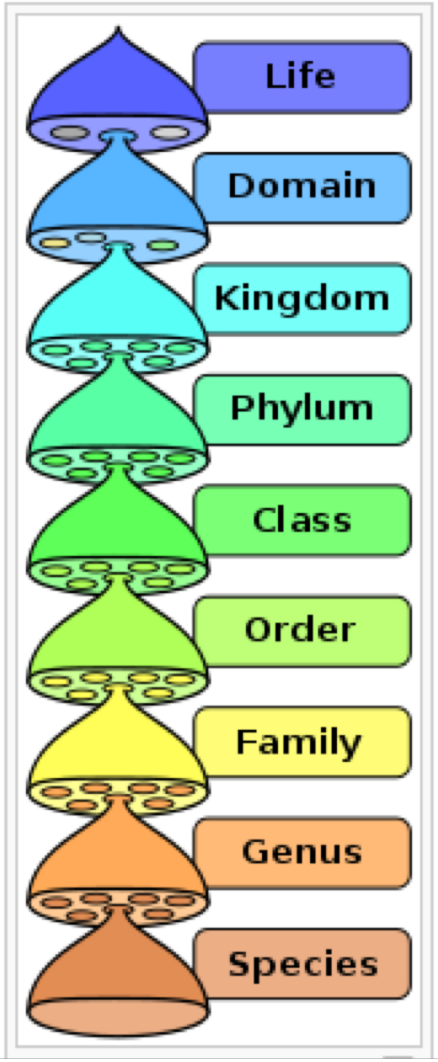
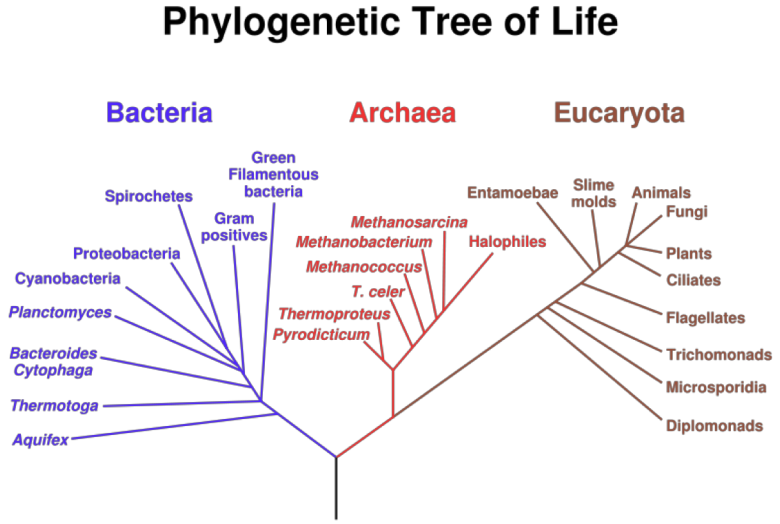
PPI und Mikrobiom

Assoz. Prof. Dr. Vanessa Stadlbauer-Köllner

Medizinische Universität Graz

Bakterielle Taxonomie



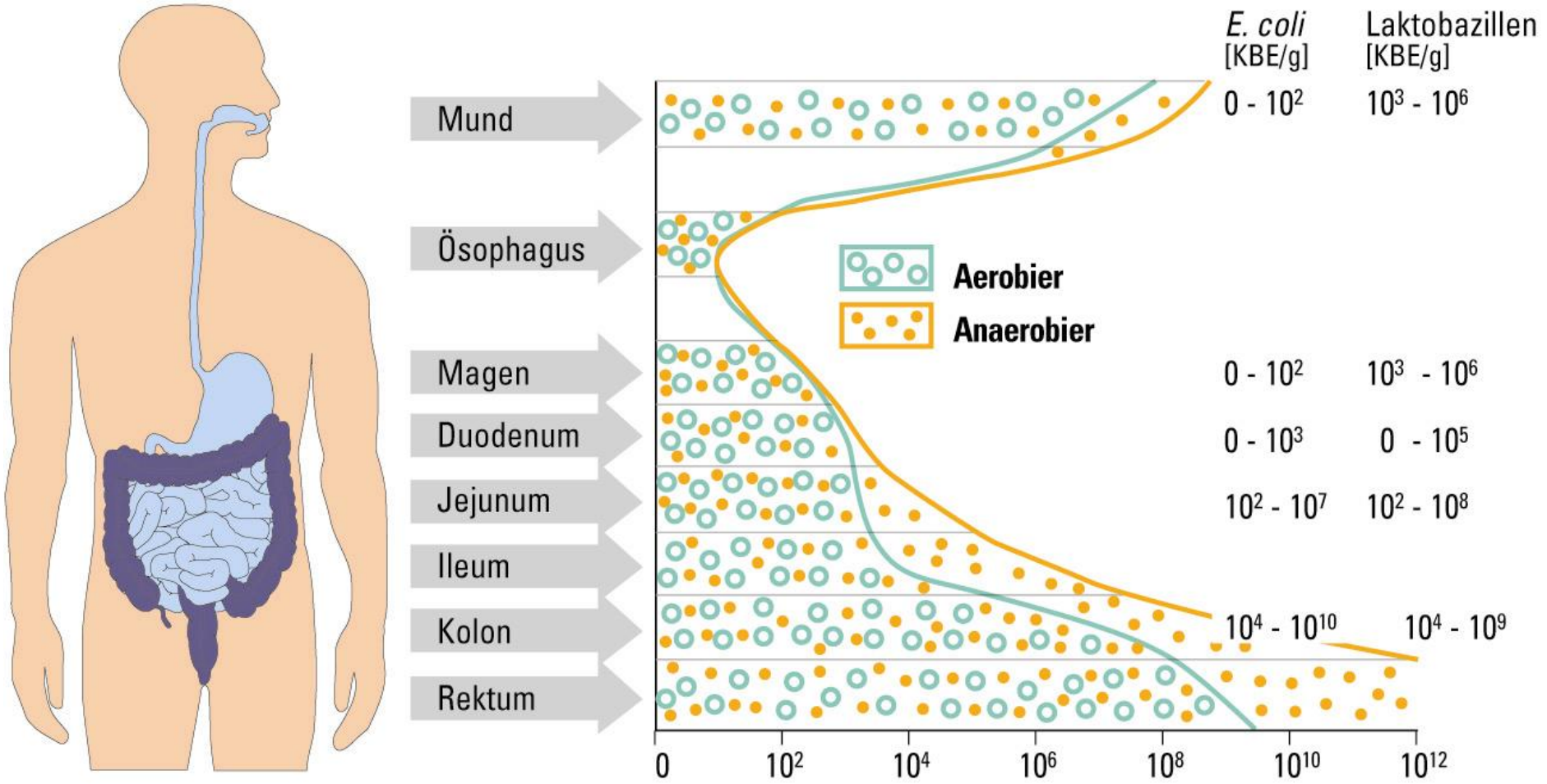


Scientific classification	
Domain:	Bacteria
Kingdom:	Eubacteria
Phylum:	Proteobacteria
Class:	Gammaproteobacteria
Order:	Enterobacteriales
Family:	Enterobacteriaceae
Genus:	*Escherichia*
Species:	***E. coli***

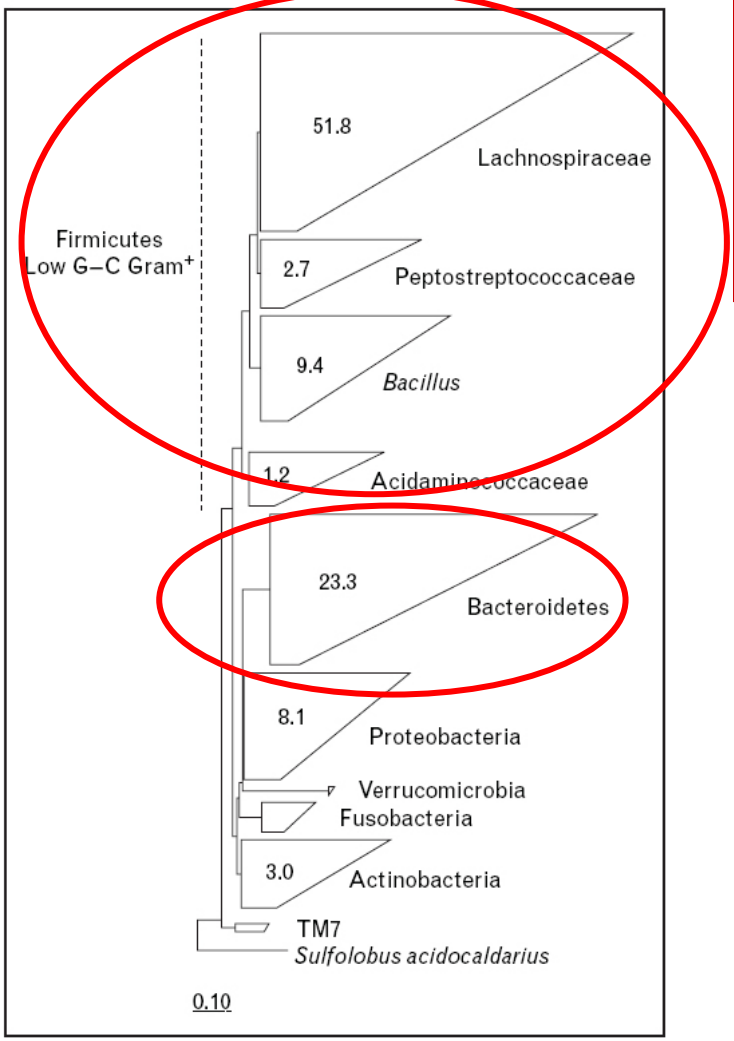
In phylogenetischen Analysen:

OTU (operational taxonomic unit)

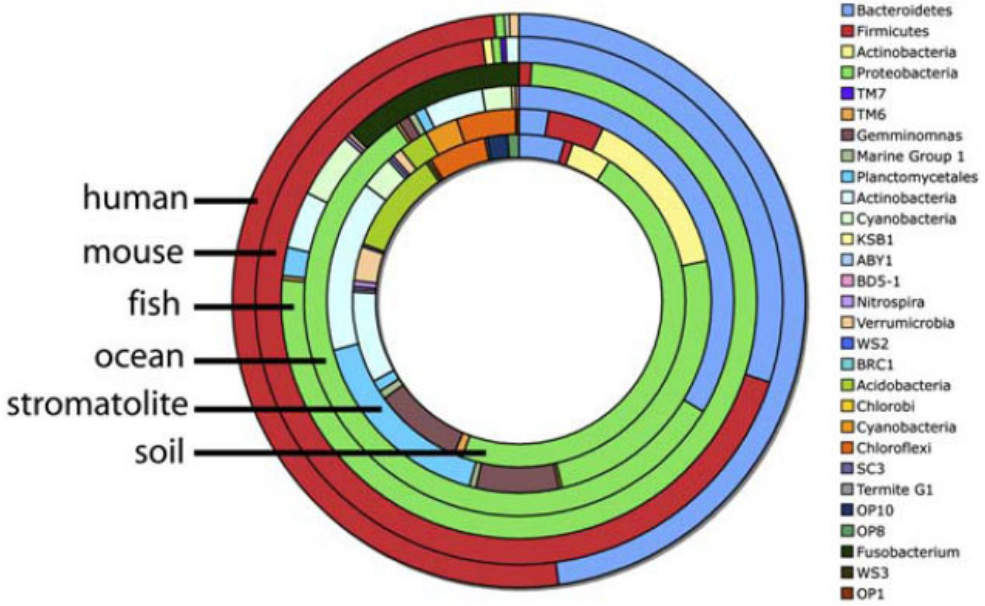
Verteilung


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

Humanes Darm-Mikrobiom



Dominanz (> 90%) von zwei Bakteriengruppen (*Phyla*):
Gram-positive **Firmicutes** (z.B.: *Clostridium*, *Bacillus*)
Gram-negative **Bacteroidetes** (z.B.: *Bacteroides*).



Ley RE et al. Cell 2006
Frank DN et al. Curr Opin Gastroenterol 2008

Bakterielle „Mitbewohner“

- 2-2.5 kg bakterielles Material
- Verhältnis Bakterien : humane Zellen = ca 1.5:1

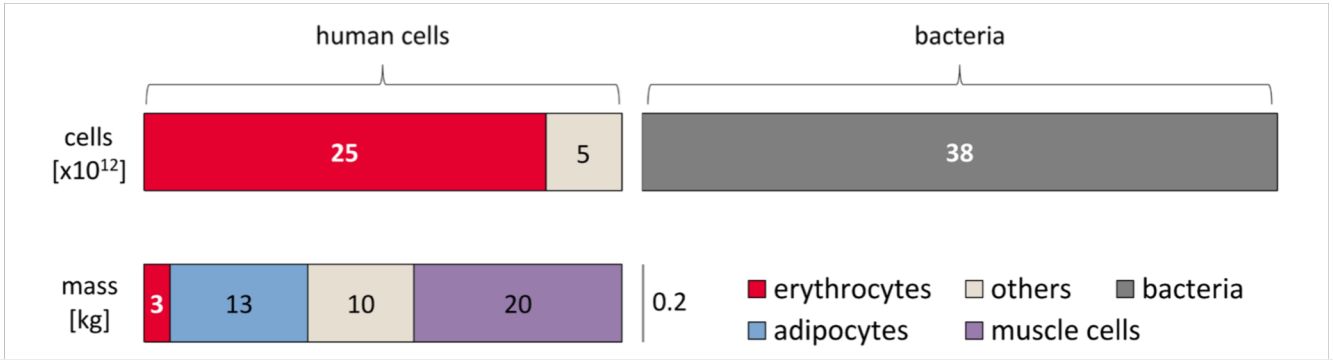
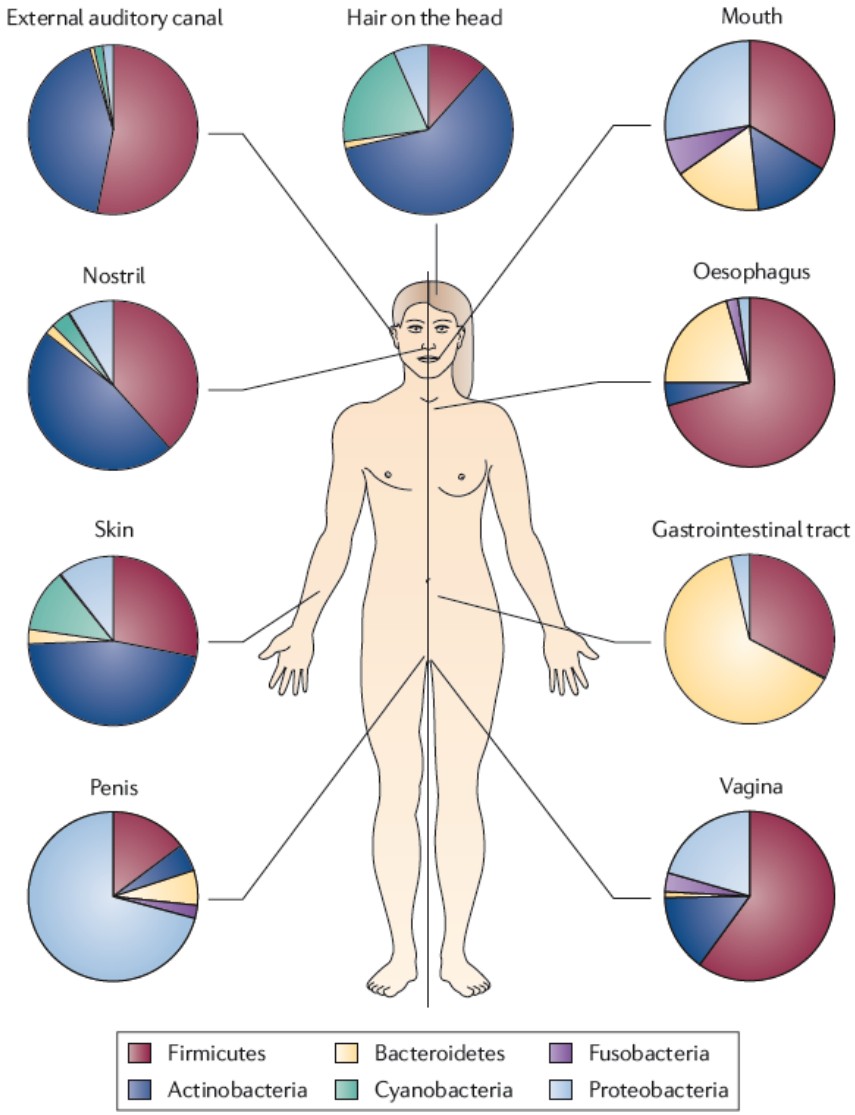


Table 3. B/H ratio for different population. See Table B in S1 Appendix for full references.

population segment	body weight [kg]	age [y]	blood volume [L]	RBC count [10^{12}/L]	colon content [g]	bac. conc. [10^{11}/ g wet] (1)	total human cells [10^{12}] (2)	total bacteria [10^{12}]	B:H
ref. man	70	20–30	4.9	5.0	420	0.92	30	38	**1.3**
ref. woman	63		3.9	4.5	480	0.92	21	44	**2.2**
young infant	4.4	4 weeks	0.4	3.8	48	0.92	1.9	4.4	**2.3**
infant	9.6	1	0.8	4.5	80	0.92	4	7	**1.7**
elder	70	66	3.8 (3)	4.8	420	0.92	22	38	**1.8**
obese	140		6.7	5.0(4)	610(5)	0.92	40	56	**1.4**

(Sender 2016)

Unterschiede

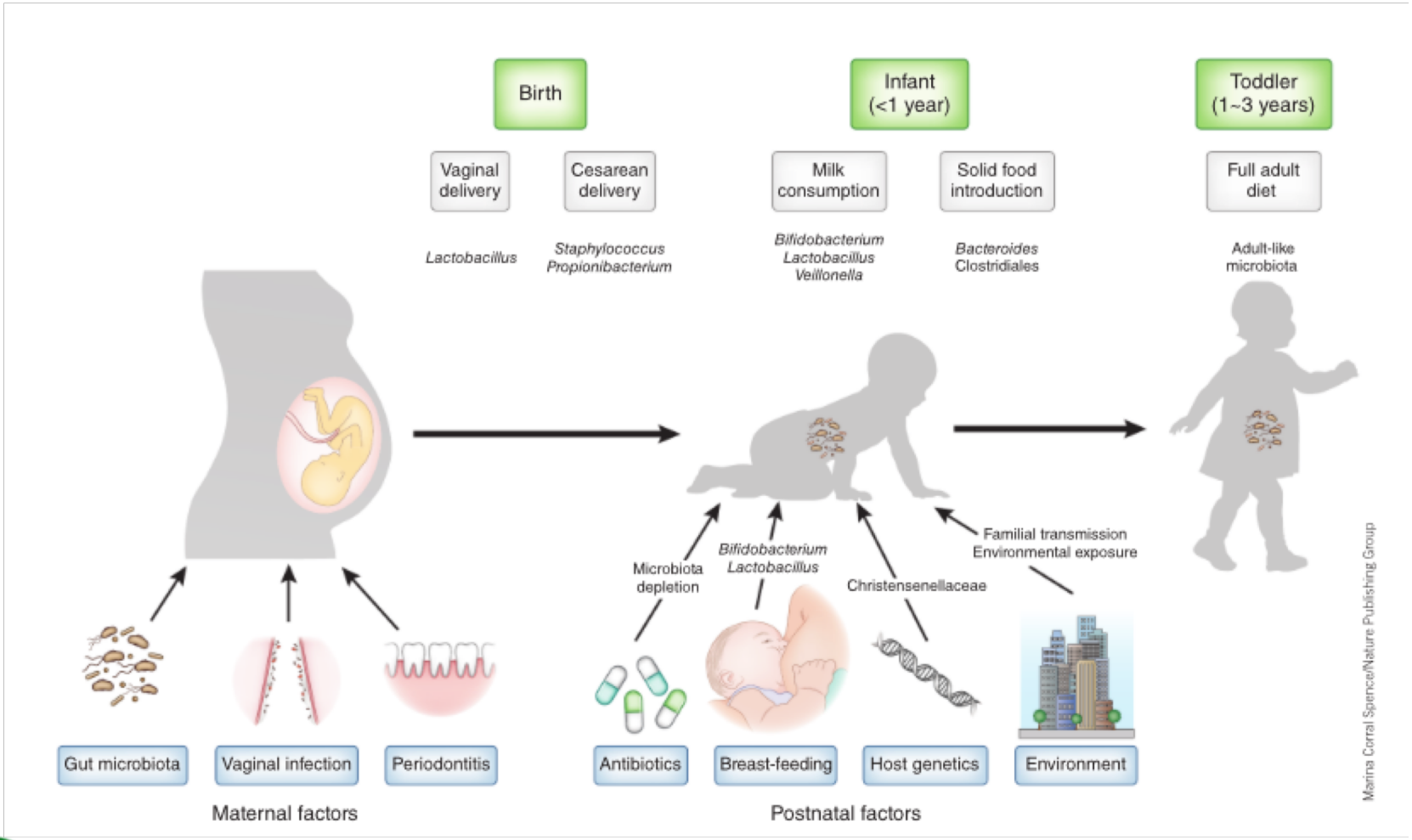


Spor A et al.
Nat Rev Microbiol 2011

Einflussfaktoren

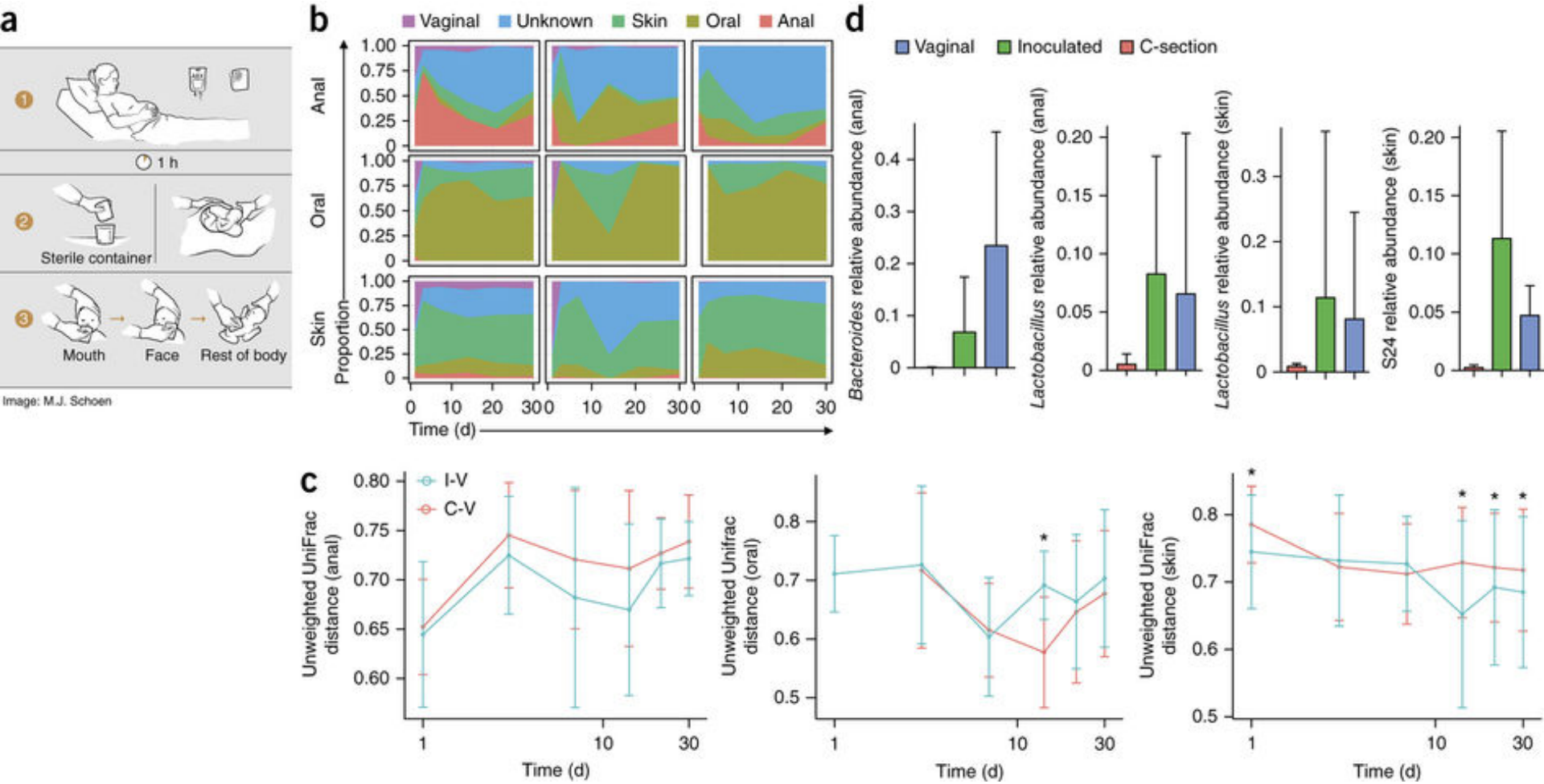
- **Nahrung**
  - Art der Lebensmittel (Ballaststoffe)
  - Mikroorganismen in der Nahrung
  - Zeitpunkt der Nahrungsaufnahme
- **Medikamente**
  - Antibiotika, Protonenpumpenhemmer,...
- **Genetische Faktoren**
  - Immunsystem - Polymorphismen
- **Umwelteinflüsse**
  - Infektionen
- **Frühkindliche Faktoren**
  - Sectio vs. natürliche Geburt
  - Ernährung
- **Geschlecht**

Entwicklung



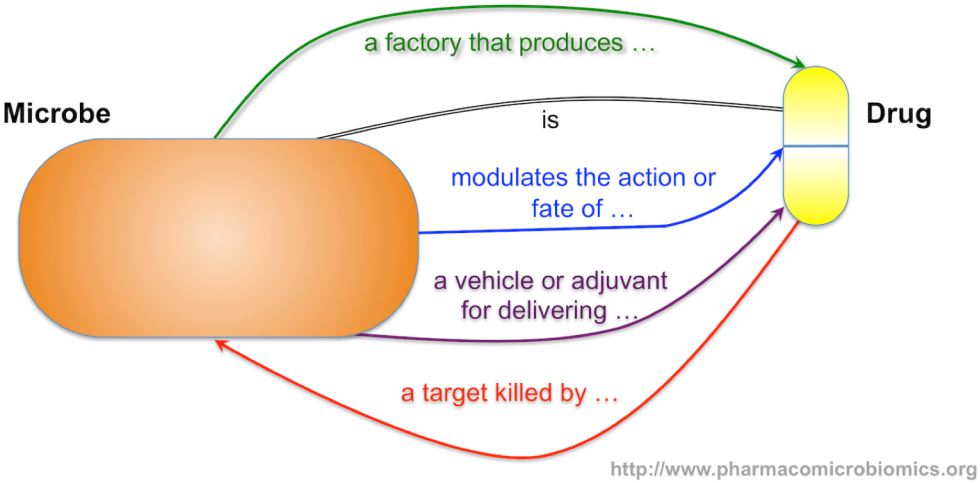
(Tamburini 2016)

Geburtsmodus



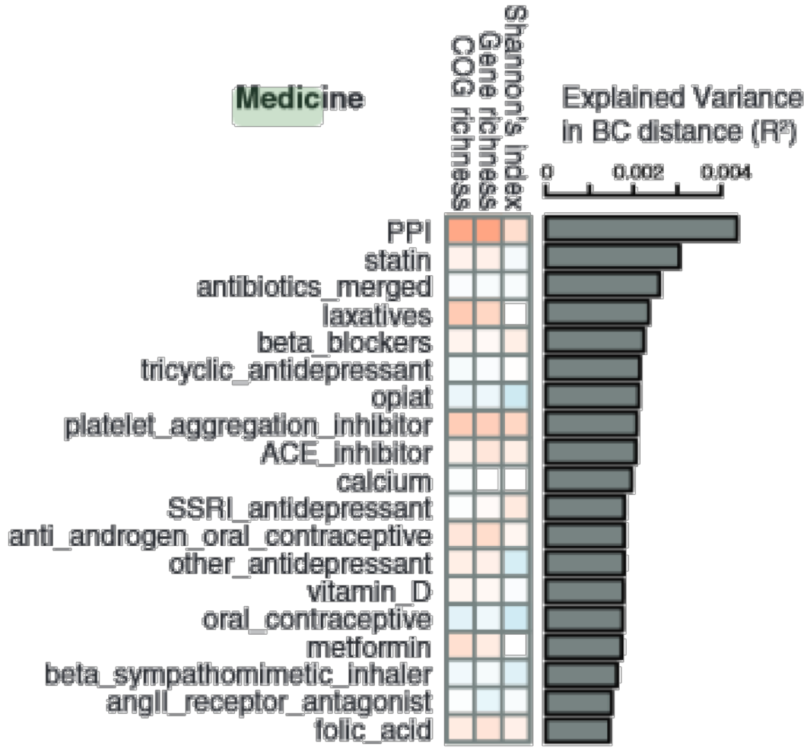
(Dominguez-Bello 2016)

Medikamente



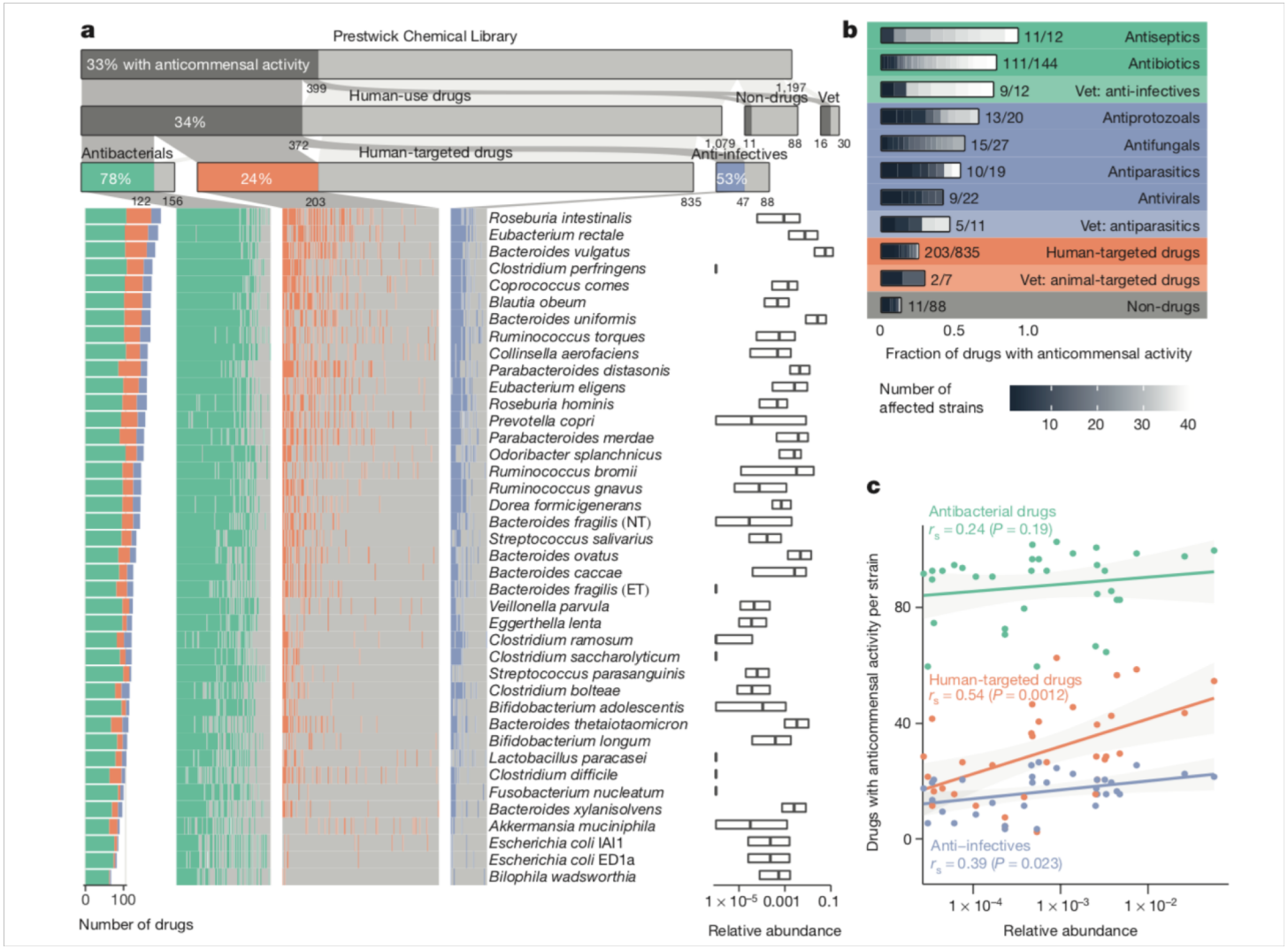
From a pharmacological stand point, a microbe can be regarded as a factory to produce drugs (e.g., antibiotics, digestive enzymes); a vehicle or adjuvant for drug delivery or vaccine, respectively; a target of a drug's action (e.g., antibiotics and other antimicrobials); a positive or negative modulator of a drug's fate and action; and finally the microbe itself can sometimes be considered as a drug (e.g., probiotics). From Rizkallah et al. 2010. CPPM 8(3) 182 (DOI: 10.2174/187569210792246326)

http://www.pharmacomicrobiomics.org



(Zhernakova 2016)

Viele Medikamente beeinflussen das Mikrobiom



(Maier, Nature 2018)

Protonenpumpenhemmer

Ende 1960
Hässle/Astra
Suche nach
Substanz zur
Säuresuppression

1972 Vorläufer
von Omeprazol
entwickelt

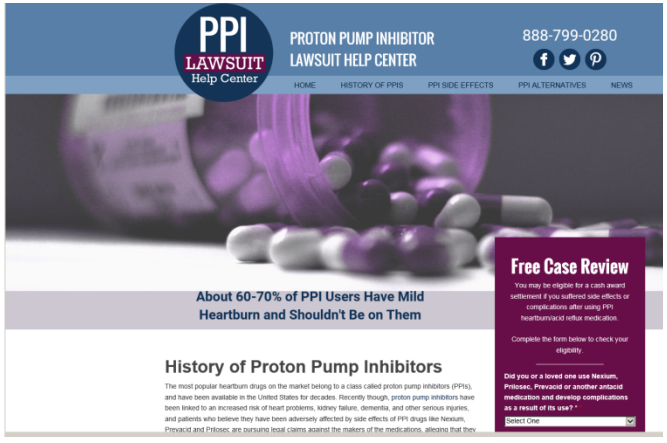
1988 Losec ® in
Europa
zugelassen

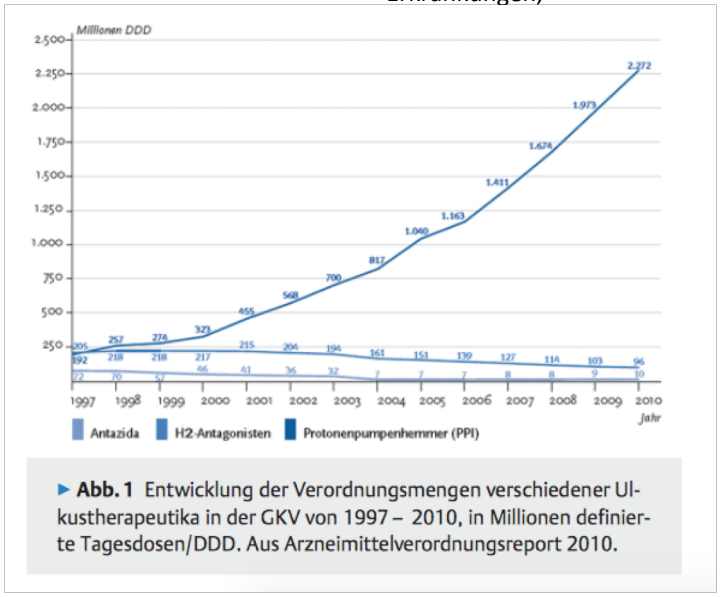
1989-1994 Suche
nach optimierten
Substanzen:
Esomeprazol

1996 Losec
meistverkauftes
Medikament aller
Zeiten

Ab 2006

Berichte über Frakturen,
Osteoporose, Demenz,
kardiovaskulären
Erkrankungen,

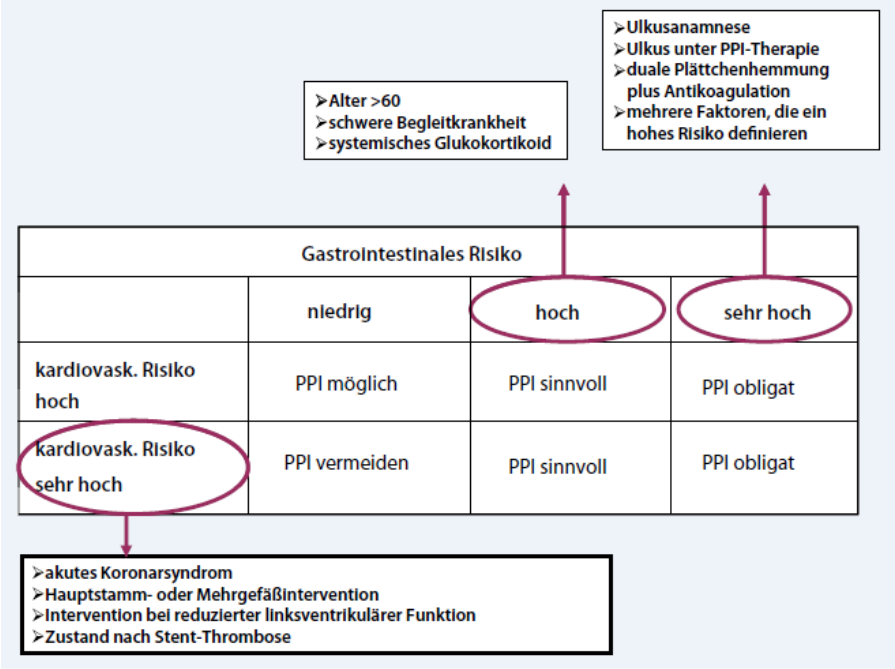




► **Abb. 1** Entwicklung der Verordnungsmengen verschiedener Ulkustherapeutika in der GKV von 1997 – 2010, in Millionen definierte Tagesdosen/DDD. Aus Arzneimittelverordnungsreport 2010.

Indikationen PPI

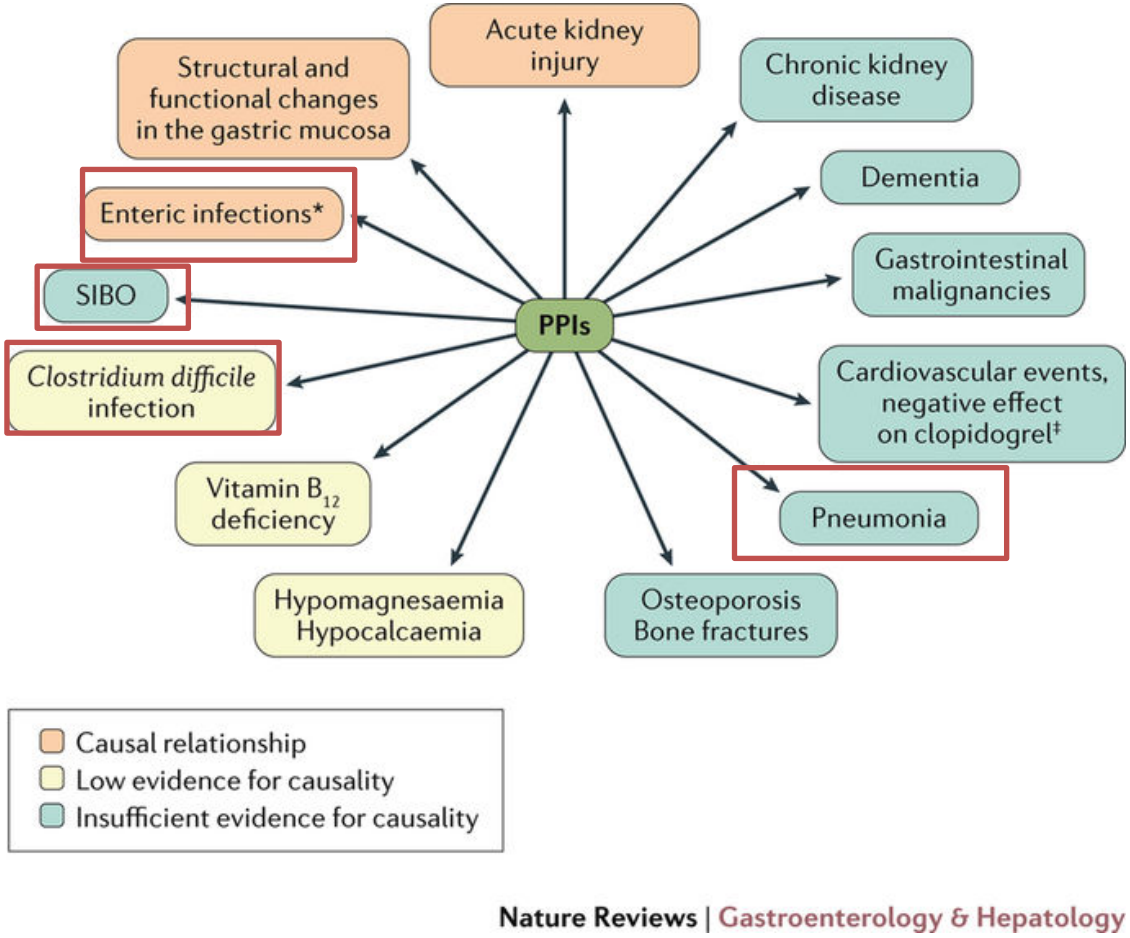
- Kurzzeittherapie
  - erosive Ösophagitis
  - peptisches Ulcus
  - Helicobakter-Gastritis/Ulcus
- Dauertherapie
  - GERD
  - Zollinger-Ellison Syndrom
- Prävention von Ulcuserkrankung bei Hochrisiko-Konstellationen (NSAR plus Steroid, kardiale Risikosituation)



„Wenn behauptet wird, dass eine Substanz keine Nebenwirkungen zeigt, so besteht der dringende Verdacht, dass sie auch keine Hauptwirkung hat.“

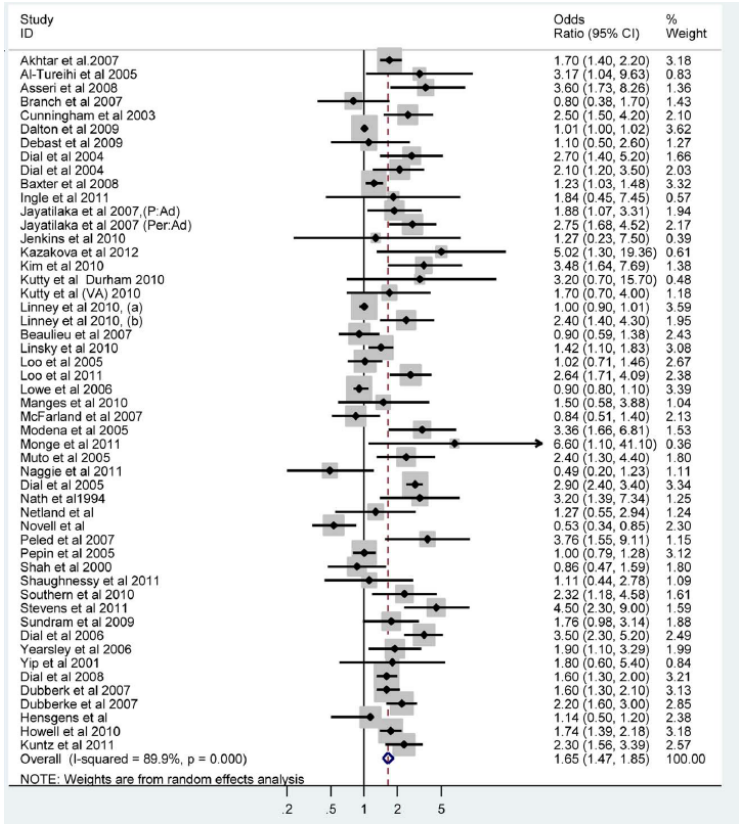
G. Kuschinsky

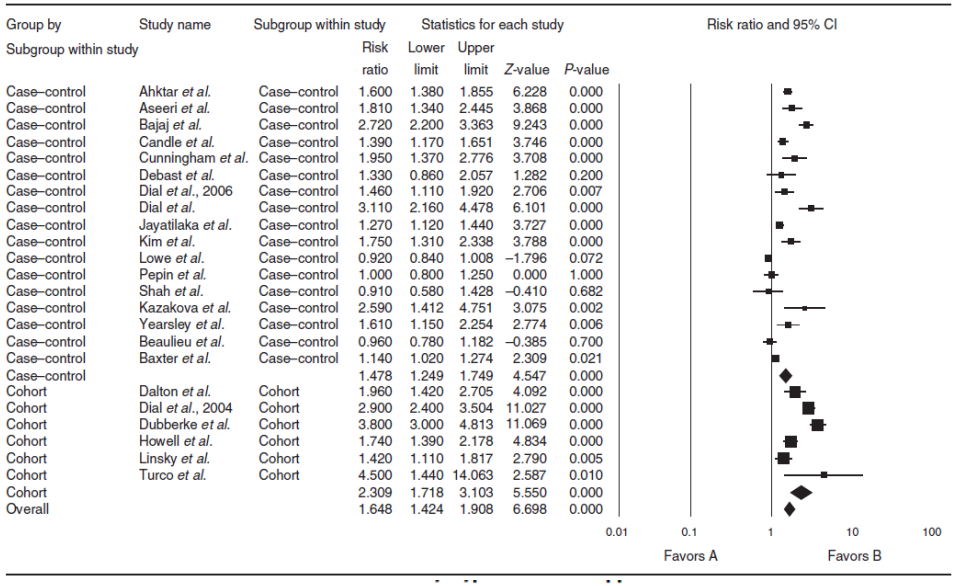
Nebenwirkungen



(Malfertheiner, Nature reviews 2017)

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 Darminfektionen

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

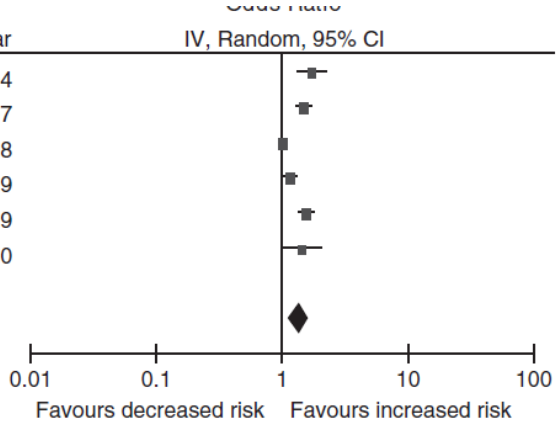
(Bavishi 2011)

Pneumonie

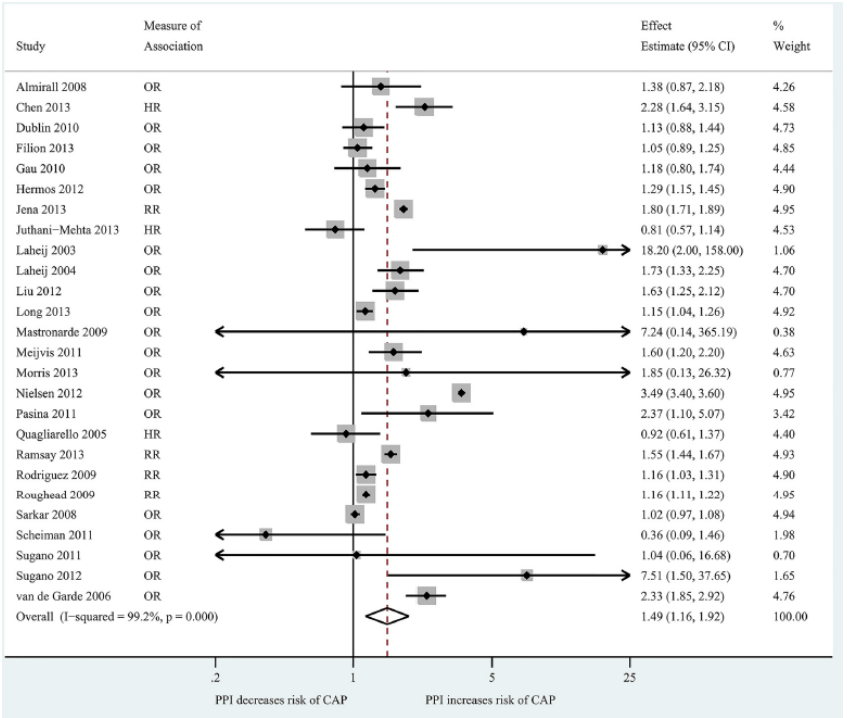
Study or Subgroup	log [Odds Ratio]	SE	Weight	IV, Random, 95% CI	Year
Laheij *et al* 2004	0.54812141	0.13412022	14.4%	1.73 [1.33, 2.25]	2004
Gulmez *et al* 2007	0.40546511	0.06843469	17.9%	1.50 [1.31, 1.72]	2007
Sarkar *et al* 2008	0.01980263	0.02740312	19.3%	1.02 [0.97, 1.08]	2008
Rodriguez *et al* 2009	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: $Z = 3.10$ ($P = 0.002$)



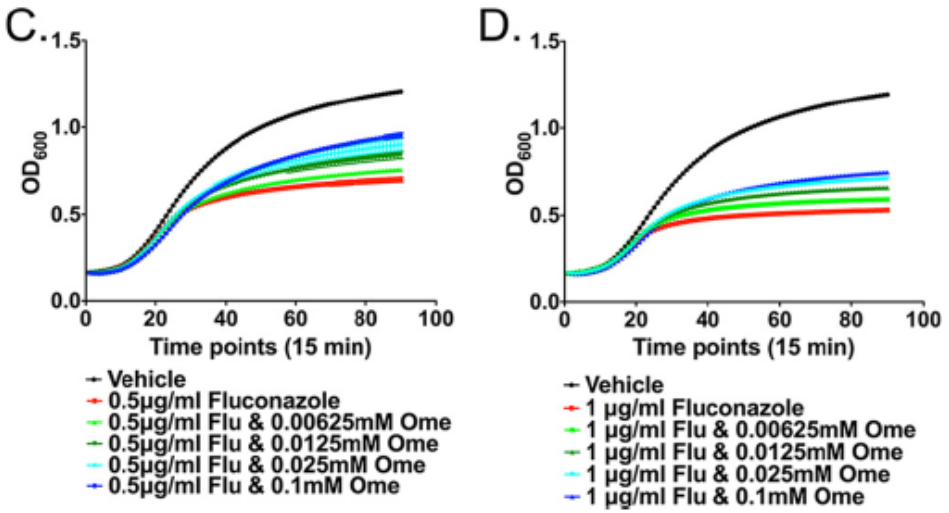
- Vor allem innerhalb der ersten 30 Tage der PPI Einnahme
- Keine Risikoerhöhung bei H2 Blockern
- Gründe
  - pH-Erhöhung
  - Mikrobiomveränderungen
  - Mikroaspiration
  - direkter Effekt auf Protonenpumpen im Respirationstrakt



(Johnstone 2010)

Pilzinfektionen

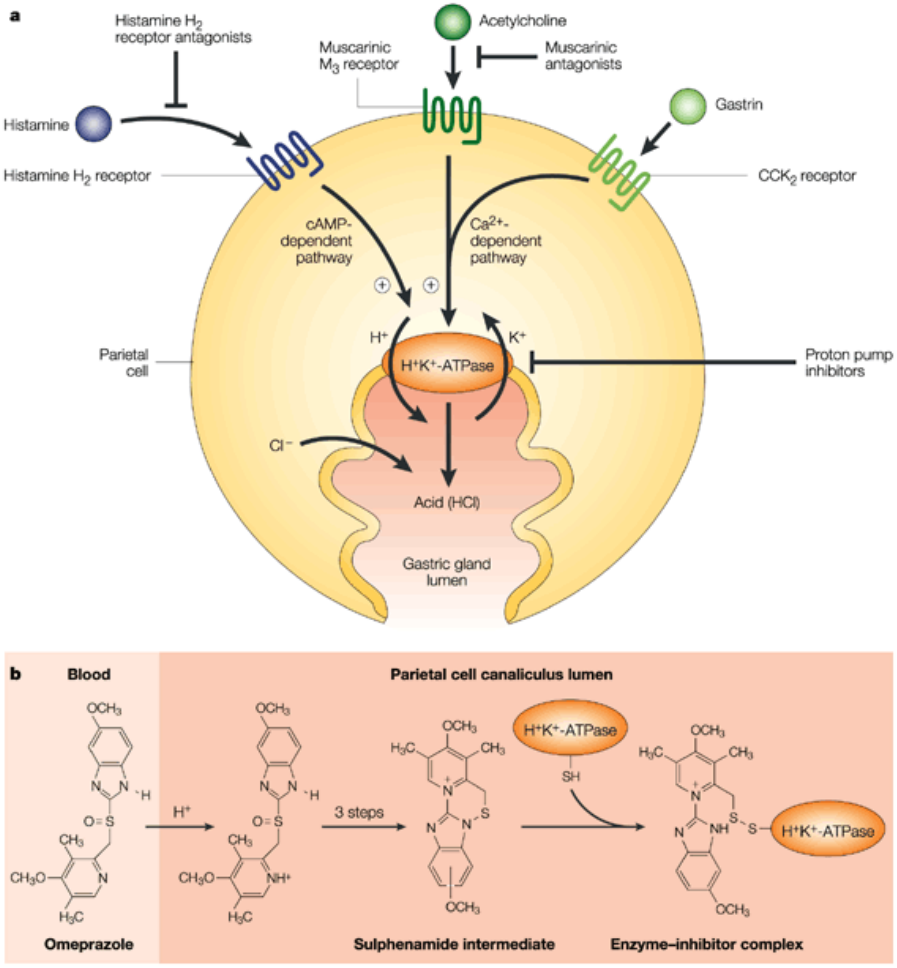
- Postoperative intraabdominelle Candida-Infektionen häufiger
- Risiko für Candidainfektionen in Oropharynx und Ösophagus erhöht



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

PPI und Mikrobiom

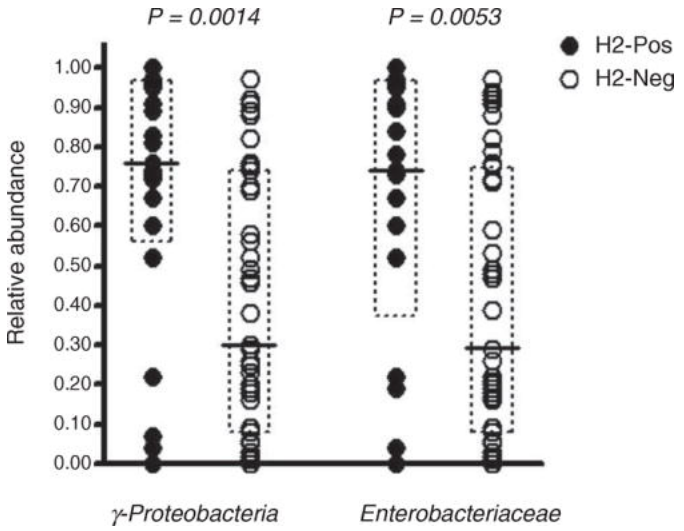
- Direkte und indirekte Effekte
- Direkt
  - PPIs hemmen H+/K+ P-Typ ATPase
  - Bakterien, Pilze, Protozoen haben diese ATPase auch
- Indirekt
  - pH Änderung beeinflusst Zusammensetzung des Mikrobioms
    - Bakterien können sich besser vermehren
    - Eingebrachte Bakterien können nicht vernichtet werden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



Nature Reviews | Drug Discovery

Säuresuppression oder Substanzeffekt?

- Daten vor allem aus der Pädiatrie
- “Dosis“-abhängiger Effekt: Stärke der Säuresuppression
- Niedriger Diversität und taxonomische Unterschiede auch durch H2 Blocker



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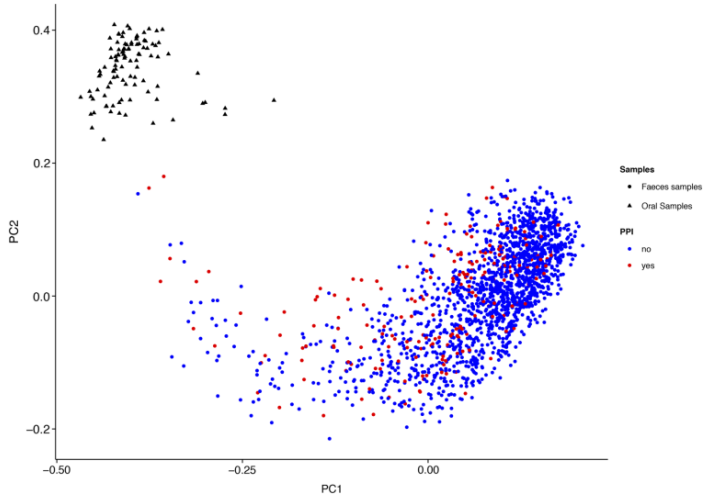
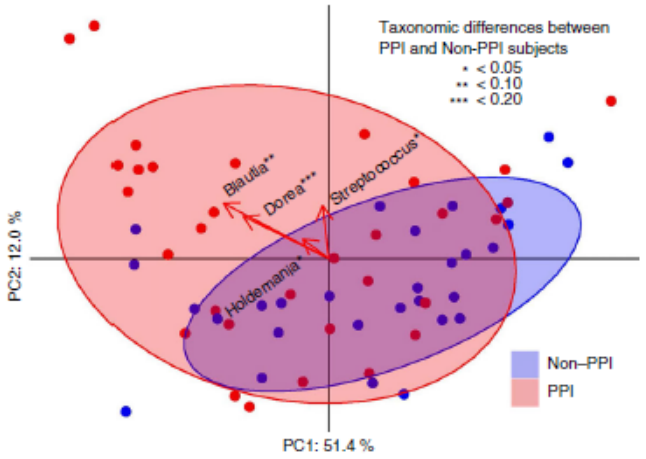
Proton pump inhibitor with or without H2RA (n = 14)	12	2	21.5 (4.71–98.6)

(Freedberg D., Clin Infect Dis. 2015, Gupta R., Journal of Pediatric Gastroenterology and Nutrition 2013)

PPI verändern das Mikrobiom

- „Oralisierung“
  - Keime aus dem Mund steigen im Darm an (Veillonella, Staphylococcus, Streptococcus)
  - Speichel und Magensaft werden sich ähnlicher („clustern“)
- Verminderte Kolonisations-Resistenz
  - Verminderte Diversität
  - Vermehrte Gesamt-Bakterienzahl
  - Enterococcus, E. coli ↑

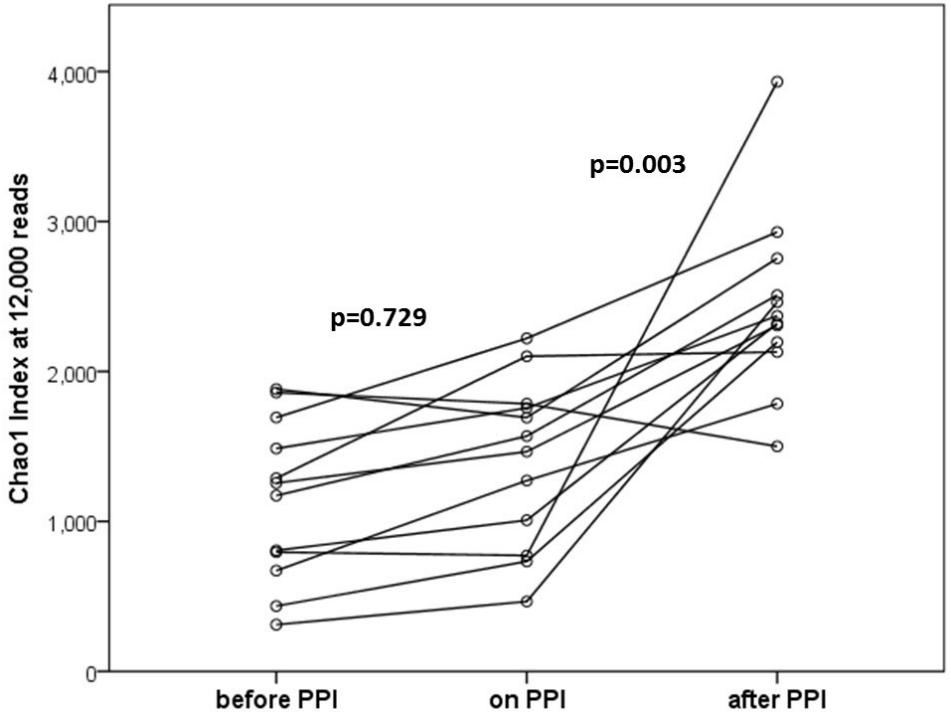




(Tsuda 2015, Clooney 2016, Imhann 2016, 2017)

Säuremangel und Mikrobiomentwicklung

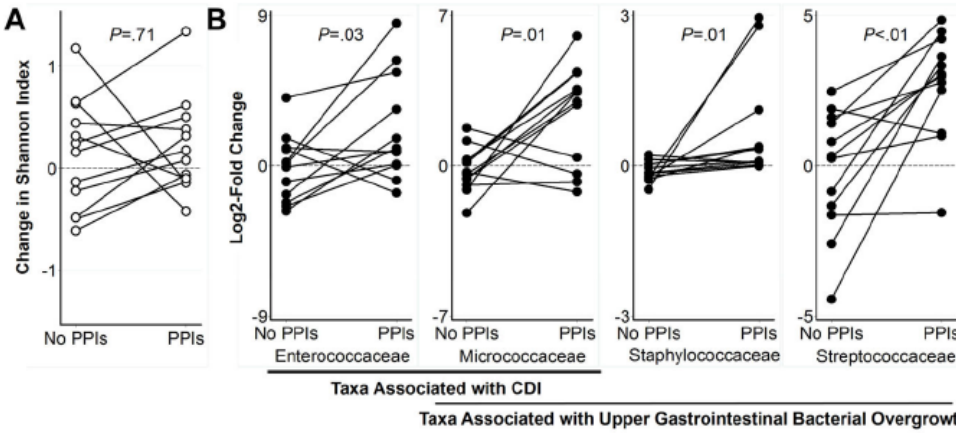
- 12 Kinder mit Reflux
- PPI für 18 (8-44) Wochen
- Diversitätsentwicklung verhindert!

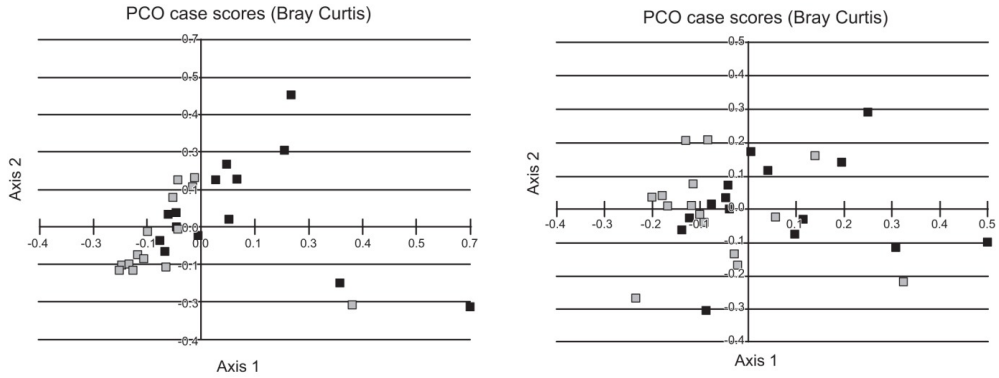


(Castellani 2017)

PPI verändern das Mikrobiom: Longitudinal

- gesunde Probanden
  - Oralisierung
  - funktionelle Änderungen
  - Einfluss auf Diversität nach 14-28 Tagen noch nicht sehr ausgeprägt
- Wenn Mikrobiom bereits geschädigt:
  - stärkere Effekte





(Bajaj 2014, Freedberg, 2015, Reveles 2018)

Einfluss auf Mortalität?

- >5.4 Millionen Patienten
- PPI Einnahme >1 Jahr: 50% höheres Risiko zu sterben

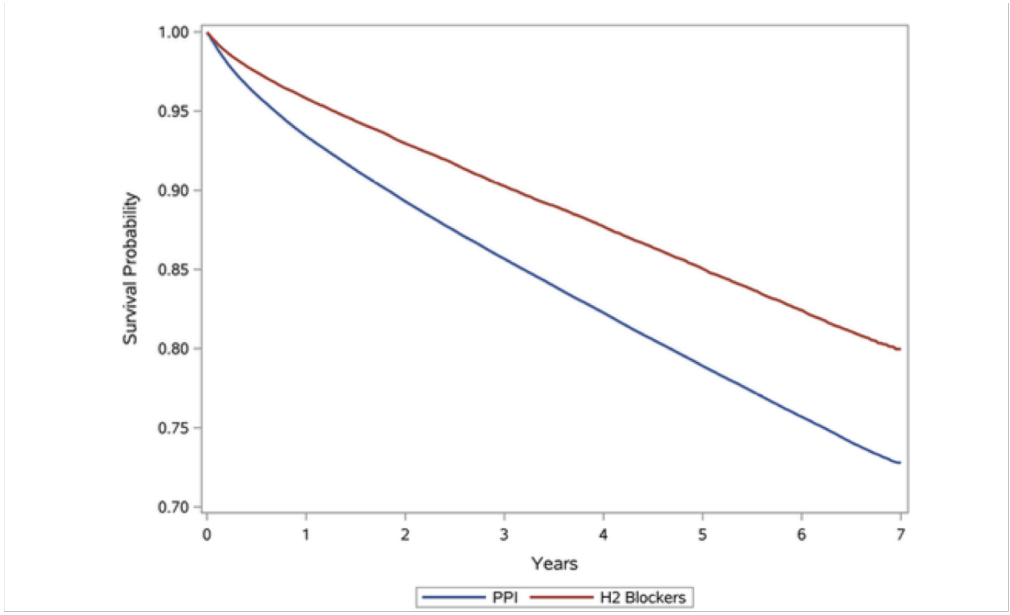


Table 3 Duration of exposure to PPI and risk of death among new users of PPI (n=1 66 098)

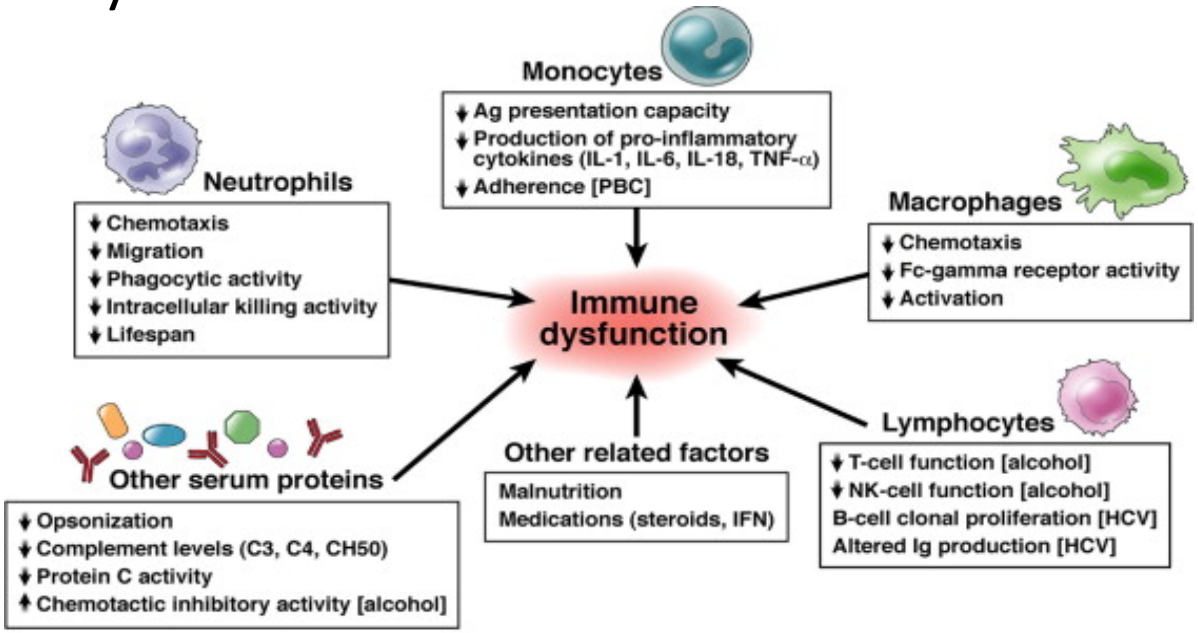
Duration (days)	≤30	31–90	91–180	181–360	361–720
N (%)	24 748 (14.90)	39 345 (23.69)	29 334 (17.66)	33 907 (20.41)	38 764 (23.34)
HR (95% CI)	1	1.05 (1.02 to 1.08)	1.17 (1.13 to 1.20)	1.31 (1.27 to 1.34)	1.51 (1.47 to 1.56)

Within people exposed to PPI between 1 and 720 days.

(Xie 2017)

Hochrisikogruppe: Leberzirrhose

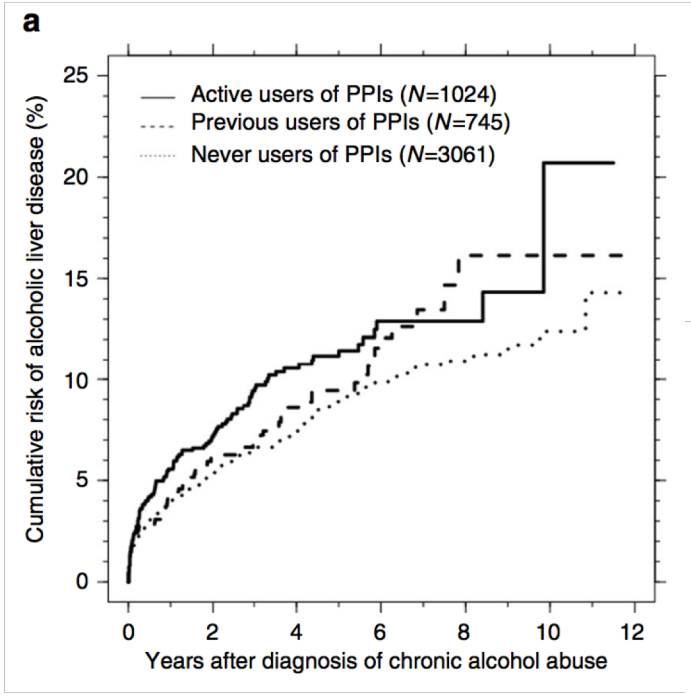
- PPI Verschreibung häufig
  - Zunehmend mit Schweregrad
  - 50% der Verschreibungen ohne evidenzbasierte Indikation
- Dysbiose
- Immundysfunktion

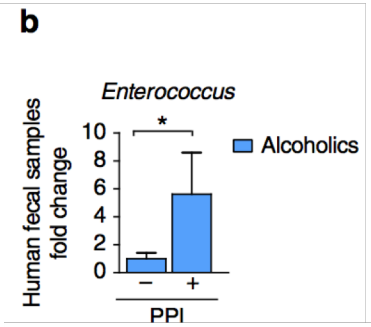


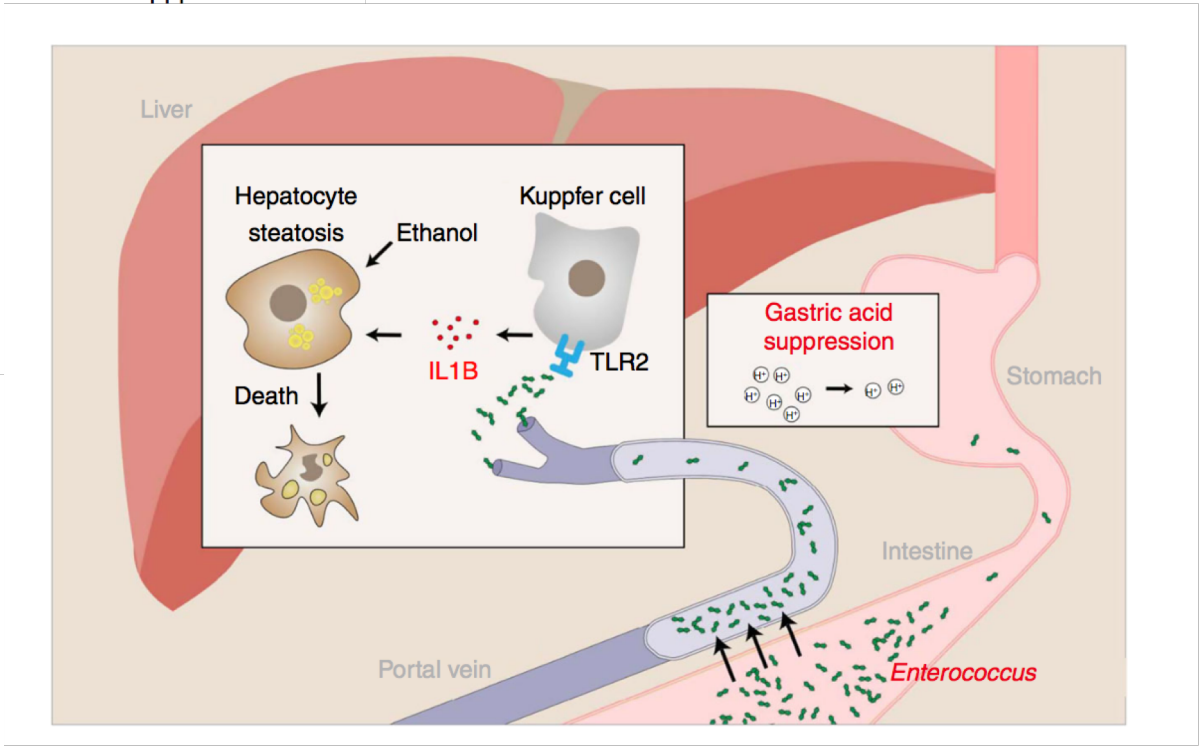
Ag, antigen; HCV, hepatitis C virus, IFN, interferon; Ig, immunoglobulin; NK, natural killer; PBC, primary biliary cirrhosis

(Bonell 2011)

Verlust der Magensäure erhöht Risiko für chronische Lebererkrankungen



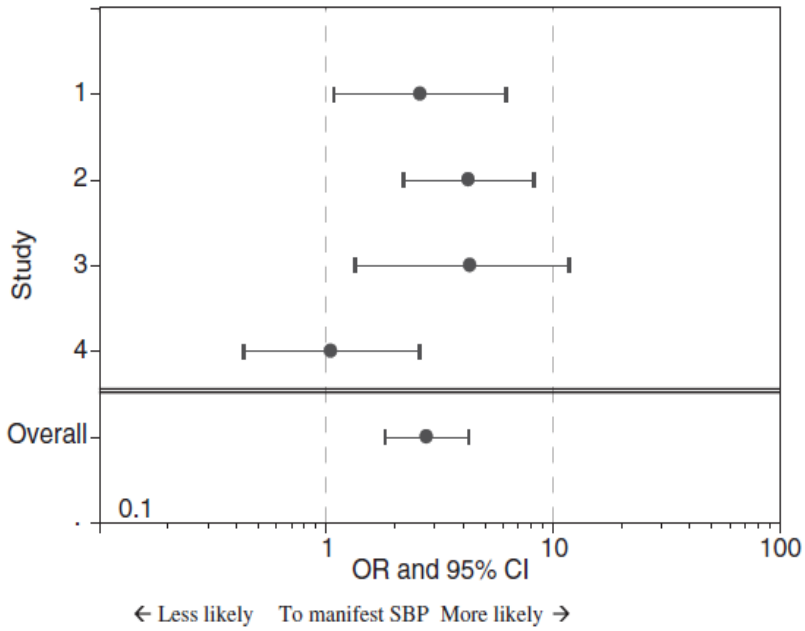




(Llorente 2017)

Infektionsrisiko bei Zirrhose + PPI

- Risiko für neuerliche Infektion fast 3fach erhöht
- Risiko für spontan bakterielle Peritonitis fast 3fach erhöht



		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

(Trikudanathan, 2011, O´Leary 2015)

Komplikationen und Mortalität

- Risiko für hepatische Enzephalopathie steigt
- Dosisabhängiger Effekt
- PPI und Mortalität?

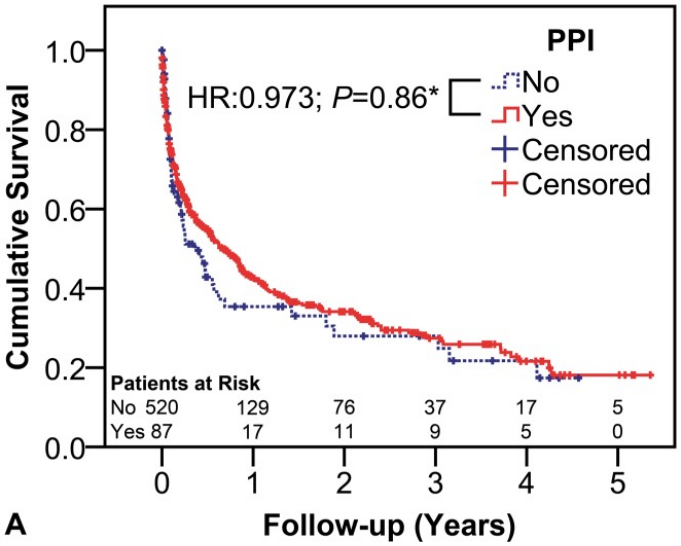
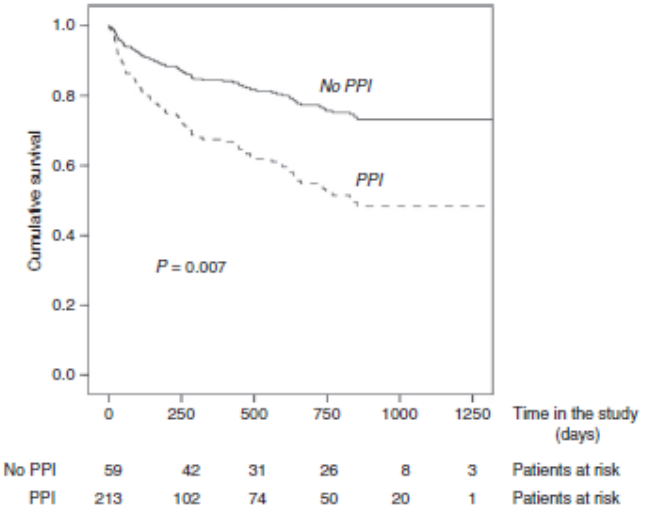


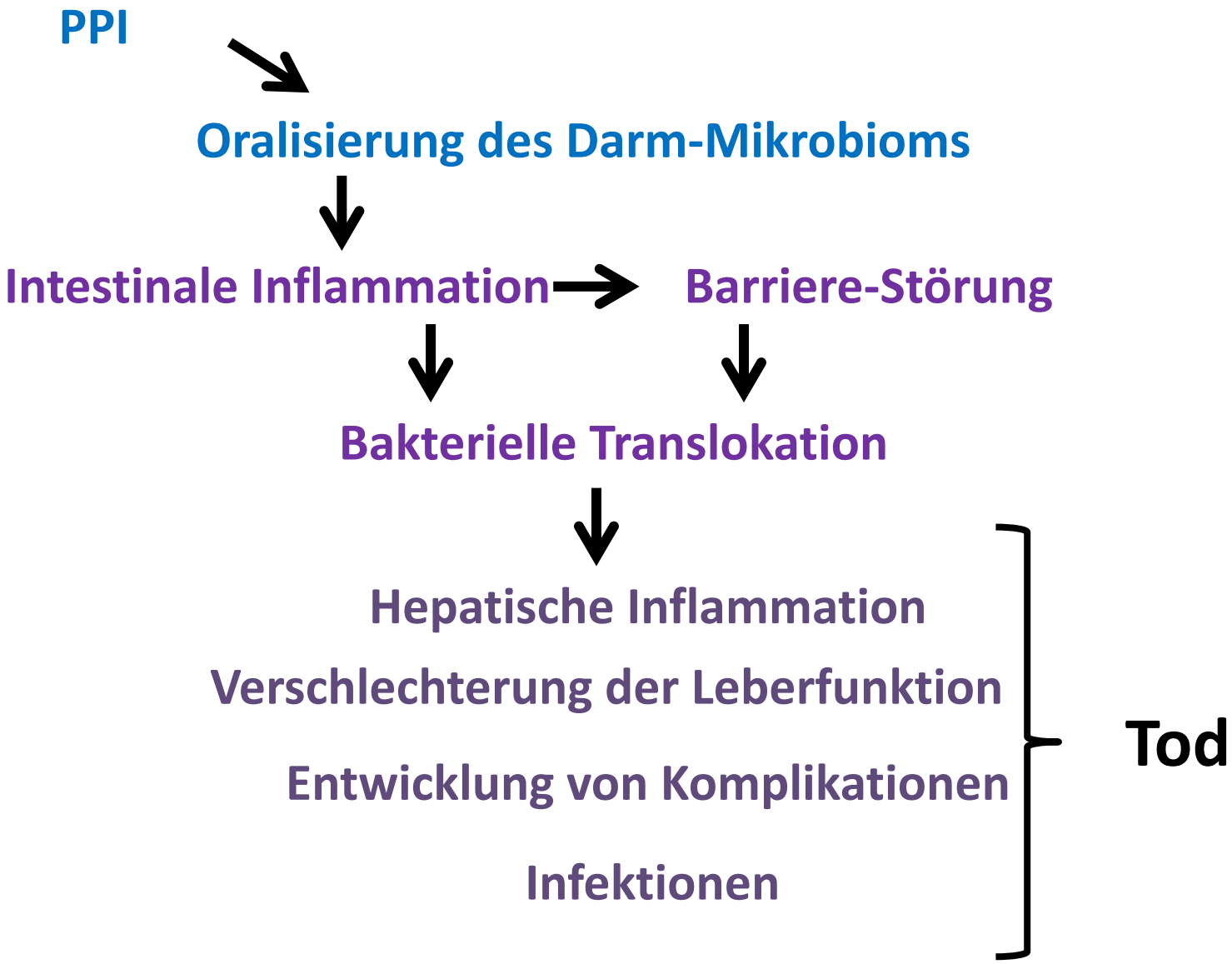
Table 2. Risk of Subsequent Hepatic Encephalopathy Among Patients With Cirrhosis

	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)**



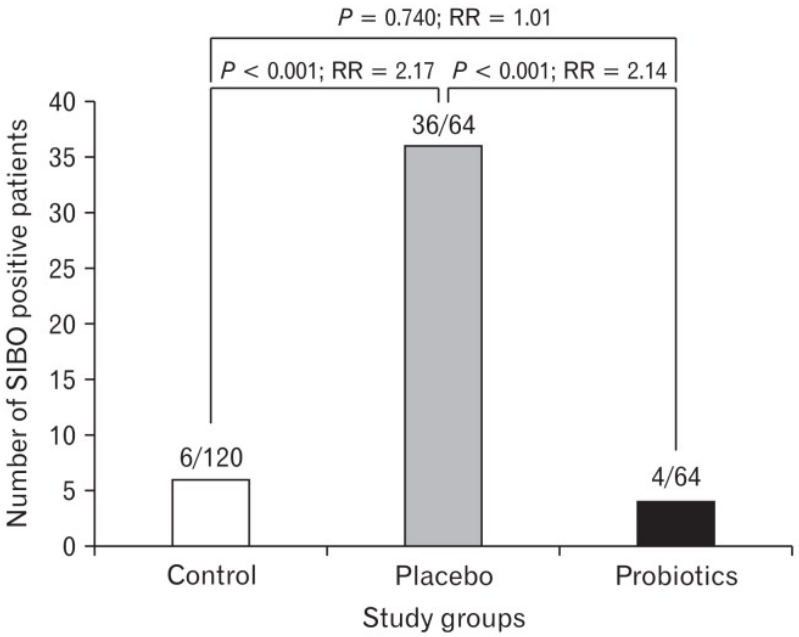
(Tsai 2017, Mandorfer 2014, Dultz 2015)

Hypothese


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

Probiotika als Therapieansatz

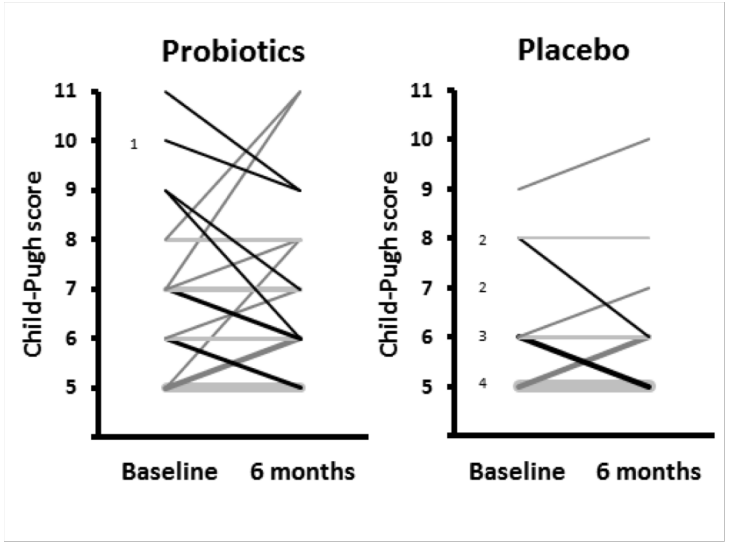
- Kinder mit Reflux
- PPI +/- *Lactobacillus reuteri* DSM 17938 für 12 Wochen
- SIBO (H2-Atemtes)



(Belei 2018)

Omnibiotic® Hetox

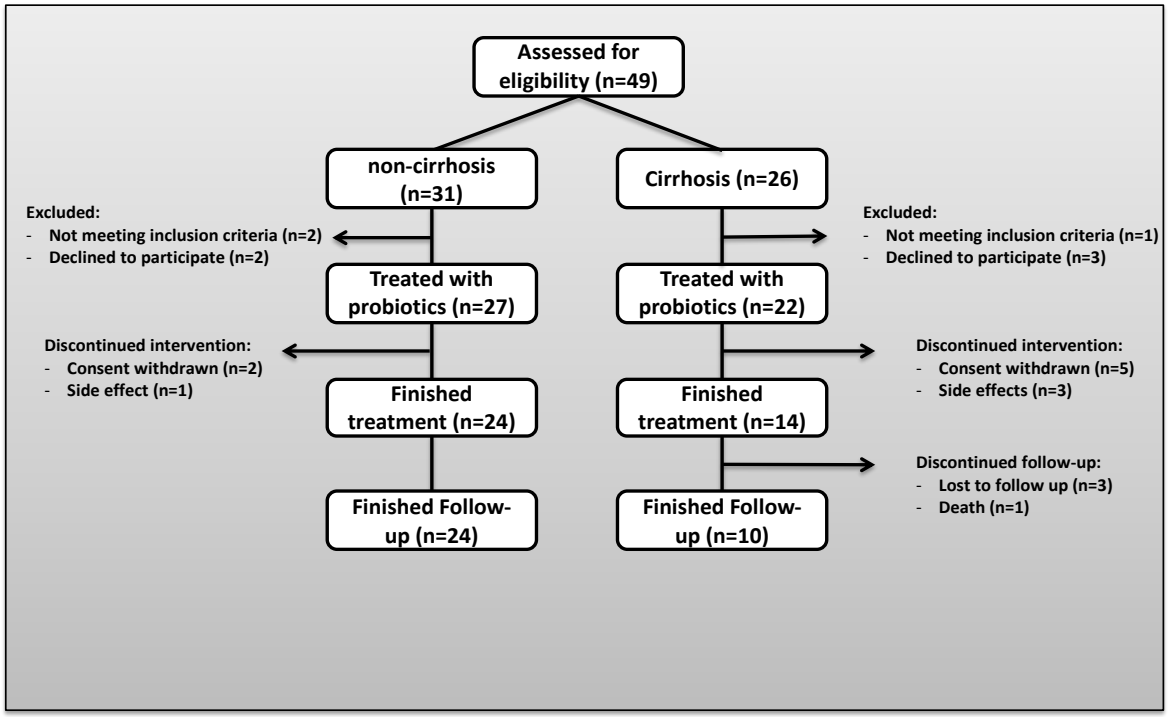
Omnibiotic® Hetox	*B. bifidum* W23	*B. lactis* W52	*L. acidophilus* W37	*L. brevis* W63	*L. casei* W56	*L. salivarius* W24	*Lc. lactis* W19	*Lc.* Lactis W58
In vitro strengthening of the epithelial barrier after a pathogenic bacteria stressor	−	+	−	−	+	−	−	+
In vitro strengthening of the epithelial barrier after an inflammatory stressor	+	−	+	+	+	−	+	−
Inhibition of mast-cell activation	+	+	−	−	+	+	−	−
Stimulation of anti-inflammatory cytokine Il-10	+	+	+	+	+	−	−	+
Decreasing lipopolysachardide load	+	−	+	−	−	−	+	−



(van Hermet 2014, Horvath, 2016)

Probiotika zur Vermeidung von PPI induzierter Dysbiose

- Pilotstudie
- open-label, 12 Wochen
- 11 Stämme
  - *Bacillus coagulans* W183
  - *Bacillus subtilus* W201
  - *Bifidobacterium bifidum* W23
  - *Bifidobacterium lactis* W52
  - *Bifidobacterium lactis* W51
  - *Lactobacillus acidophilus* W37
  - *Lactobacillus acidophilus* W22
  - *Lactobacillus casei* W56
  - *Lactobacillus salivarius* W24
  - *Lactococcus lactis* W19
  - *Propionibacterium freudenreichii* W200
- 2 x 10^9 CFU/g
- Fructo-oligosaccharide und Inulin



Zusammenfassung

- Dysbiose – Resilienz
- Einflussfaktor Medikamente
- Beispiel PPI
  - Säuresuppression + zusätzliche Substanzeffekte
- Nebenwirkung:
  - Mikrobiomveränderung
  - Inflammation
  - Permeabilitätsstörung
  - Auswirkung auf Outcome
- Probiotika
  - Effekte auf Leberfunktion, Darm-Permeabiliät und Lebensqualität

Danke!

FWF Der Wissenschaftsfonds.

Das Land Steiermark
Wissenschaft und Forschung

GRAZ WISSENSCHAFT

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WINCLOVE BIO INDUSTRIES BV

FRESENIUS KABI