Antibiotika und PPI: Wie können wir unser Mikrobiom schützen?

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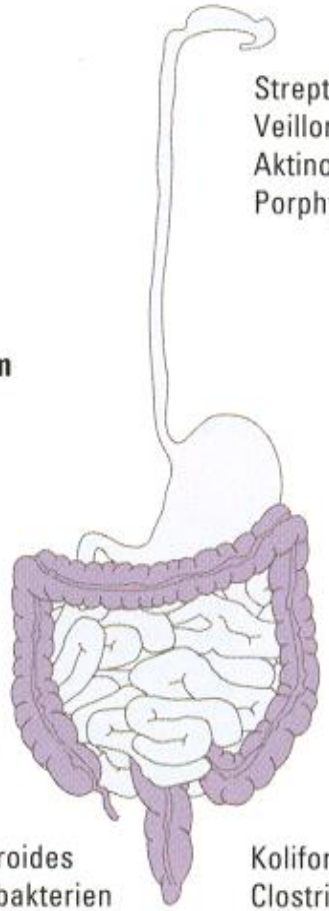
Bakterielle „Mitbewohner“



Bakterienarten

Mund
(ca. 10^{11} Keime)
Streptokokken
Veillonellen
Aktinomyzeten
Porphyromonas
Fusobakterien
Eubacterium
Prevotella

Magen und Zwölffingerdarm
(10^1–10^3 Keime)
Laktobazillen
Streptokokken
Hefen

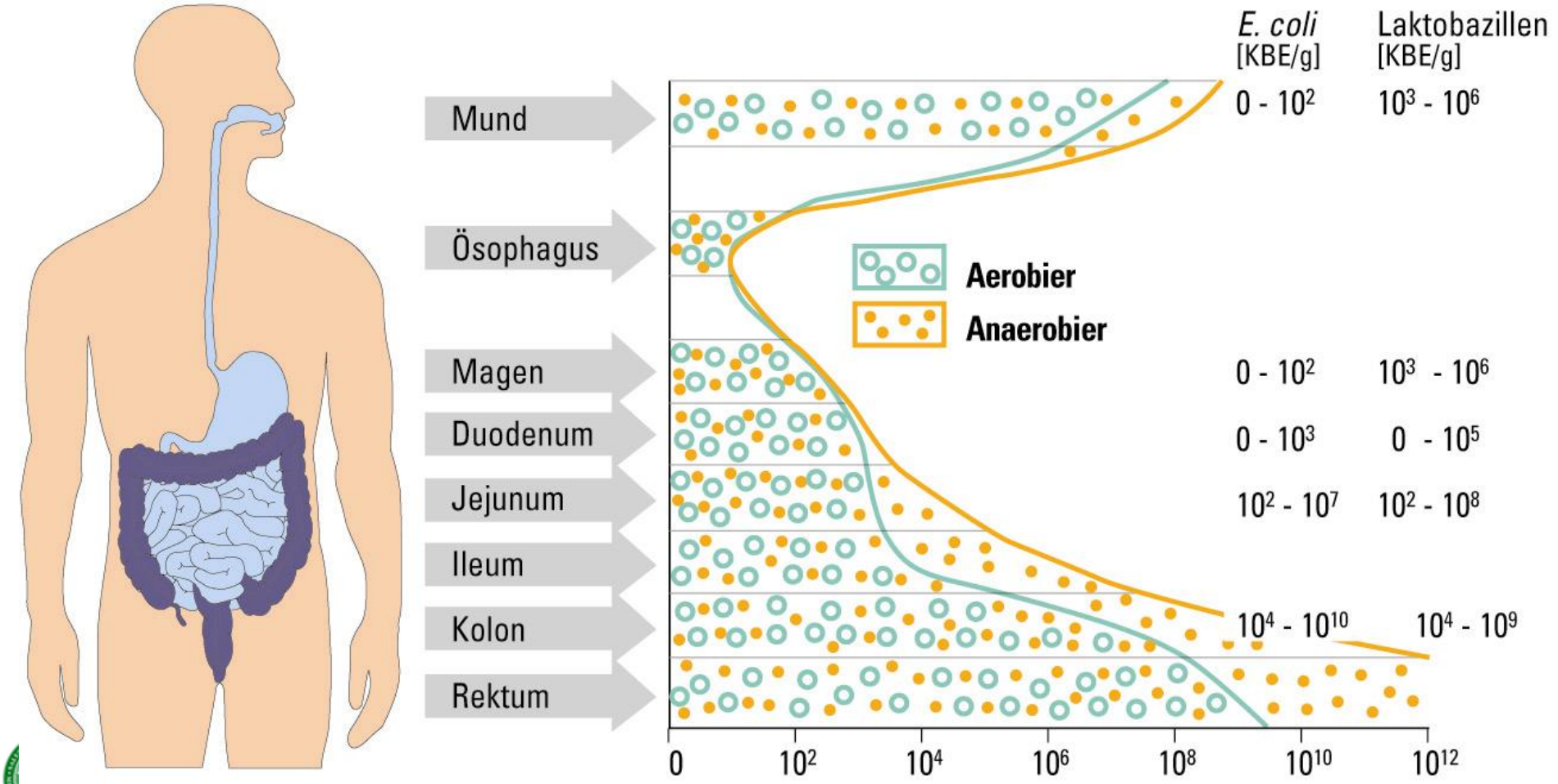
Dünndarm
(10^4–10^8 Keime)
Laktobazillen
Koliforme
Streptokokken
Bacteroides
Bifidobakterien
Fusobakterien

Dickdarm
(10^{10}–10^{12} Keime)
Bacteroides
Bifidobakterien
Streptokokken
Eubacterium
Fusobakterien
Koliforme
Clostridien
Veillonellen
Laktobazillen
Proteus
Staphylokokken
Pseudomonaden
Hefen / Protozoen

Mikrobiom

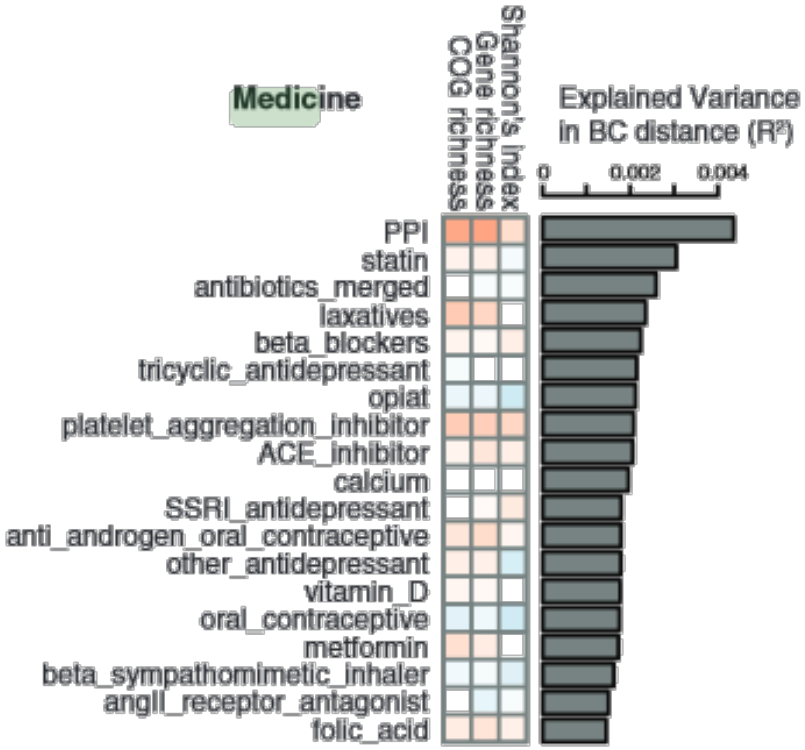
- Mehr Bakterien als menschliche Zellen
- 100 Billionen Bakterien (10^{14})
- Mehr als 1000 Spezies
- Gewicht 1.5-2 kg
- Ohne Bakterien Leben unmöglich

Verteilung


Mund
Ösophagus
Magen
Duodenum
Jejunum
Ileum
Kolon
Rektum
E. coli [KBE/g]
Laktobazillen [KBE/g]
0 - 10²
10³ - 10⁶
Aerobier
Anaerobier
0 - 10²
10³ - 10⁶
0 - 10³
0 - 10⁵
10² - 10⁷
10² - 10⁸
10⁴ - 10¹⁰
10⁴ - 10⁹
0
10²
10⁴
10⁶
10⁸
10¹⁰
10¹²

Einflussfaktoren

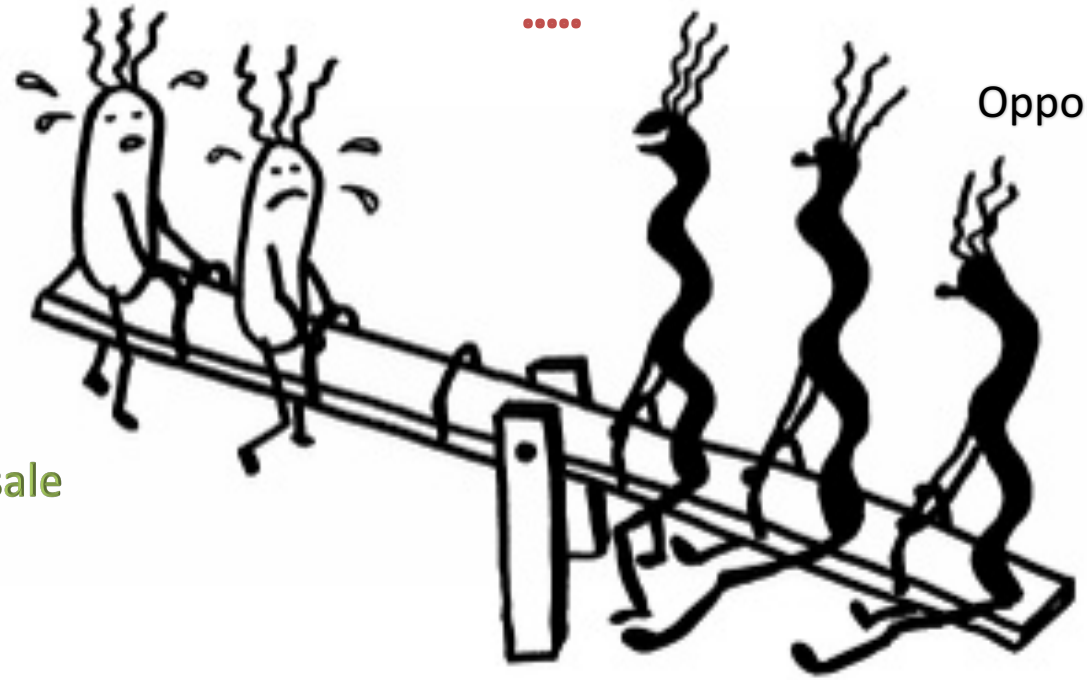
- **Nahrung**
  - Art der Lebensmittel (Ballaststoffe)
  - Mikroorganismen in der Nahrung
- **Medikamente**
  - Antibiotika, Protonenpumpenhemmer, Statine, Betablocker….
- **Immunsystem**
- **Genetische Faktoren**
- **Umwelteinflüsse**
  - Infektionen
- **Frühkindliche Faktoren**
  - Sectio vs. natürliche Geburt
  - Stillen



(Zhernakova 2016)

Dysbiose

Fett
Alkohol
Medikamente
.....

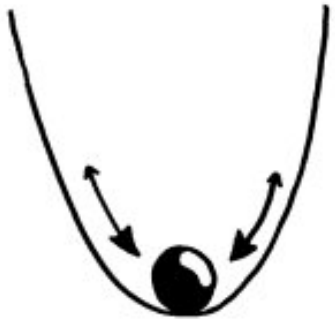


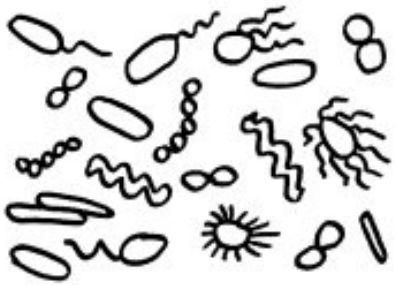
Opportunistische Pathogene

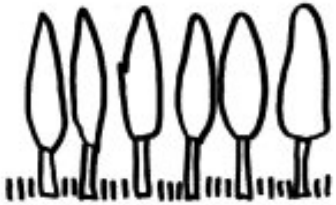
Kommensale

Erhöhte Permeabilität
Bakterielle Translokation
Inflammation

Resilienz







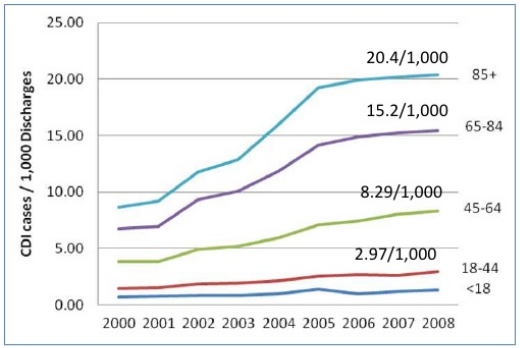
ANTIBIOTIKA

Antibiotika-assoziierte Diarrhoe

- Definition
  - Durchfall während oder bis 2 Monate nach Antibiotikatherapie
- Häufigkeit 5-25%
- Höchstes Risiko
  - Kinder und ältere Menschen

Häufig	Selten
Cephalosporine (3./4. Generation)	Metronidazol
Ampicillin/Amoxicillin	Fluorochinolone
Clindamycin	Rifampin
Andere Penicilline	
Makrolide	
Tetrazykline	
Trimethoprim/Sulph-methoxazol	

Increased incidence especially in patients ≥ 65 years

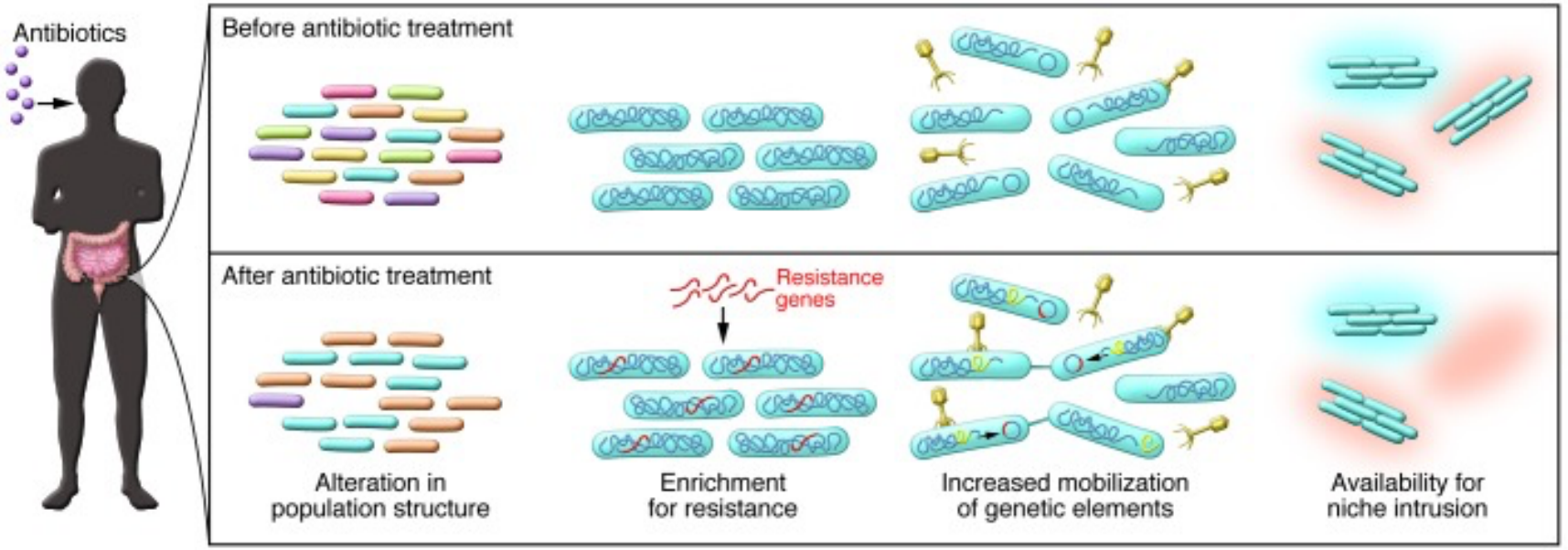


Healthcare Cost and Utilization Project (HCUP).
http://hcupnet.ahrq.gov.

Pathogenese

- Überwucherung pathogener Mikroorganismen
  - Clostridium difficile (10–20 %)
  - C. perfringens, Staph. aureus, Klebsiella oxytoca, Salmonella sp.
- Beeinflussung der Funktion der normalen intestinalen Flora
  - Kohlenhydratmetabolismus
  - Gallensäuremetabolismus
- Direkte Nebenwirkung von Antibiotika:
  - Allergisch/toxischer Effekt
  - pharmakologische Einflüsse auf Darm-Motilität

Effekt auf das Mikrobiom



(Modi, JCI 2014)

Prophylaxe

- Sinnvoller Antibiotika-Einsatz
- Isolation bis 48h nach Sistieren der Diarrhoe
- Händewaschen (SEIFE!, Desinfektionsmittel wirkungslos gegen Sporen)
- Kontakthygienemassnahmen

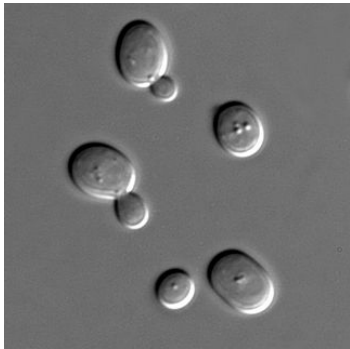
Modulation des Mikrobioms

(adaptiert nach Nature, 2012)

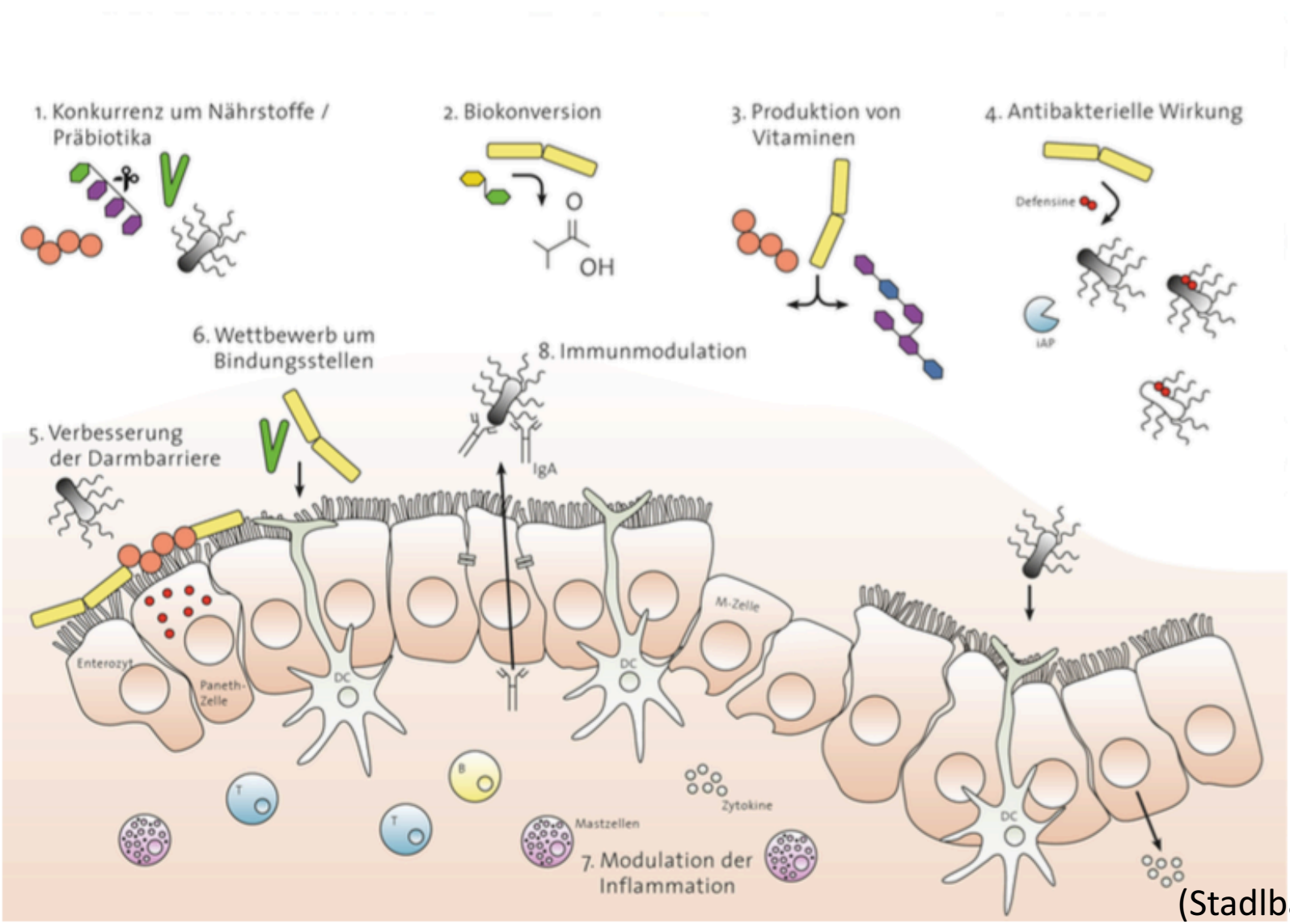
Probiotische Stämme

- Lactobacillus
  - rheuteri
  - rhamnosus
  - casei
  - acidophilus
- Bifidobacterium
  - infantis
  - longum
  - breve
  - lactis
  - bifidum

- Streptococcus thermophilus
- E. coli Nissle
- Enterococcus faecium
- Lactococcus
- Saccharomyces boulardii

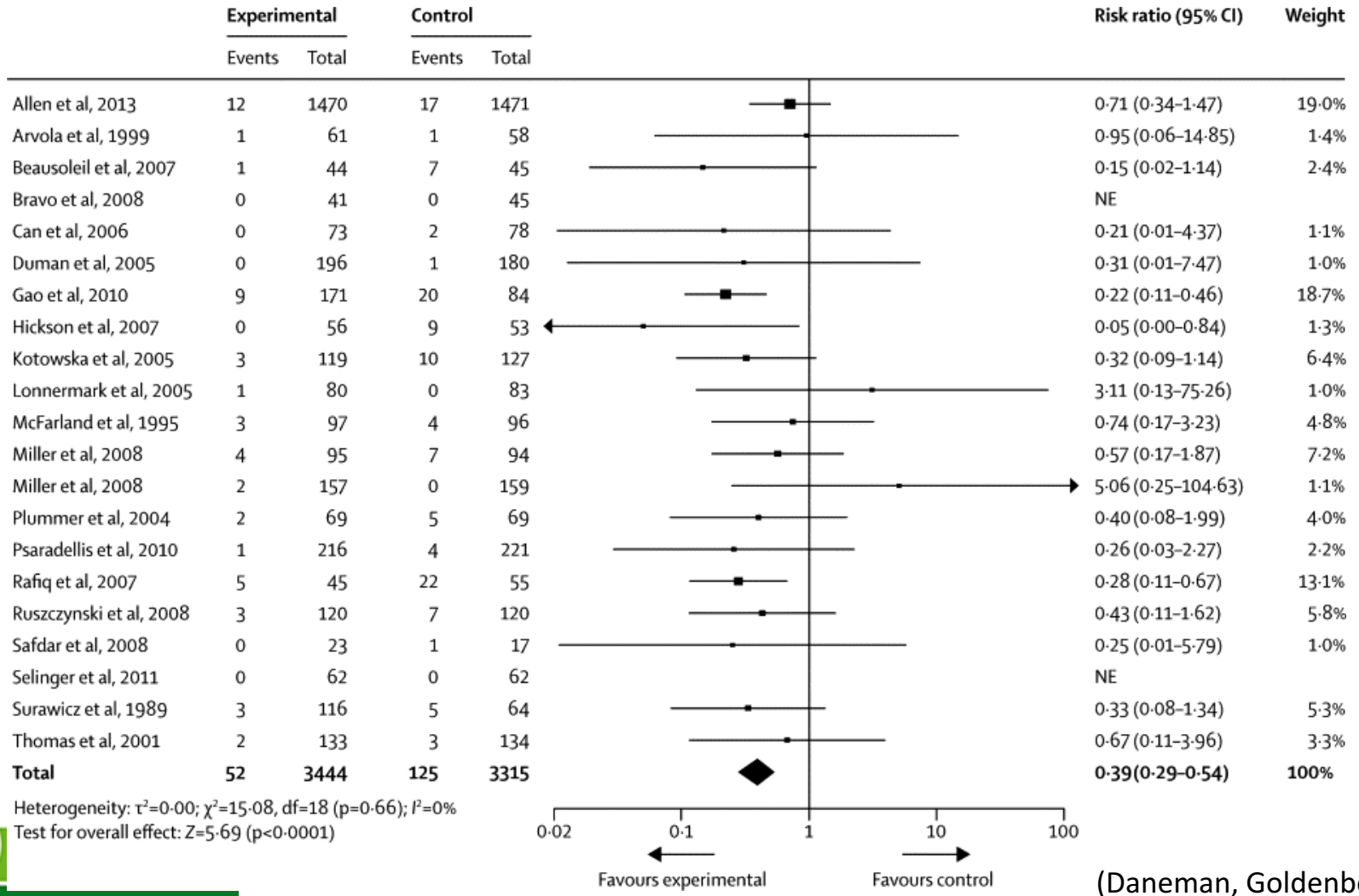


Wie wirken Probiotika?



(Stadlbauer 2015)

Prophylaxe mit Probiotika



	Experimental		Control		Risk ratio (95% CI)	Weight
	Events	Total	Events	Total		
Allen et al, 2013	12	1470	17	1471	0·71 (0·34–1·47)	19·0%
Arvola et al, 1999	1	61	1	58	0·95 (0·06–14·85)	1·4%
Beausoleil et al, 2007	1	44	7	45	0·15 (0·02–1·14)	2·4%
Bravo et al, 2008	0	41	0	45	NE	
Can et al, 2006	0	73	2	78	0·21 (0·01–4·37)	1·1%
Duman et al, 2005	0	196	1	180	0·31 (0·01–7·47)	1·0%
Gao et al, 2010	9	171	20	84	0·22 (0·11–0·46)	18·7%
Hickson et al, 2007	0	56	9	53	0·05 (0·00–0·84)	1·3%
Kotowska et al, 2005	3	119	10	127	0·32 (0·09–1·14)	6·4%
Lonnermark et al, 2005	1	80	0	83	3·11 (0·13–75·26)	1·0%
McFarland et al, 1995	3	97	4	96	0·74 (0·17–3·23)	4·8%
Miller et al, 2008	4	95	7	94	0·57 (0·17–1·87)	7·2%
Miller et al, 2008	2	157	0	159	5·06 (0·25–104·63)	1·1%
Plummer et al, 2004	2	69	5	69	0·40 (0·08–1·99)	4·0%
Psaradellis et al, 2010	1	216	4	221	0·26 (0·03–2·27)	2·2%
Rafiq et al, 2007	5	45	22	55	0·28 (0·11–0·67)	13·1%
Ruszczynski et al, 2008	3	120	7	120	0·43 (0·11–1·62)	5·8%
Safdar et al, 2008	0	23	1	17	0·25 (0·01–5·79)	1·0%
Selinger et al, 2011	0	62	0	62	NE	
Surawicz et al, 1989	3	116	5	64	0·33 (0·08–1·34)	5·3%
Thomas et al, 2001	2	133	3	134	0·67 (0·11–3·96)	3·3%
Total	**52**	**3444**	**125**	**3315**	**0·39(0·29–0·54)**	**100%**

Heterogeneity: τ^2=0·00; χ^2=15·08, df=18 (p=0·66); I^2=0%
Test for overall effect: Z=5·69 (p<0·0001)

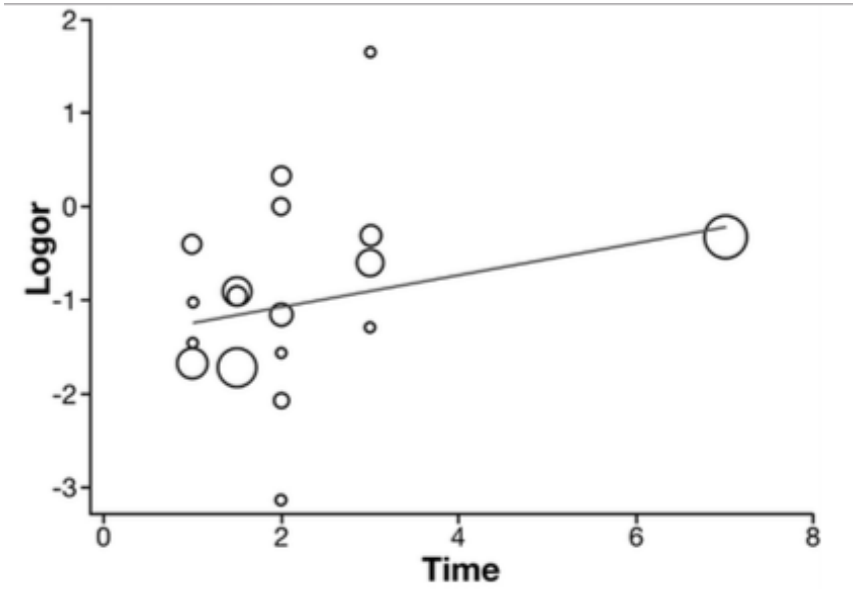
(Daneman, Goldenberg 2013)

Wann?

- 19 RCTs, C. difficile Infektion verhindern
- Effekt am stärksten wenn innerhalb der ersten 2 Tage nach Antibiotikastart gegeben
- 18% Risikoerhöhung mit jedem Tag, an dem das Probiotikum später gegeben wird

Table 3. Summary of Subgroup Analyses

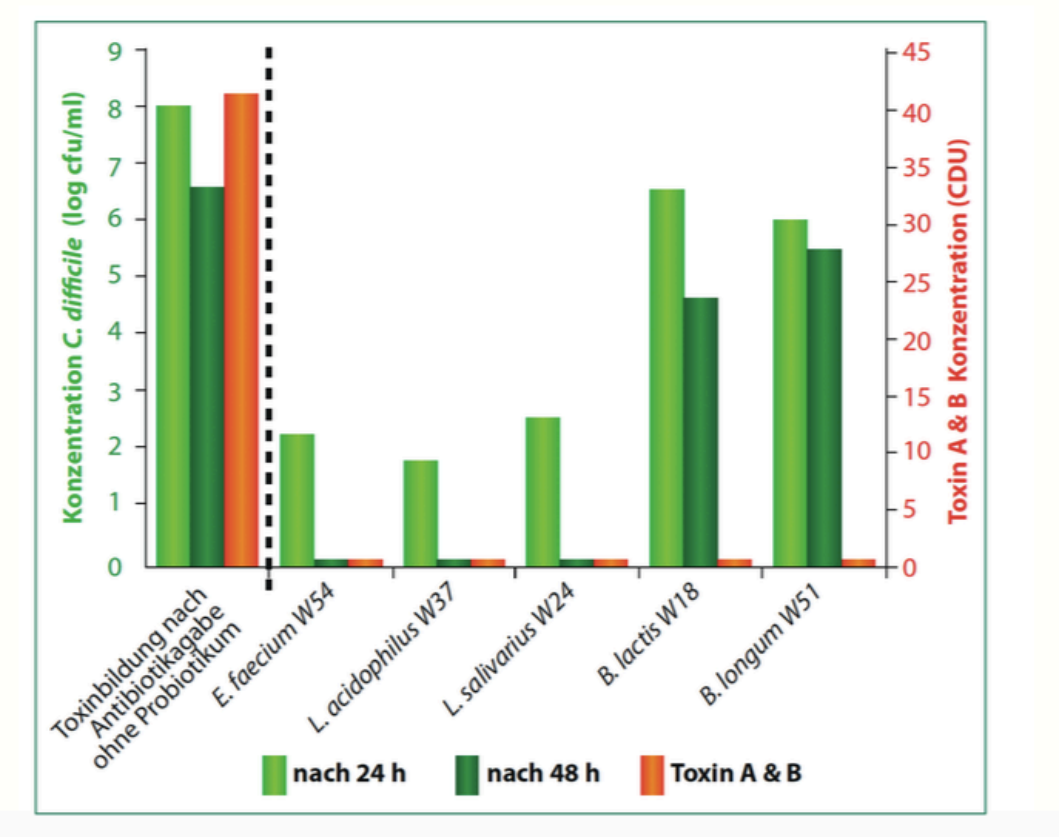
Variable	No. of studies	Summary RR	95% CI	I^2, %	*P* value for interaction
Overall	19	0.42	0.30–0.57	0.0	
Timing: study protocol specifying maximum interval from starting antibiotics to starting probiotics					
1–2 d	14	0.32	0.22–0.48	0.0	.02
3–7 d	5	0.70	0.40–1.23	0.0	
Risk of study bias					
High	11	0.44	0.27–0.71	0.0	.81
Low	8	0.40	0.24–0.67	14.7	
Probiotic species[a]					
Lactobacillus acidophilus	1	0.25	0.01–5.79	0.0	.34
L acidophilus, Bifidobacterium bifidum	1	0.40	0.08–1.99	0.0	
L acidophilus, B bifidum, Bifidobacterium lactis	1	0.70	0.34–1.47	0.0	
L acidophilus, Lactobacillus bulgaricus, B bifidum, Streptococcus thermophilus	1	0.28	0.11–0.68	0.0	
L acidophilus, Lactobacillus casei	2	0.21	0.11–0.42	0.0	
L acidophilus, Lactobacillus paracasei, B lactis	1	0.41	0.14–1.20	0.0	
L casei, Lactobacillus bulgaris, S thermophilus	1	0.05	0.00–0.87	0.0	
L casei Shirota	1	0.36	0.02–8.69	0.0	
Lactobacillus rhamnosus GG	3	0.73	0.29–1.88	0.0	
L rhamnosus GG, L acidophilus, B lactis	1	0.29	0.01–6.76	0.0	
Saccharomyces boulardii	5	0.63	0.29–1.37	0.0	
Probiotic formulation					
Capsule	14	0.44	0.32–0.62	0.0	.28
Drink	5	0.15	0.04–0.58	0.0	



(Shen 2017)

Welche Präparate?

- Lactobacillus (rhamnosus, casei)
- Bifidobakterien
- Enterococcus faecium
- Saccaromyces boulardii
- einfache Probiotika, mehrstämmige Probiotika, Multi-Spezies-Präparate?



(Steyer 2012)

Welche Präparate?

- Auf Keimzahl achten
- Multispeziespräparate
  - größere Überlebenschancen
  - bessere Chance auf Besiedelung
  - finden von ökologischen Nischen
  - größere Vielfalt an Eigenschaften

- additive/synergistische Wirkung
- Symbiose von Stämmen

Omnibiotic AAD

Table 4. Defecation Score Between Day 1 and Day 13

	Placebo N = 19	Probiotic N = 19
1. Stool frequency ≥3 per day for at least 2 days	11%	11%
2. Stool consistency1* ≥5 for at least 2 days	42%	21%
3. Stool frequency ≥3 per day and a consistency† ≥ 5 for at least 2 days	26%	16%
4. Stool frequency ≥3 per day and/or a consistency ≥5 for at least 2 days (being the sum of 1–3)	79%*	48%

*$P < 0.05$.
†Consistency ranging from 1 (hard lumps) to 7 (watery) according to the Bristol stool form scale.

(Chapman 2011-2014, Bischoff, Coning 2008)

Verfügbare Präparate

Einfache Probiotika

Enterococcus faecium SF68 (Bioflorin)

- Kapseln, Keimzahl 7.5 x 10^6/Kapsel

Lactobacillus casei rhamnosus (LCR 35) (Antibiophilus)

- Kapseln, Beutel, 2,5 x 10^6/Kapsel bzw. 1.5 x 10^9/Beutel

Saccharomyces boulardii (Yomogi)

- Kapseln, 2,5x10^9/pro Kapsel

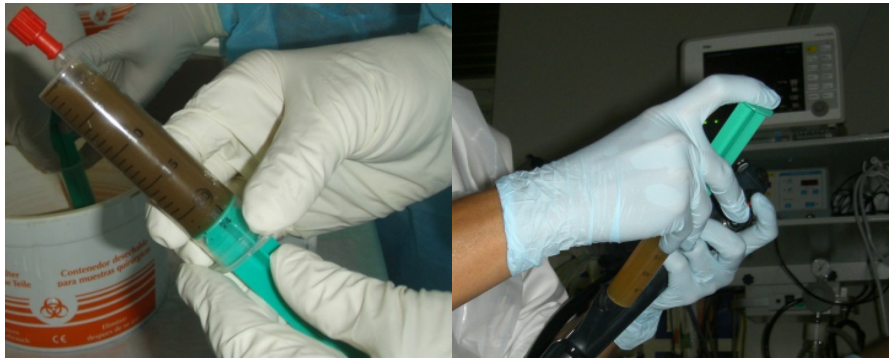
$$C_6H_{12}O_6 + 2\,ADP + 2\,P_i \rightarrow 2\,C_2H_5OH + 2\,CO_2 + 2\,ATP$$

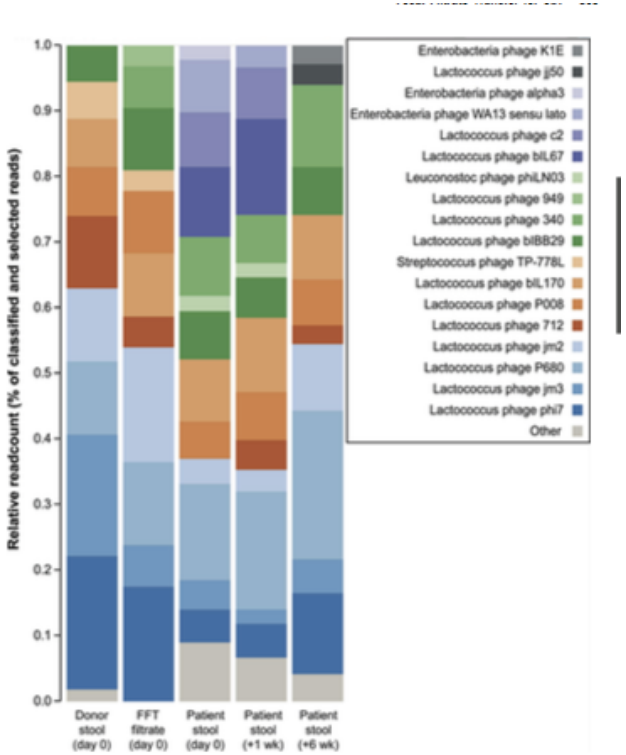
Multispeziespräparate

Omnibiotic 10 AAD, Omniflora, Kijimea, Lactobact, Colomed, Sanfloral, Nutrimmun…

Mikrobiom-Modulation als Therapie

- Fäkale Mikrobiota-Transplantation
  - Ab der 3. Erkrankung/2. Rezidiv
  - Nach adäquater Vortherapie
  - Bei fulminanter C. diff Infektion nach Versagen der Standardtherapie nach 48h (Ultima Ratio)
- Auch steriler Stuhl wirkt
  - Bakteriophagen?



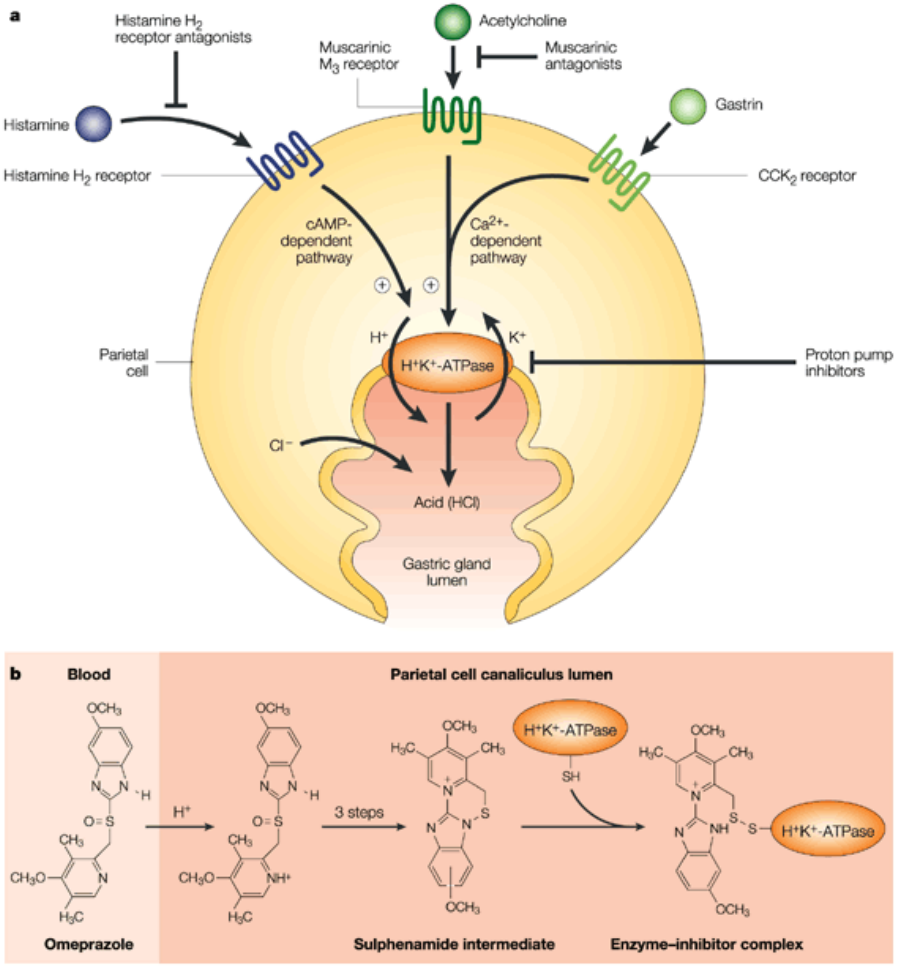


(Kump 2014, Ott 2017)

PROTONENPUMPENHEMMER

Wie könnten PPIs das Mikrobiom beeinflussen ?

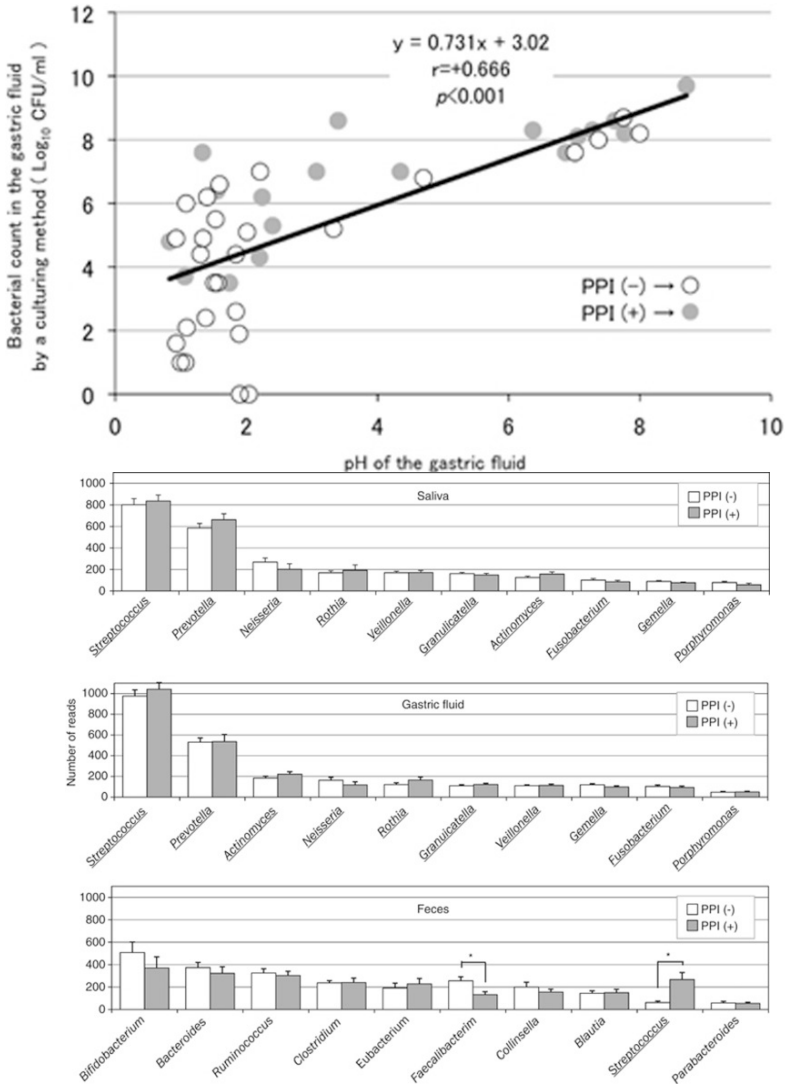
- Direkte und indirekte Effekte
- Direkt
  - PPIs hemmen H+/K+ P-Typ ATPase
  - Bakterien, Pilze, Protozoen haben diese ATPase auch
- Indirekt
  - pH Änderung beeinflusst Zusammensetzung des Mikrobioms
    - Bakterien können sich besser vermehren
    - Eingebrachte Bakterien können nicht vernichtet werden



Nature Reviews | Drug Discovery

Verändern PPI die Mikrobiomzusammensetzung?

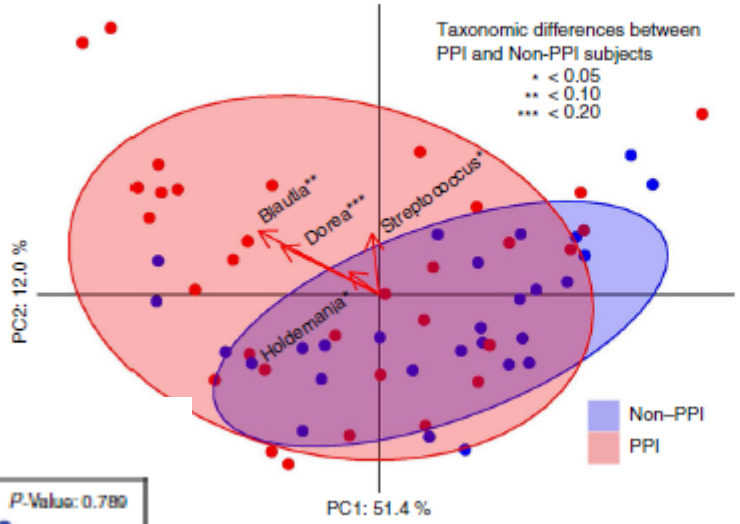
- 45 Patienten, 18 mit PPI
  - Keine Änderung in alpha-Diversität und taxonomischer Zusammensetzung
  - Bakterienanzahl 100x höher mit PPI (Kultur)
  - Mit PPI: Sputum und Magensaft clustern zusammen

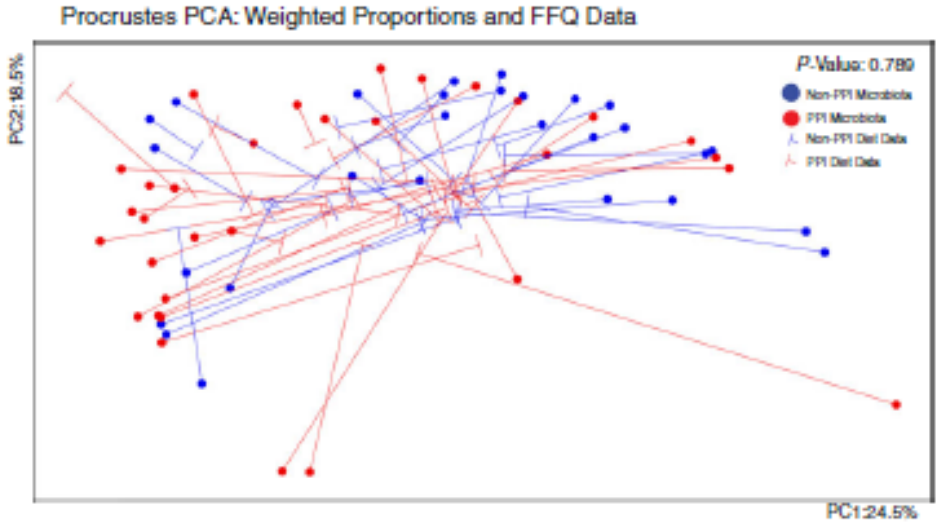


(Tsuda 2015)

Verändern PPI die Mikrobiomzusammensetzung?

- Cross-sectional, PPI >5 Jahre, 61 Probanden
  - Keine Unterschiede in alpha-Diversity
  - Bacteroides ↓ Firmicutes↑

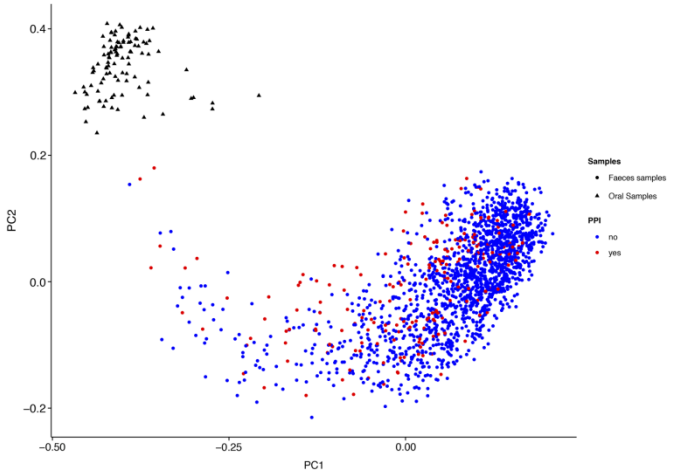


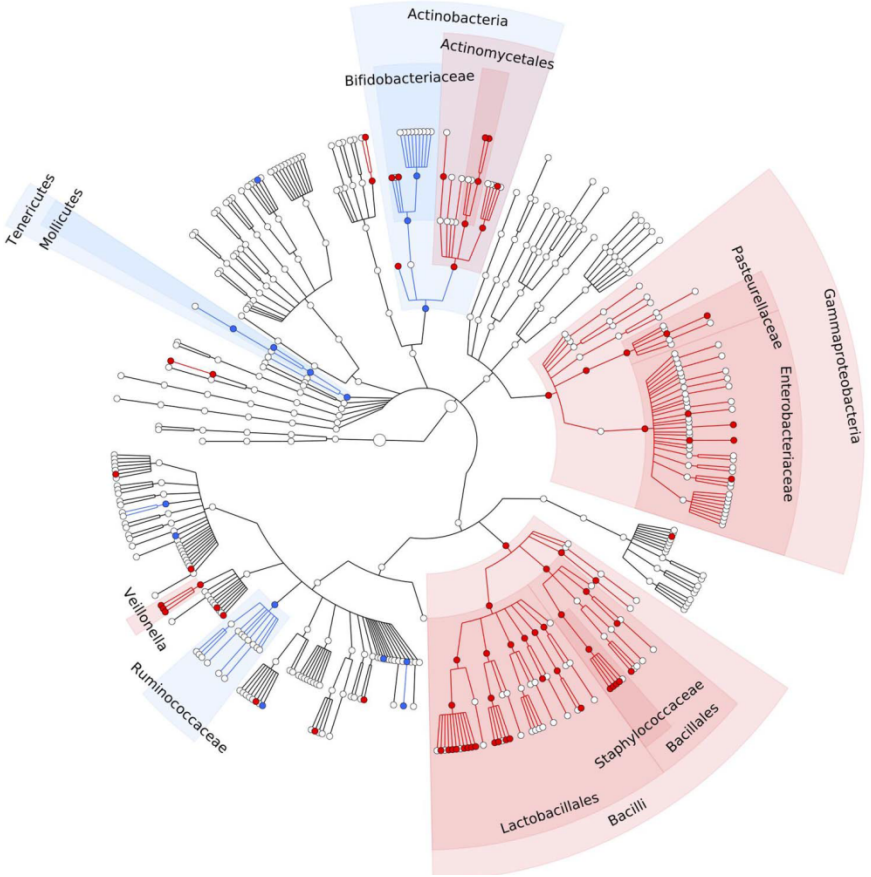


(Clooney 2016)

Verändern PPI die Mikrobiomzusammensetzung?

- 1815 Individuen, 211 PPI Einnahme
- PPI vermindern Diversität
- Keime der Mundflora, Enterococcus, Staphylococcus, E. coli ↑

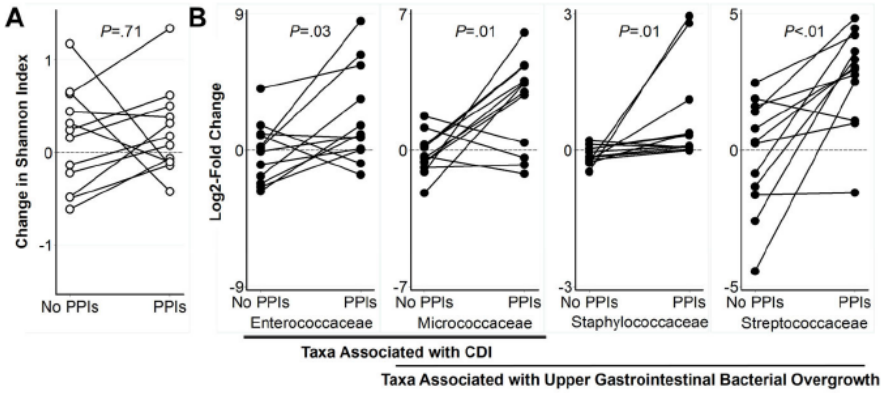


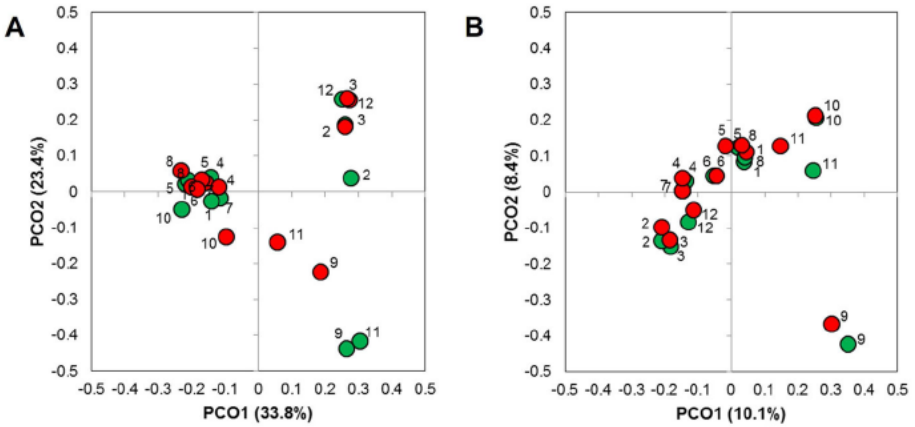


(Imhan 2016)

Verändern PPI die Mikrobiomzusammensetzung?

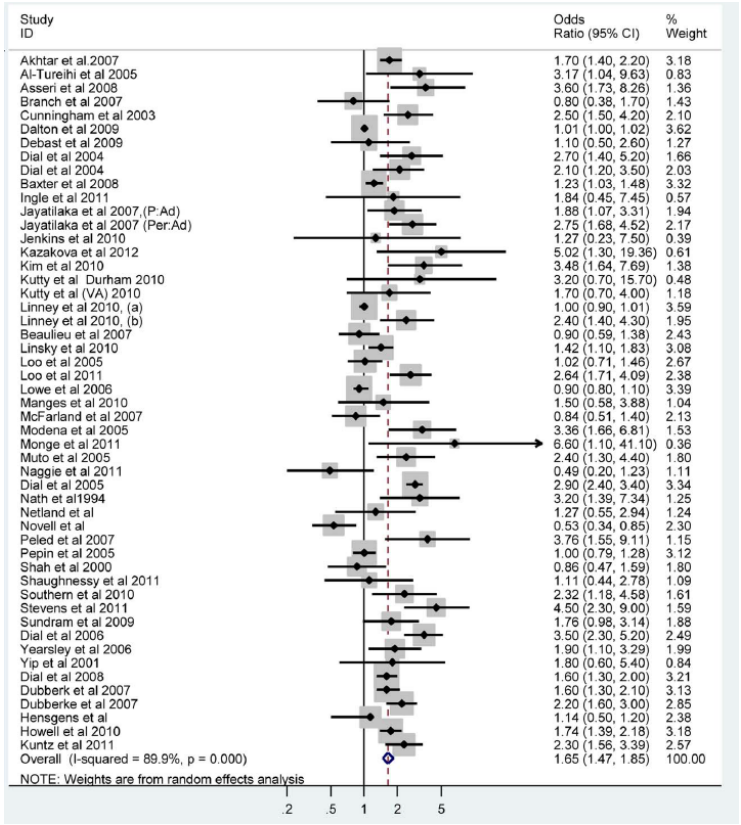
- Cross-over, 12 Probanden, 4 Wochen PPI
  - Enterokokken, Streptokokken, Mikrokokken, Staphylokokken↑, Clostridiales ↓
- Anstieg in Genen, die mit bakterieller Invasion zu tun haben
- Höheres Risiko für C.diff?

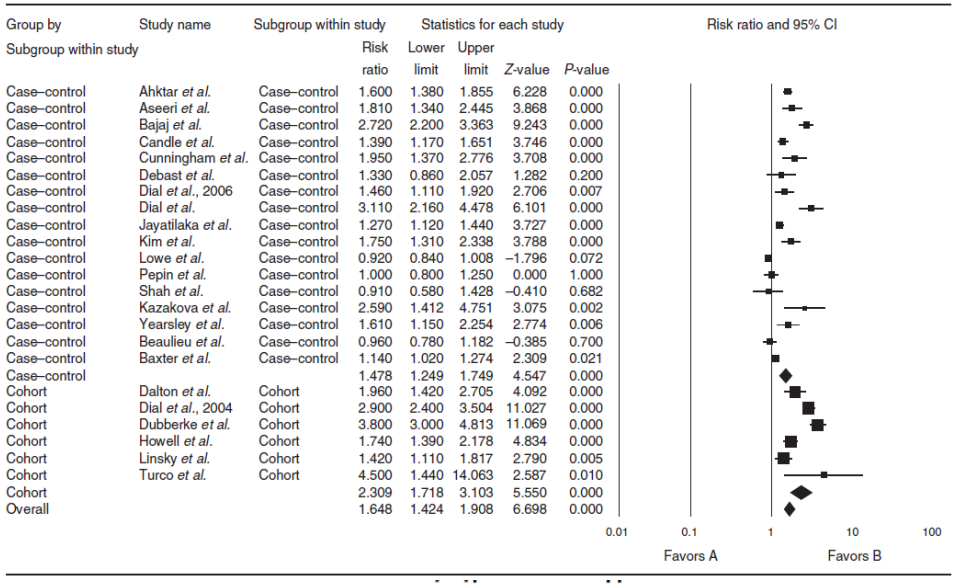




(Freedberg, 2015)

Clostridium difficile





Type of Acid Suppression	Cases (n = 650)	Controls (n = 3200)	Odds Ratio (95% Confidence Interval)[a]
Neither (n = 3825)	633	3192	Reference
H2RA only (n = 11)	5	6	2.64 (.93–10.4)
Proton pump inhibitor with or without H2RA (n = 14)	12	2	21.5 (4.71–98.6)

Abbreviation: H2RA, histamine-2 receptor antagonist.

[a] Conditioned on age, sex, follow-up time, and practice; adjusted for use of antibiotics or steroids and hospitalization.

- 23 Studien: RR 1.69
- 47 Studien: RR 1.47, NNH 1:3825/Jahr
- USA: 7-8 Millionen Verschreibungen/Jahr
- Bei Kindern: Risiko 10x höher als bei H2 Blockern

(Janarthanan AJG 2012, Alhamdi PONE 2016, Freedberg 2015)

Andere Darminfekionen

Table 1 | Published studies of the relationship between use of PPIs and development of non-typhoid *Salmonella* gastroenteritis

Reference	Study description	Strength of association (with 95% CI)*†	Comments
(83)	Nested case control study: 374 cases and 2000 controls	The article established CI for bacterial diarrhoea, not specifically for the subgroup with *Salmonella* infection	A relative risk of 1.6 (1.0–2.4) was reported between PPI use and bacterial gastroenteritis in general. Among the 374 total diarrhoea cases in the study, 136 (36.4%) cases were caused by *Salmonella*.
(84)	Case control study: 167 *S. enteritidis*, 193 *S. typhimurium* cases and 3119 controls	*S. enteritidis*: 4.2 (2.2–7.9) *S. typhimurium*: 8.3 (4.3–15.9)	Population attributable risk was also observed to be very high for PPIs.
(85)	Case control study: 6414 cases and 50 000 controls	The article established CI for bacterial diarrhoea, not for the subgroup with *Salmonella*	A relative risk of 2.9 (2.5–3.5) was reported between PPI use and bacterial gastroenteritis in general. Among the 6414 total diarrhoea cases in the study, 1885 (29.4%) cases were caused by *Salmonella*.
(86)	Case control study: 573 cases and 3409 controls	4.3 (2.9–6.5)	The association was reported for PPI use and recurrent cases of *Salmonella* gastroenteritis.

CI, confidence interval; PPI, proton pump inhibitor.

* Strength of association: multivariate odds ratio or relative risk is reported wherever possible rather than univariate values.

† Values were rounded to nearest first decimal wherever necessary.

Table 2 | Published studies of the relationship between *Campylobacter jejuni* diarrhoea and use of PPIs

Reference	Study description	Strength of association (with 95% CI)*†	Comments
(87)	Case control study: 211 cases and 422 controls	11.7 (2.5–54.0)	Omeprazole use within 1 month before infection showed the strongest association.
(88)	Case control study: 313 cases and 512 controls	3.5 (1.1–12.0)	Foreign travel explained 25% of cases of *Campylobacter* diarrhoea
(83)	Nested case control study: 374 cases and 2000 controls	The article established CI for bacterial diarrhoea, not for the subgroup with *Campylobacter*	A relative risk of 1.6 (1.0–2.4) was reported between PPI use and bacterial gastroenteritis in general. Among the 374 total diarrhoea cases in the study, 201 (53.7%) cases were caused by *Campylobacter*.
(85)	Case control study: 6414 cases and 50 000 controls	The article established CI for bacterial diarrhoea, not for the subgroup with *Campylobacter*	A relative risk of 2.9 (2.5–3.5) was reported between PPI use and bacterial gastroenteritis in general. Among the 6414 total diarrhoea cases in the study, 4124 (64.3%) cases were caused by *Campylobacter*.
(86)	Case control study: 1446 cases and 3409 controls	4.5 (3.3–6.1)	PPI use and recurrent cases of *Campylobacter* gastroenteritis were associated.
(89)	Case control study: 1,019 cases and 3119 controls	4.3 (2.9–6.2)	For elderly patients, the OR was observed to be 2.9 (1.5–5.7).

CI, confidence interval; PPI, proton pump inhibitor.

* Strength of association: multivariate odds ratio (OR) or relative risk is reported wherever possible rather than univariate values.

† Values were rounded to nearest first decimal wherever necessary.

- Erhöhtes Risiko für Salmonellen, Campylobacter jejuni, E.coli, Vibrio cholerae, Listerien
- Reisediarrhoe: OR 6,9
- pH im Magen, Translokation, bakterieller Overgrowth, verminderte Diversität, Immunmodulation

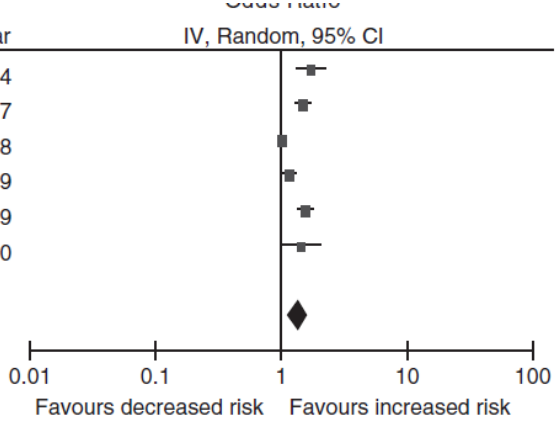
(Bavishi 2011)

Pneumonie

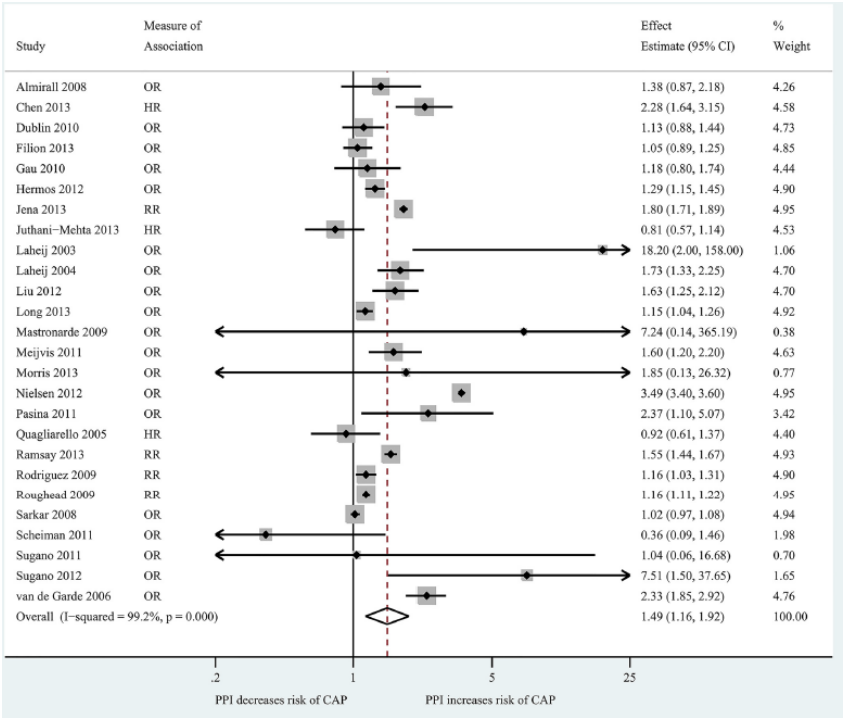
Study or Subgroup	log [Odds Ratio]	SE	Weight	IV, Random, 95% CI	Year
Laheij *et al* 2004	0.54812141	0.13412022	14.4%	1.73 [1.33, 2.25]	2004
Gulmez *et al* 2007	0.40546511	0.06843469	17.9%	1.50 [1.31, 1.72]	2007
Sarkar *et al* 2008	0.01980263	0.02740312	19.3%	1.02 [0.97, 1.08]	2008
Rodriguez *et al* 2009	0.14842	0.06134396	18.2%	1.16 [1.03, 1.31]	2009
Myles *et al* 2009	0.43825493	0.06721807	18.0%	1.55 [1.36, 1.77]	2009
Eurich *et al* 2010	0.37156356	0.17433444	12.2%	1.45 [1.03, 2.04]	2010
Total (95% CI)			100.0%	1.36 [1.12, 1.65]	

Heterogeneity: Tau² = 0.05; Chi² = 65.01, df = 5 ($P < 0.00001$); $I^2 = 92\%$

Test for overall effect: $Z = 3.10$ ($P = 0.002$)



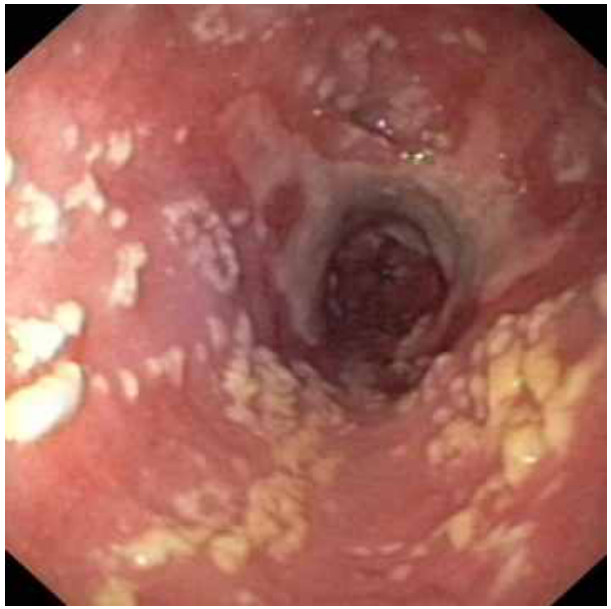
- Vor allem innerhalb der ersten 30 Tage der PPI Einnahme
- Keine Risikoerhöhung bei H2 Blockern
- Gründe
  - pH-Erhöhung
  - Mikrobiomveränderungen
  - Mikroaspiration
  - direkter Effekt auf Protonenpumpen im Respirationstrakt

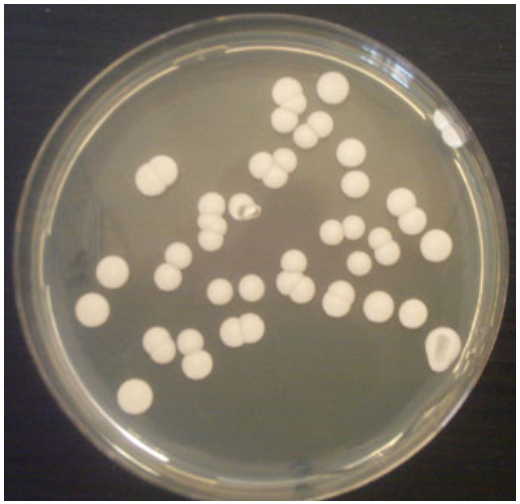


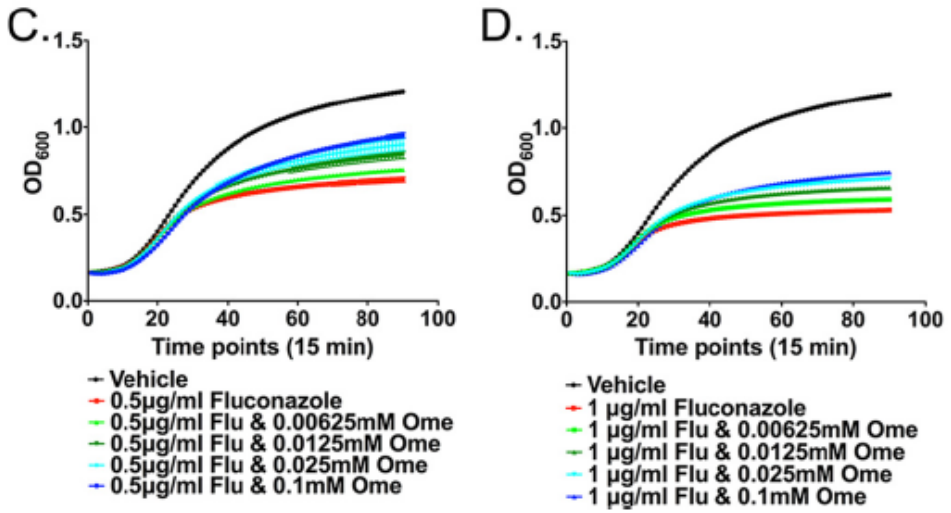
(Johnstone 2010)

Pilzinfektionen

- Postoperative intraabdominelle Candida-Infektionen häufiger
- Risiko für Candidainfektionen in Oropharynx und Ösophagus erhöht







(Liu 2015, Cat 2008, Daniell 2015, Kim 2013)

Infektionsrisiko bei Zirrhose

- NACSELD Kohorte
- PPI Einnahme: OR 2,94 für neuerliche Infektion

		No Subsequent Infection	Subsequent Infections	P-value
Number		104	84	
Age		55.1 (9.6)	57.7 (9.2)	0.06
Male		56.9%	51.2%	0.44
Etiology of liver disease	HCV	31.7%	15.5%	0.13
	Alcohol	30.8%	34.5%	
	HCV + Alcohol	12.5%	14.3%	
	NASH/CC	15.4%	22.6%	
	Other	9.6%	13.1%	
MELD score		18.35 (7.59)	19.3 (6.8)	0.36
Child-Turcotte-Pugh Score		10 (8, 12)	10 (9,11.5)	0.37
Bilirubin mg/dL		5.4 (6.9)	5.1 (4.6)	0.7
INR		1.7 (1.4)	1.7 (0.9)	0.97
Creatinine mg/dL		1.42 (1.1)	1.45 (1.2)	0.86
Sodium mEq/L		132.0 (6.7)	132.6 (6.5)	0.57
Albumin g/dL		2.79 (0.7)	2.7 (0.7)	0.64
Platelets 10^3/uL		32.4 (69.8)	24.2 (58.7)	0.39
Mean arterial pressure (mmHg)		83.0 (14.3)	83.4 (15.9)	0.87
WBC 10^3/uL		8.6 (7.7)	7.6 (5.5)	0.34
SBP Prophylaxis		21.2%	53.6%	<0.001
Rifaximin		27.9%	52.4%	<0.001
Proton Pump Inhibitor		52.9%	72.6%	0.006
B-Blocker		39.4%	31.0%	0.23

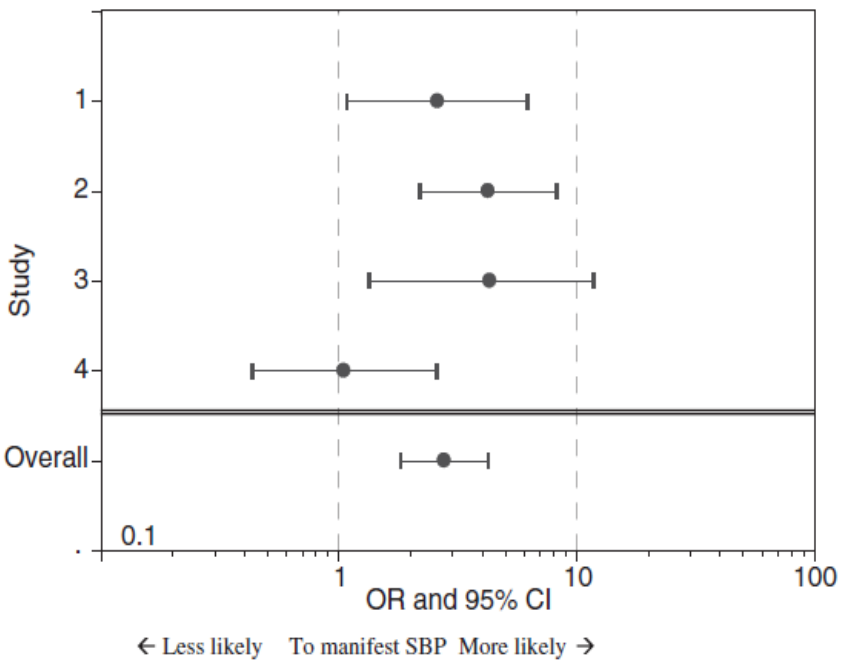
(O´Leary 2015)

Spontan bakterielle Peritonitis

Table 1 Characteristics of individual studies

Study	Sample size	Inclusion(s)	Exclusion(s)	Study population	Study period
Campbell MS et al.[10] University of Pennsylvania	116	Cirrhotics with paracentesis proven SBP	1. Prior liver transplant 2. HIV 3. Exposure to antibiotics 2 weeks prior to diagnosis	Cases-32 Controls-84 Matched 1 : 3	2002–2005 (48 months)
Bajaj JS et al.[6] Medical College of Wisconsin	140	Cirrhotics with paracentesis proven SBP	1. Without proper medication list 2. GI bleeding within 2 weeks prior to diagnosis 3.Exposure to antibiotics 2 weeks prior to diagnosis 4. Prior liver transplant 5. HIV	Cases-70 Controls-70 Matched 1 : 1	2002–2007 (60 months)
Bulsiewicz WJ et al.[7]	403	Cirrhotics with paracentesis during first 2 days of diagnosis	1. Without paracentesis 2. Without proper laboratory or historical data 3. Prior portosystemic shunt 4. Prior liver transplant		January 2003–December 2007 (60 months)
Goel GA et al.[8] Cleveland Clinic	113	Cirrhotics with paracentesis proven SBP		Cases-69 Controls-44 Matched 3 : 2	October 2006–August 2009 (34 months)

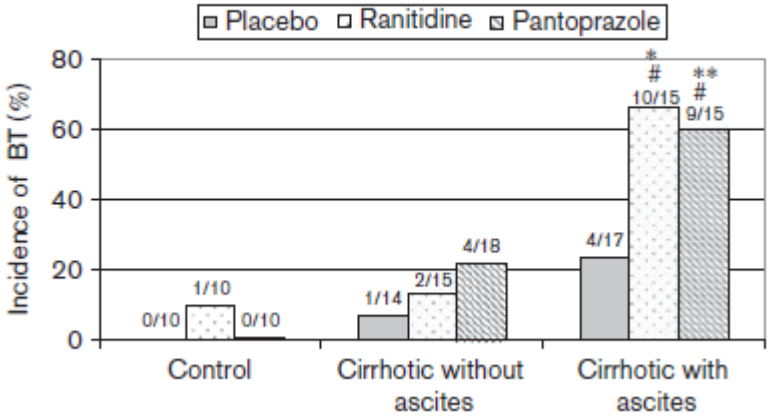
All interventions were proton pump inhibitors; all studies were population-based, retrospective, case–control studies in which the outcomes were risk of SBP among hospitalised patients.

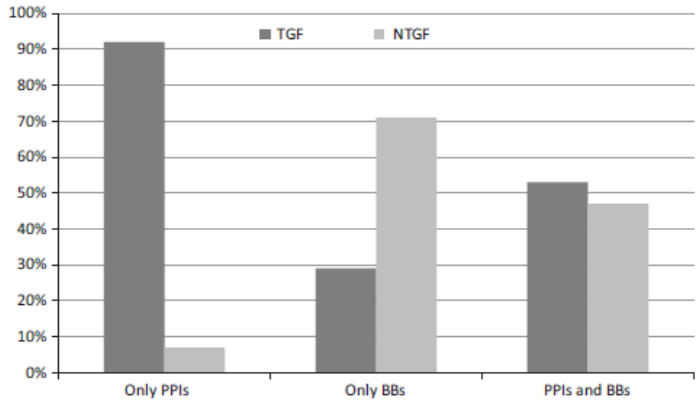


(Trikudanathan, 2011)

Ursache: Bakterielle Translokation

- Zirrhose: erhöhte Permeabilität und Translokation
- Magensäure-Reduktion erhöht intestinale Permeabilität und bakterielle Translokation weiter
- Verschreibung häufig wegen portal hypertensiver Gastropathie und Ösophagusvarizen





(Sanchez 2015, Merli 2015, Trikudanathan 2011)

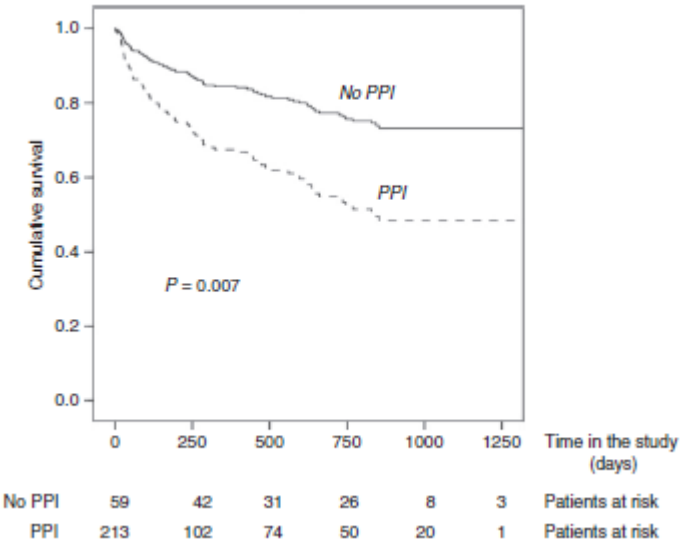
Komplikationen und Mortalität

- Risiko für HE steigt
- Dosisabhängiger Effekt
- Hypothese
  - Mikrobiomveränderungen
  - Mikronährstoff-Mangel

- PPI sind unabhängiger Prädiktor für Mortalität

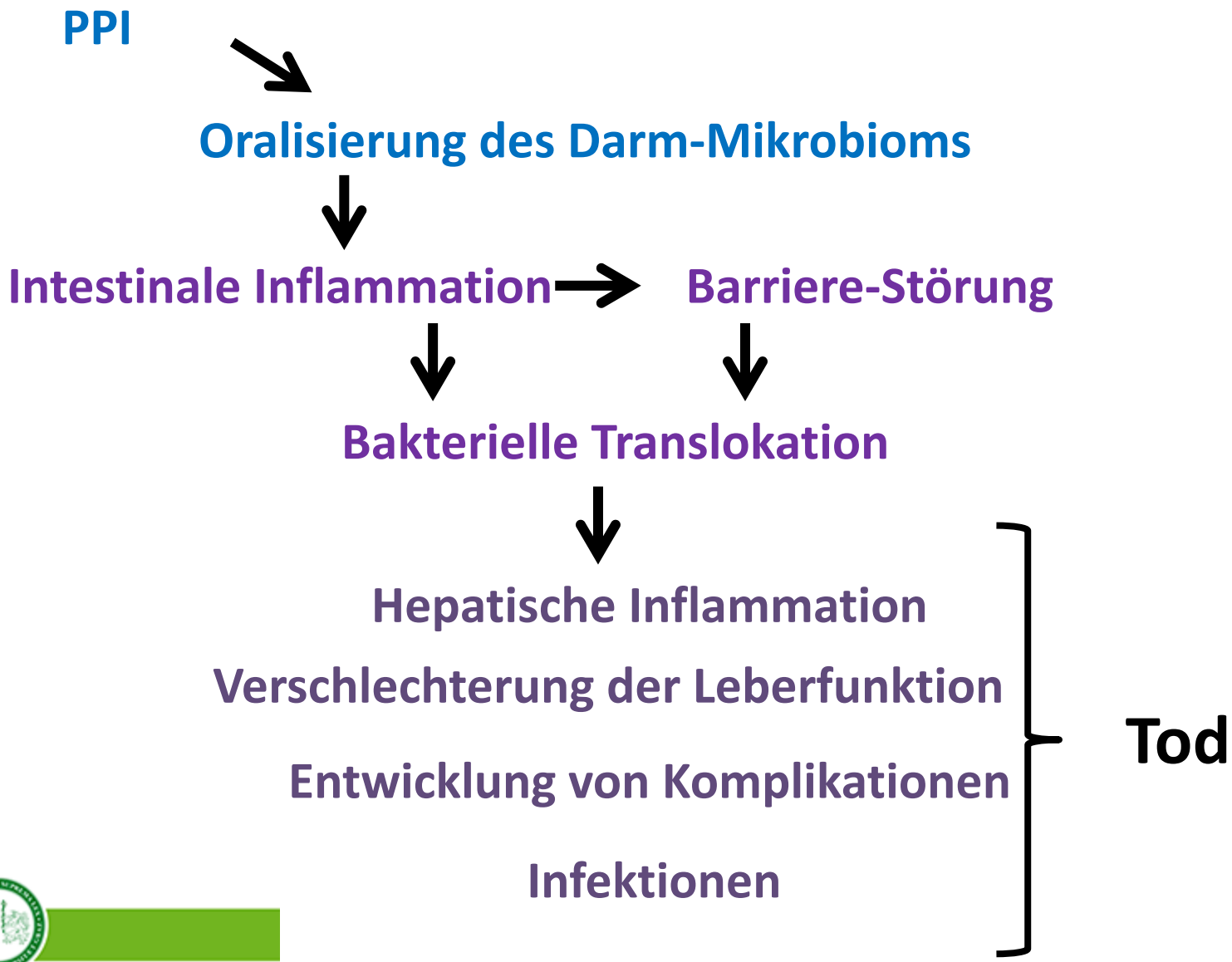
Table 2. Risk of Subsequent Hepatic Encephalopathy Among Patients With Cirrhosis

	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Use of PPI during follow-up period				
cDDD, ≤30	1	1	1	1
cDDD, 31–120	**1.87 (1.47–2.39)**	**1.84 (1.44–2.36)**	**1.58 (1.22–2.03)**	**1.41 (1.09–1.84)**
cDDD, 121–365	**2.38 (1.80–3.14)**	**2.32 (1.75–3.07)**	**1.77 (1.32–2.39)**	**1.51 (1.11–2.06)**
cDDD, 365	**4.49 (2.73–7.38)**	**4.43 (2.69–7.30)**	**3.87 (2.33–6.43)**	**3.01 (1.78–5.10)**
Use of PPI in the past 6 months before enrollment	0.91 (0.59–1.40)	0.87 (0.56–1.34)	0.83 (0.53–1.30)	0.87 (0.56–1.36)
Charlson Comorbidity Index score at enrollment		**1.10 (1.04–1.16)**	**1.09 (1.04–1.15)**	**1.09 (1.03–1.15)**
Medical comorbidities in recent 3 months				
Upper GI bleeding			**4.45 (2.97–6.68)**	**4.58 (3.05–6.87)**
Intra-abdominal infection			**3.33 (2.02–5.48)**	**3.16 (1.91–5.21)**
Pneumonia			**1.68 (1.09–2.59)**	**1.64 (1.06–2.53)**
Urinary tract infection			1.29 (0.85–1.96)	1.26 (0.83–1.91)
Use of medications during follow-up evaluation				
Benzodiazepine				**1.28 (1.05–1.56)**
Antipsychotics				0.69 (0.43–1.11)
Opioid analgesics				**1.44 (1.10–1.88)**



(Tsai 2017, Dultz 2015)

Hypothese


PPI
Oralisierung des Darm-Mikrobioms
Intestinale Inflammation
Barriere-Störung
Bakterielle Translokation
Hepatische Inflammation
Verschlechterung der Leberfunktion
Entwicklung von Komplikationen
Infektionen
Tod

Zusammenfassung

- Dysbiose – Resilienz
- Einflussfaktor Medikamente
  - Antibiotika
  - PPI
- Kein Medikament ohne Nebenwirkungen
  - Indikationen beachten
  - Risikogruppen beachten
- PPI bei Zirrhose: besonders gefährliche Kombination
- Modulation des Mikrobioms
  - Bei AAD etabliert
  - Bei PPI in Entwicklung