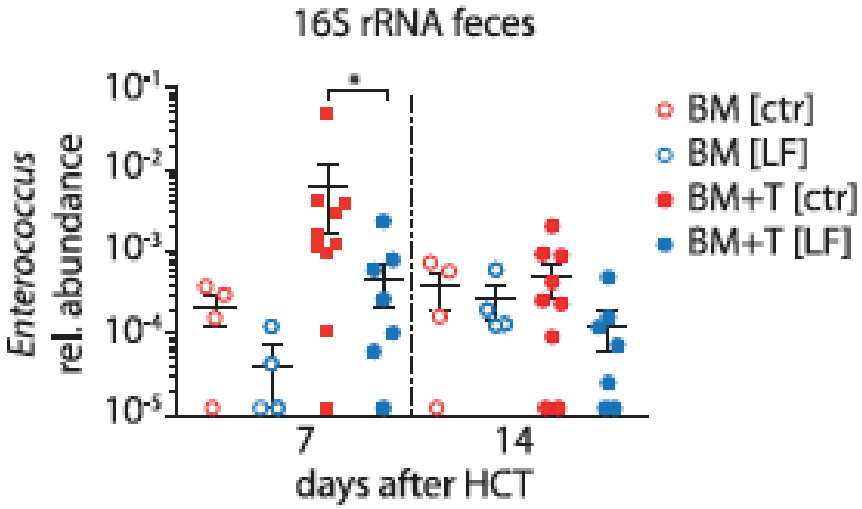
BM [- EF] (n=4)
BM [+ EF] (n=5)
BM+T [- EF] (n=10)
BM+T [+ EF] (n=12)



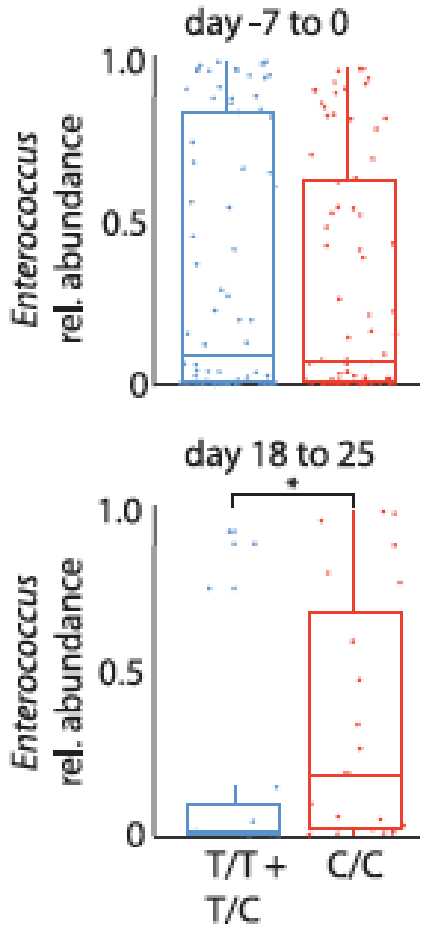
Vpliv laktoze na GVHD



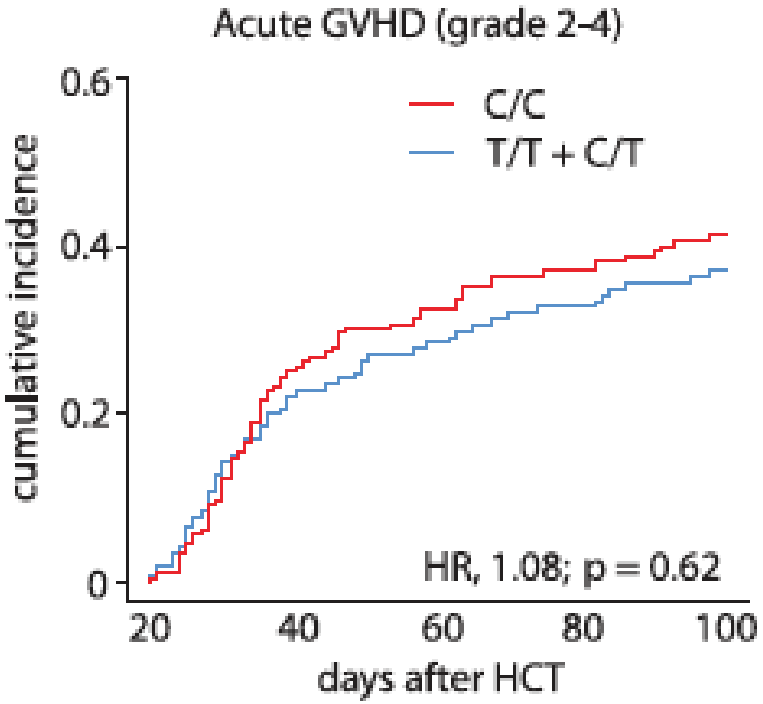




Laktoza pospeši razrast enterokokov in vodi k poslabšanju GVHD



dnevi po antibiotični terapiji



Zaključki študije

- po PKMC sprememba mikrobiote, ki vpliva na težo GVHD (in pojav?)
- razrast enterokokov, izginotje komensalnih klostridijev
- izguba protektivnega butirata in izguba laktaze
- laktozna intoleranca predisponira k hujšemu GVHD
- rešitev? laktaza ali brezlaktozna dieta