Faecotherapie „StuhlTransplantation“

– Perspektiven –

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Faecotherapie
Timeline (I)

- **Erstbeschreibung der Prozedur im 4. Jahrhundert n. Chr. (Ge Hong, China)**
  - **orale Therapie mit sog. „gelber Suppe“ im Buch „Kleine Therapie der Notfälle“**

Ge H. Zhou Hou Bei Ji Fang. Nachdruck: Tianjin Press 2000

- **systematische Beschreibung durch Li Shezhen im 16. Jahrhundert**
  - **verschiedene Präparationen angewandt**

Le S. Ben Can Ga Mu. Nachdruck: Huaxia Press, Bejing 2011

Faecotherapie
Timeline (II)

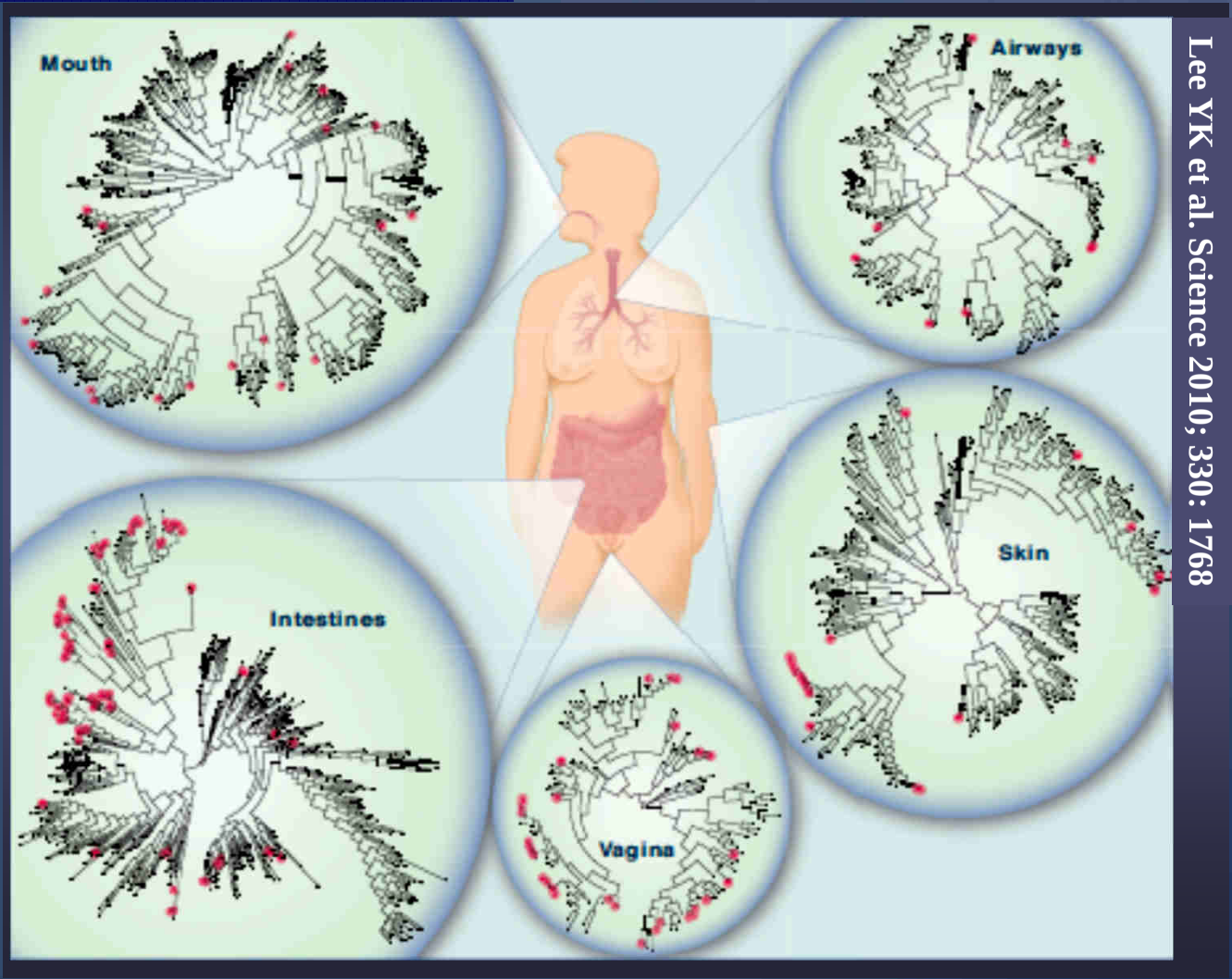
- **Anwendung bei Pferden mit Diarrhoe durch Fabricius Aquapendente (Italien, 17. Jahrhundert)**
  - **Therapie mittels Einläufen**

Borody TJ et al. Nature Rev Gastroenterol Hepatol 2011; 9:88

- **erste Anwendung bei vier CDI-Patienten durch Eisenman (1958, USA)**
  - **promptes Ansprechen und Ausheilung**

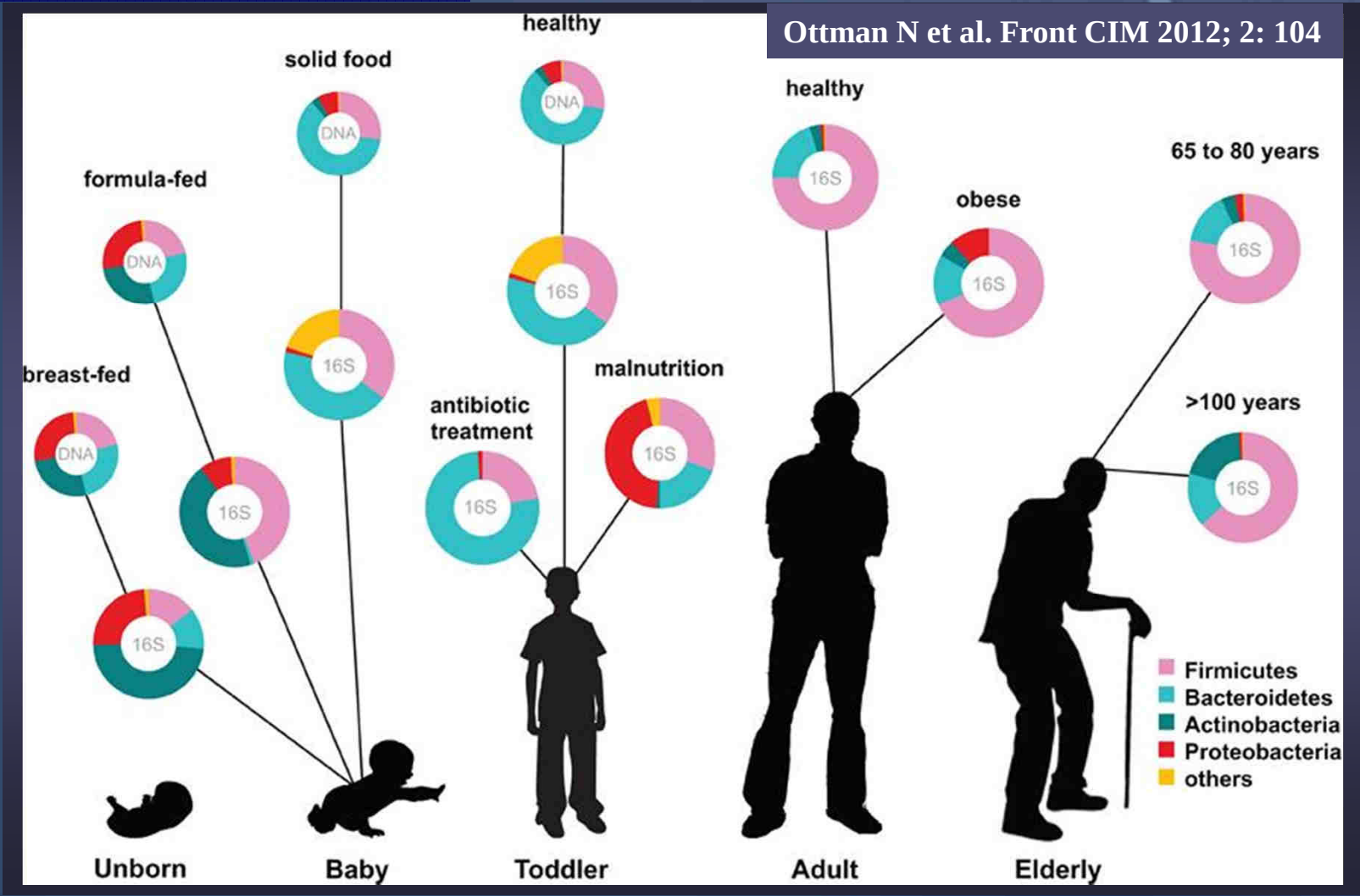
Eisenman B et al Surgery 1958; 44:854

Humanes Microbiom

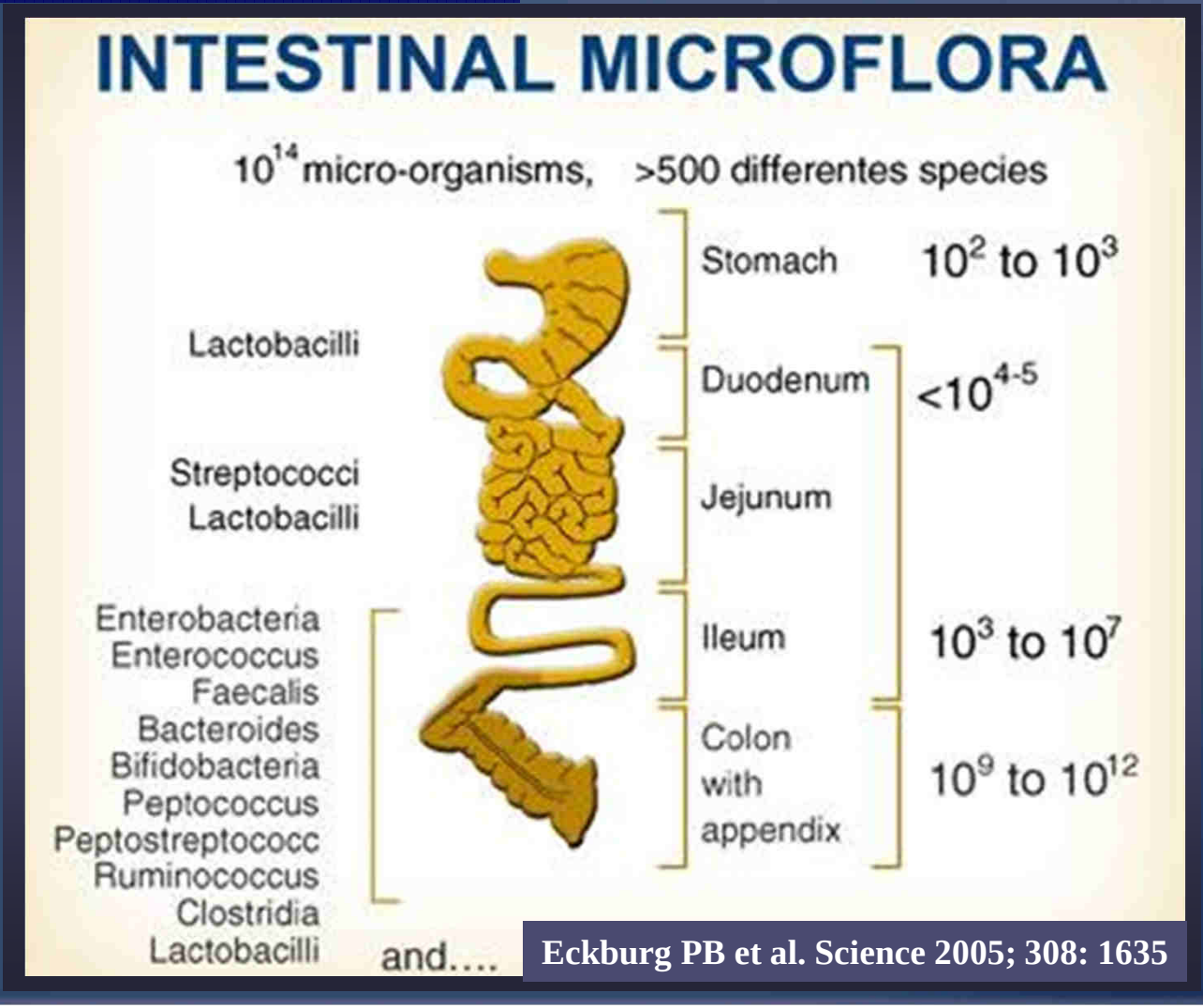


Lee YK et al. Science 2010; 330: 1768

Humanes Microbiom im Verlauf der Lebensalter



Humanes Microbiom



Eckburg PB et al. Science 2005; 308: 1635

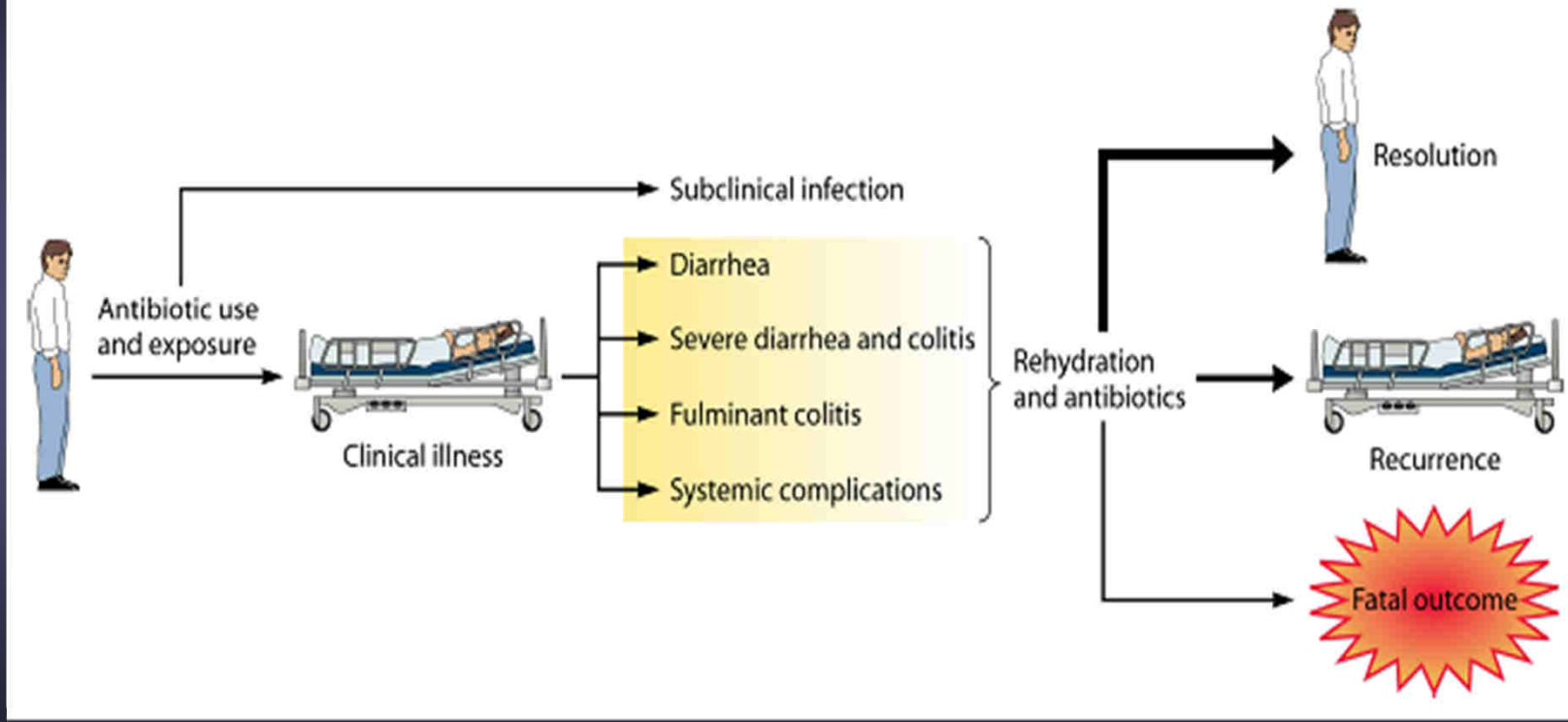
Krankheiten mit gestörtem intestinalen Mikrobiom – I

- **GI Trakt**
  - kolorektales Carzinom
  - Magenkarzinom
  - intestinales Lymphom
  - CED*
  - Colon irritabile*
  - Hepatische Enzephalopathie
  - Cholelithiasis
  - Gastroenteritis (insbesondere CDI)**

Krankheiten mit gestörtem intestinalen Mikrobiom – II

- **extraintestinal**
  - **Adipositas per magna***
  - **Diabetes mellitus***
  - **metabolisches Syndrom / Insulinresistenz****
  - **KHK**
  - **rheumatoide Arthritis***
  - **Autismus*, M. Parkinson*, Multiple Sklerose***
  - **Akne*, atopische Dermatitis***
  - **etc., etc., etc.**

C. difficile – understanding is a three-edged sword



Hunt J et al. Microbiol Mol Biol Rev 2013; 77: 567

Clostridium difficile Fakten (I)

- **Inzidenz steigend**
  - **Verdopplung der Fallzahl im eigenen Patientengut**
- **Letalität ansteigend**
  - **3.5% (1985) vs. 12.1% (2010)**

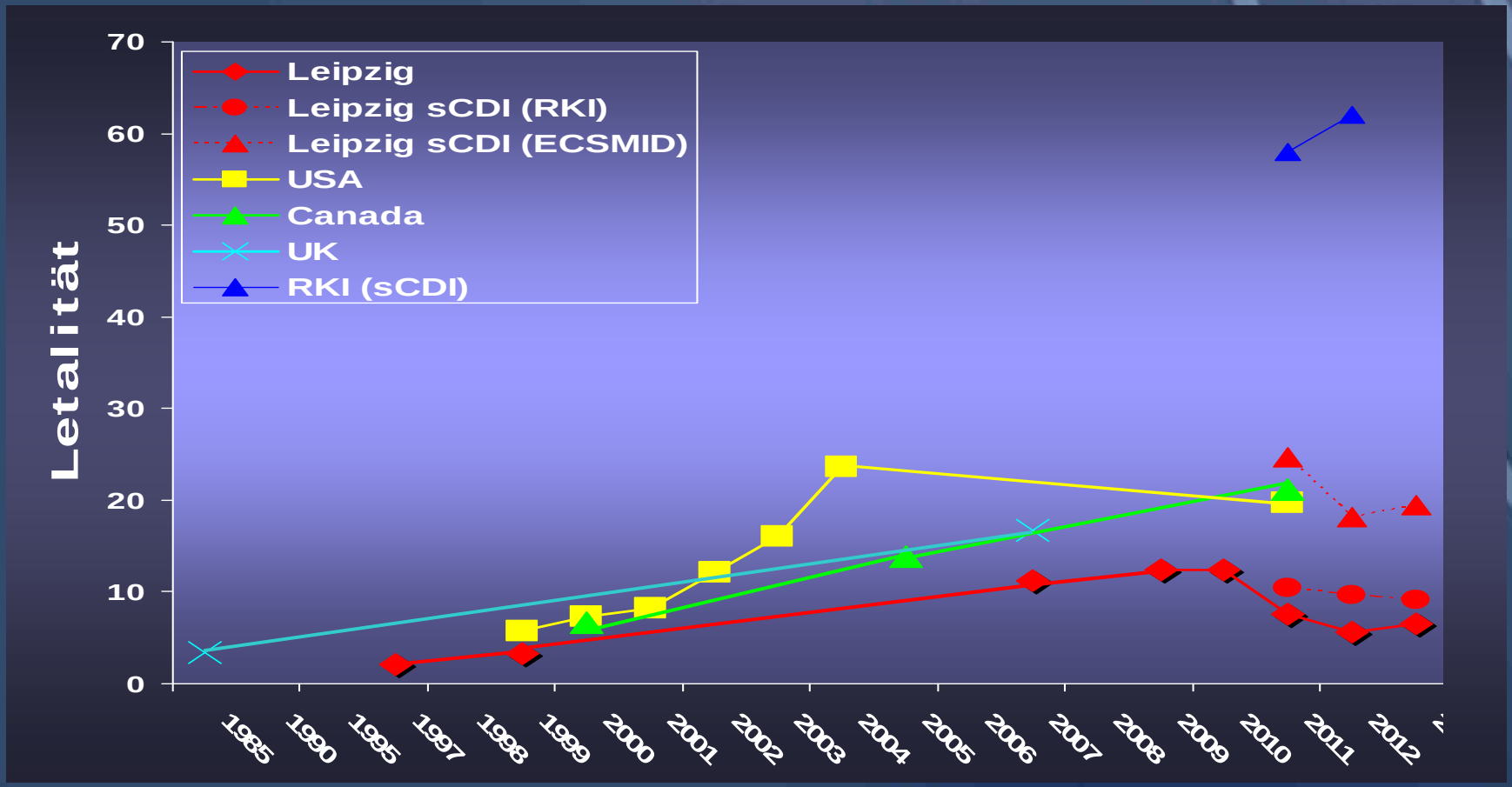
Morris et al., Arch Surg 2002;137:1096
Grünewald et al. CMI 2011

- **substantieller Kostenfaktor**
  - **3.6 Tage verlängerter Krankhausaufenthalt**
  - **2500 - 3500 € Mehrkosten**

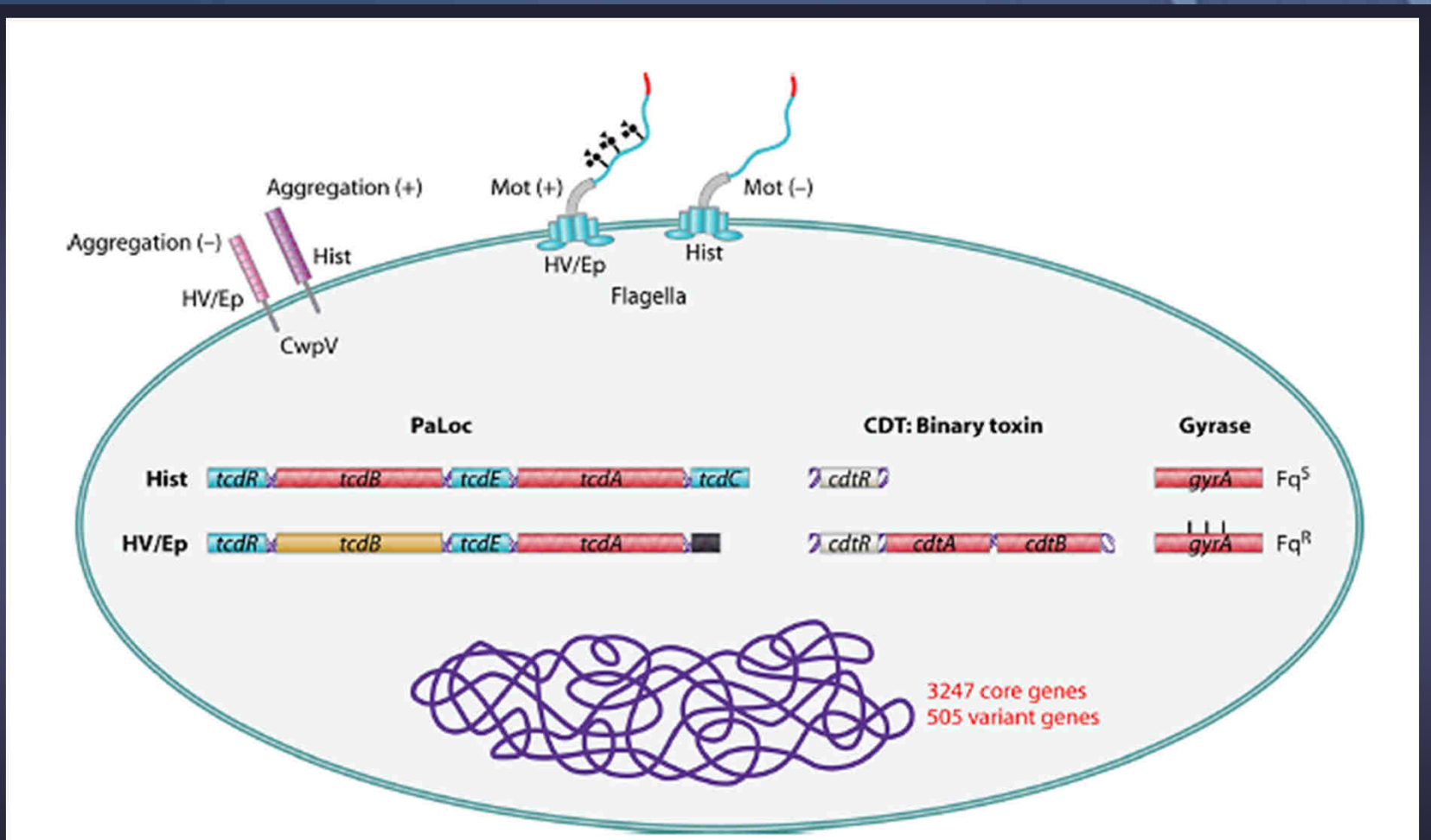
Kyne et al., CID 2002;34:346

Clostridium difficile
Letalität global

- **weltweit deutlicher Anstieg seit 1985**



C. difficile
Hypervirulenz – warum ?



Hunt J et al. Microbiol Mol Biol Rev 2013; 77: 567

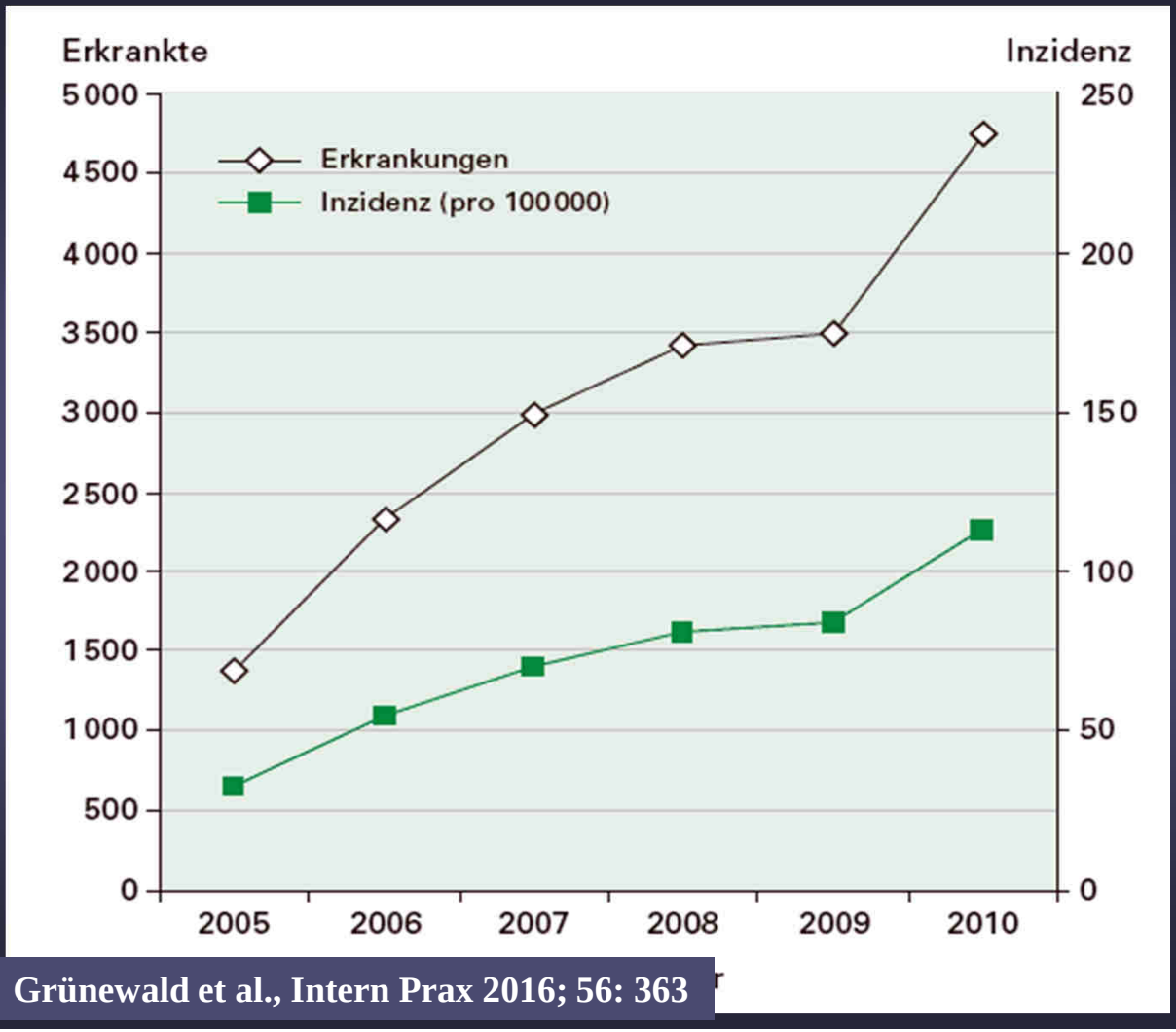
C. difficile – Ribotypen 027, 078, 017 als Risiko ?

- **027**
  - **Erstbeschreibung in Canada und USA 2002**
  - **TcdA+, TcdB+, CDT+, TcdCΔ18bp**
  - **Toxinproduktion ↑**
  - **Sporulierungsrate ↑**
  - **nahezu immer FQ (MXF)-Resistenz**
  - **klinische Verläufe schwerer und Letalität höher**

C. difficile – Ribotypen 027, 078, 017 als Risiko ?

- 078
  - Vorkommen in Italien, Irland und Canada
  - TcdA+, TcdB+, CDT+, TcdCΔ38bp
  - Toxinproduktion ↑
- 017
  - Vorkommen in Polen, Irland, NL und Canada
  - TcdA-, TcdB+, CDT-, TcdCΔ38bp
  - Toxinproduktion (↑)
  - schwere Verläufe (bis zu 40% Letalität)

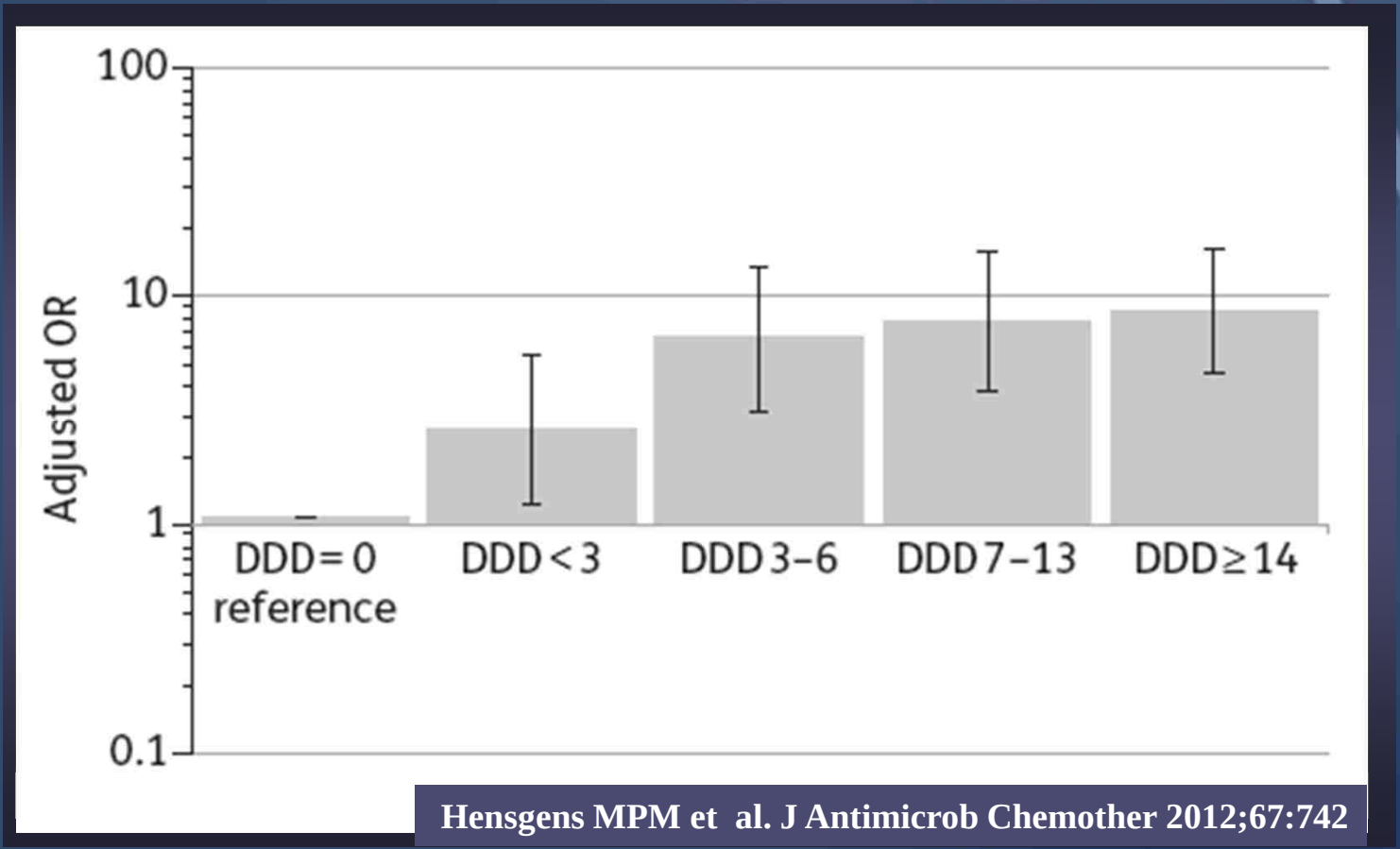
Clostridium difficile Epidemiologie (III)



Grünewald et al., Intern Prax 2016; 56: 363

Risk assessment ABx exposure

- cumulative dose



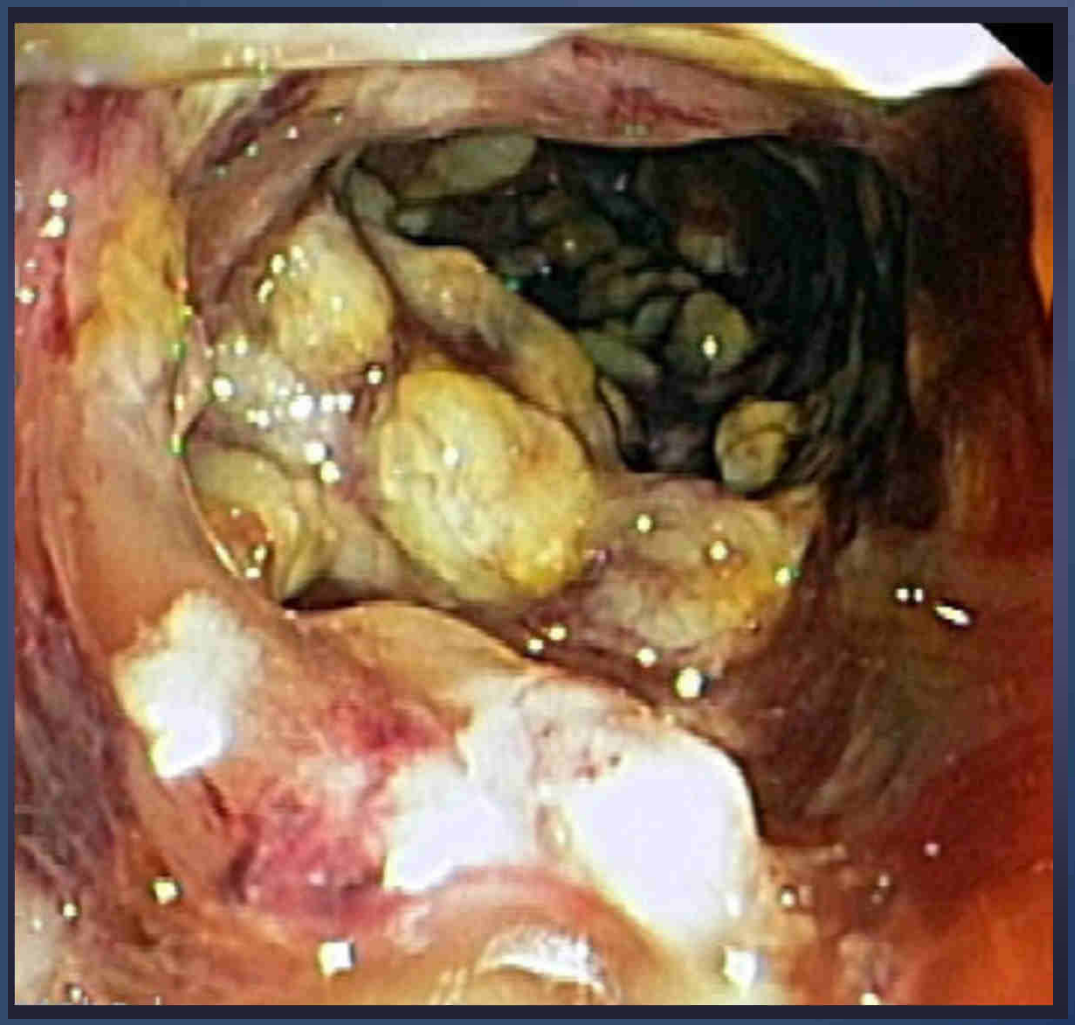
Hensgens MPM et al. J Antimicrob Chemother 2012;67:742

Clostridium difficile Diagnostik

DIAGNOSTIC TEST	TURN-AROUND TIME	SENSITIVITY	ADVANTAGES	DISADVANTAGES
Endoscopy	2 hours	51%	Diagnostic of pseudomembranous colitis	Low sensitivity
Anaerobic culture	72 hours	89%–100%	Results useful for molecular typing	Does not distinguish toxin-producing strains
Tissue cytotoxic assay	48 hours	94%–100%	Detects A-B+ strains Gold standard	False-positives Results vary with experience of the technologist
Common antigen	15–45 minutes	58%–92%	Detects A-B+ strains Easy to use	Does not distinguish toxin-producing strains Cross-reacts with other anaerobes
Enzyme-linked immunosorbent assay (ELISA)—toxin A	2 hours	80%–95%	Easy to use	Does not detect A-B+ strains
ELISA—toxin A + B	2 hours		Detects A-B+ strains	Increased sensitivity for low-level toxin production
Immunochromatographic toxin A	< 1 hour	60%–85%	Simple to use Rapid	Does not detect A-B+ strains

Sunenshine et al., Clevel Clin J Med 2006;73:187

PMC - Endoskopie



Therapie der CDI - das antimikrobielle Armamentarium

Substanz	Tagesdosierungen
Standardtherapieregime	
Metronidazol	2 x 400 mg – 4 x 500 mg
Vancomycin	4 x 125 mg – 500 mg
Fidaxomycin	2 x 200 mg
***experimentelle und/oder §in D nicht zugelassene Therapieregime**	
RIfaximin§	3 x 200 mg – 3 x 550 mg
Tigecyclin§	2 x 50 mg
Teicoplanin§	2 x 100 mg – 3 x 200 mg
Nitaxozanid*	2 – 3 x 500 mg
Bacitracin§	4 x 25000 IE
Fusidinsäure*	3 x 250 mg – 3 x 500 mg
Daptomycin§	1 x 6 mg/kg KG

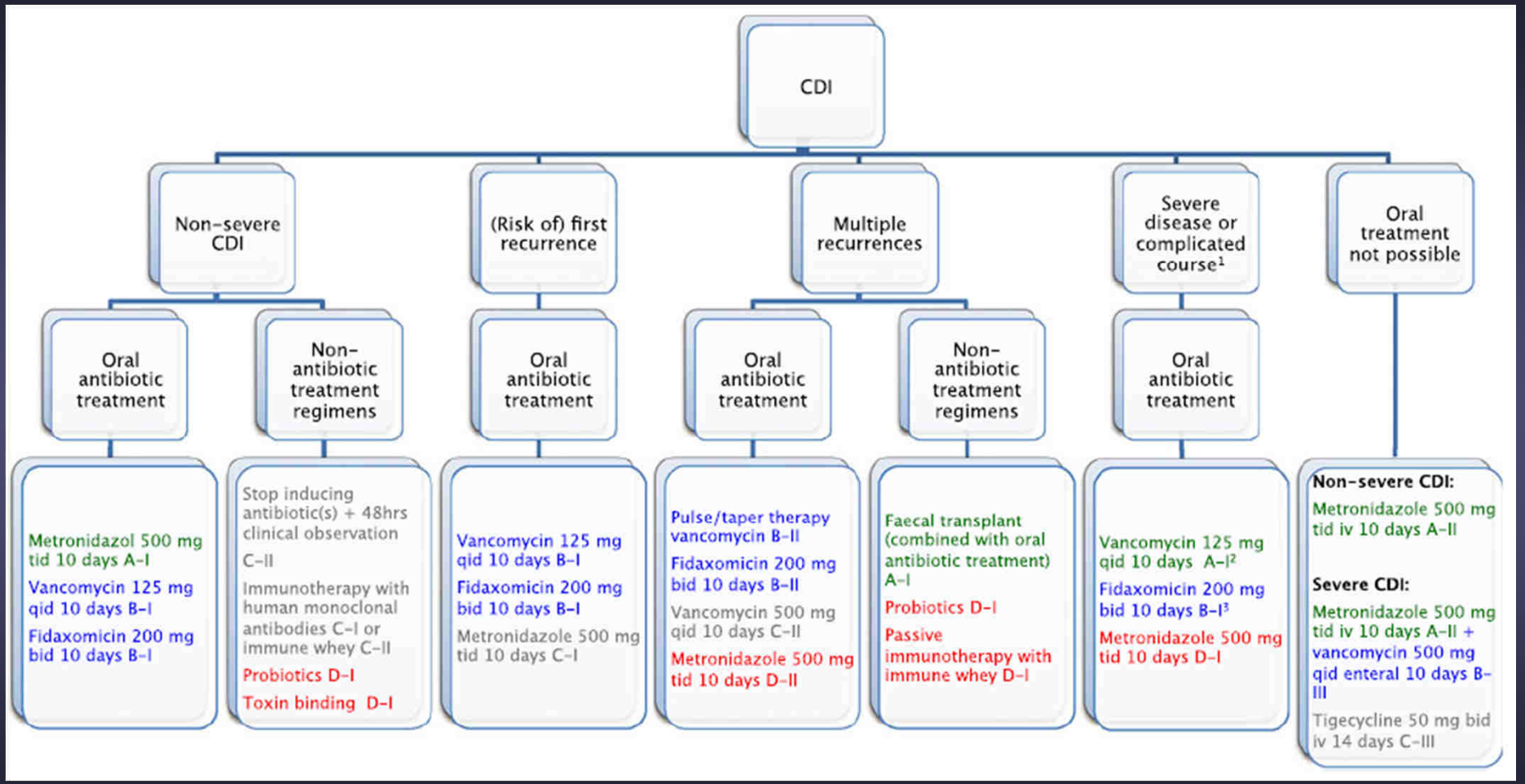
Grünewald et al. DMW 2010, Grünewald & Ruf. Intern Prax 2013

„Standard“therapie Erfolgsraten

Studies	Treatment failures [n/total (%)]	Recurrences [n/total (%)]	Duration of follow up (days)	Percentage failure plus recurrence
Metronidazole				
Cherry et al, 1982[35]	0/13	2/13 (15%)	30	15%
Teasley et al, 1983[47]	2/42 (5%)	2/39 (5%)	21	10%
Olson et al, 1994[4]	14/632 (2%)	39/632 (6%)	30	8%
Wenisch et al, 1996[40]	2/31 (6%)	5/31 (16%)	30	22%
Kyne et al, 2001[3]	..	22/44 (50%)	60	..
Fernandez et al, 2004[43]	38/99 (38%)	..	..	..
Musher et al, 2005[8]	46/207 (22%)	58/207 (28%)	90	50%
Pepin et al, 2005[9]	178/1123 (16%)	243/845 (29%)	60	45%
Vancomycin				
Bartlett et al, 1980[42]	3/79 (4%)	11/79 (14%)	30	18%
Silva et al, 1981[53]	0/16	2/16 (13%)	42	13%
Teasley et al, 1983[47]	0/52	6/51 (12%)	21	12%
Bartlett, 1984[48]	6/189 (3%)	46/189 (24%)	25	27%
Young et al, 1985[54]	8/42 (19%)	11/30 (37%)	30	56%
Dudley et al, 1986[57]	0/15	3/15 (20%)	60	20%
de Lalla et al, 1989[33]	2/25 (8%)	3/25 (12%)	30	20%
Fekety et al, 1989[55]	0/46	9/46 (20%)	42	20%
de Lalla et al, 1992[58]	0/20	4/20 (20%)	30	20%
Olson et al, 1994[4]	1/122 (1%)	12/122 (10%)	30	11%
Wenisch et al, 1996[40]	2/31 (6%)	5/31 (16%)	30	22%
Pepin et al, 2005[9]	..	31/112 (28%)	60	..
Metronidazole and vancomycin				
McFarland et al, 1994[34]	8/33 (24%)	8/33 (24%)	60	48%
Nair et al, 1998[46]	9/36 (25%)	7/36 (19%)	90	44%
Noren et al, 2004[36]	..	68/267 (25%)	60	..

Aslam et al., Lancet Infect Dis 2005;5:549

was sagen die Leitlinien ? update 2014



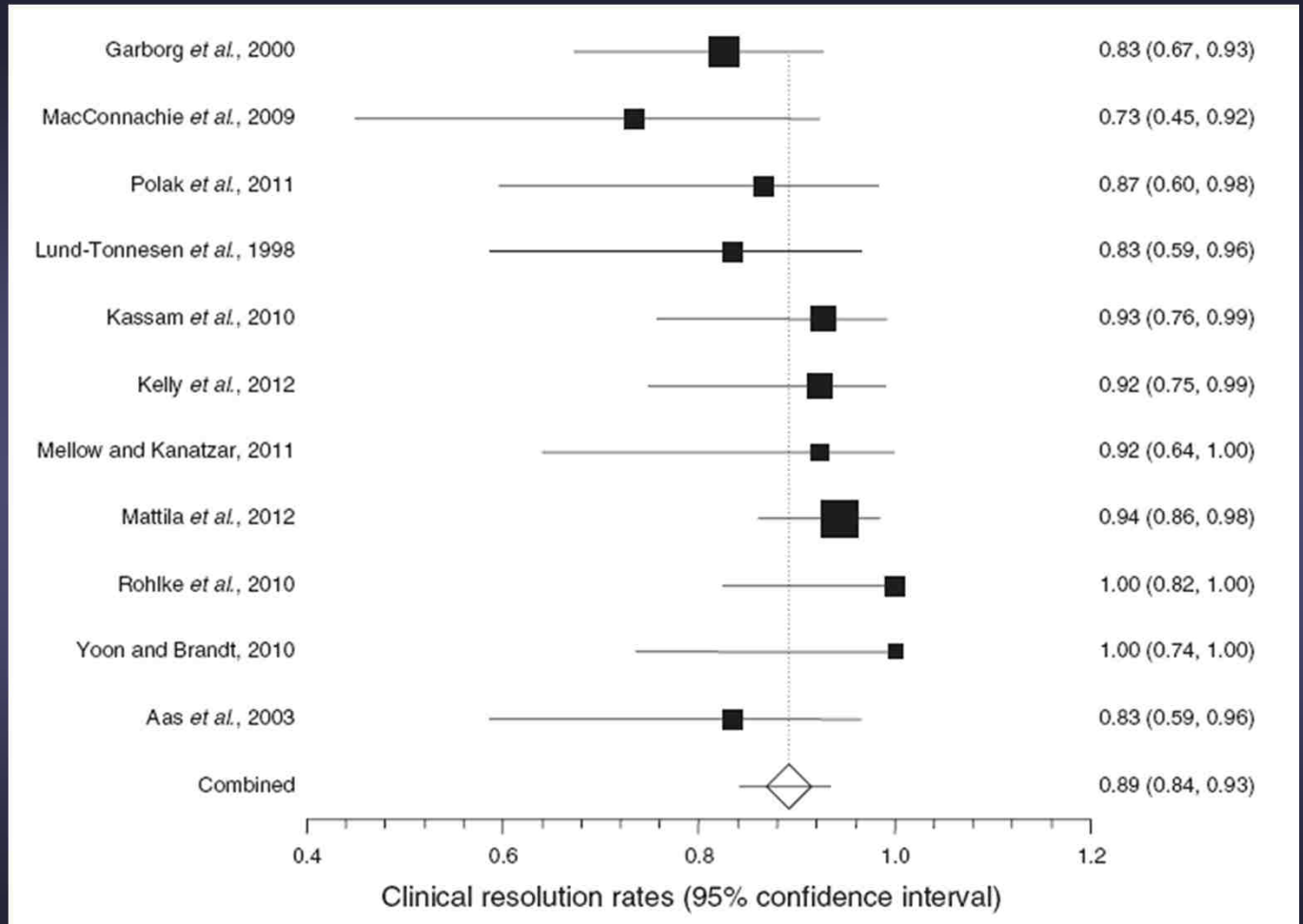
Debast SB et al. Clin Microbiol Infect 2014; 20 (Suppl 2): 1-26

Faecotherapie – Effektivität Fallserien

No. of patients receiving fecal transplantation	No. of patients responding to treatment	Treatment response rate (%)	Transplantation method	Reference
4	4	100	Rectal enema	Eiseman B et al., 1958 (12)
16	14	87	Rectal enema/jejunal tube	Bowden TA et al., 1981 (25)
55	46	84	Rectal enema	Borody TJ et al., 1989 (24)
7	7	100	Rectal enema	Paterson DL et al., 1994 (e20)
9	9	100	Rectal enema	Gustafsson A et al., 1998 (e19)
18	15	83	Nasogastric tube	Aas et al., 2003 (e18)
15	11	73	Nasogastric tube	MacConnachie AA et al., 2009 (29)
12	10	83	Nasogastric tube	Rubin TA et al., 2009 (32)
19	19	100	Colonoscopy	Rohlke F et al., 2010 (31)
12	12	100	Colonoscopy	Yoon SS et al., 2010 (33)
40	33	82.5	Duodenal tube/colonoscopy	Garborg K et al., 2010 (26)
7	7	100	Rectal enema	Silverman MS et al., 2010 (15)
77	70	91	Colonoscopy	Brandt LJ et al., 2012 (14)
43	37	86	Colonoscopy	Hamilton MJ et al., 2012 (27)
26	24	92	Colonoscopy	Kelly CR et al., 2012 (28)
70	66	94	Colonoscopy	Mattila E et al., 2012 (30)
19	13	69	Nasojejunal tube	Polak P et al., 2011 (e21)
7	7	100	Colonoscopy	Nieuwdorp M et al., 2008 (e22)

Kleger A et al. Dtsch Aerztebl 2013; 110: 108

Faecotherapie – Effektivität Meta-Analyse



Kassam Z et al. Am J Gastroenterol 2013; 108: 500

biologische Therapie Faecotherapie

- **Empfänger-Konditionierung**

Procedere:	Tag -1	Absetzen aller ABx
		2 x 100 ml Actimel oder gleichwertigen prä-/pro-biotischen Drink
		Gastroskopie mit Anlage einer distal duodenal platzierten nasalen Ernährungssonde
		Stuhlgewinnung von Donor und Recipient für Stuhlbank und zur Bestimmung von Lactoferrin sowie zur Aufbereitung* des Donorstuhls
	Tag 0	vor und nach Applikation des aufbereiteten Donorstuhls* über die liegende Sonde in das distale Duodenum Gabe von Prokinetika (vorzugsweise Domperidon)
		Stuhlprotokoll
	Tag 1-7	täglich Stuhlkulturen, Toxin-Diagnostik und Lactoferrin im Stuhl sowie Stuhl abfrieren, Bristol Stool Chart
		Stuhlprotokoll

biologische Therapie Faecotherapie

- **Stuhl-Aufbereitung**

Aufbereitung des Donorstuhls

1. von frischem Donorstuhl werden 70 – 80 g gewonnen
2. Durchführung Testung auf okkultes Blut im Stuhl => wenn negativ, dann
3. Homogenisieren und Aufschwemmen von 50 g Donorstuhl unter sterilen Bedingungen mit isotonischer Salzlösung (Volumen 550 ml)
4. Filterung durch eine Lage steriler Gaze zur Retention fester Bestandteile
5. 500 ml werden zur Instillation in sterile Blasenspritzen verbracht und gekühlt bis gelagert. Eine Stunde vor Applikation Erwärmung der Bakterien-Suspension im Plasmawärmer
6. 25 ml werden zur quantitativen Bakteriologie eingesandt (CFU)
7. 25 ml werden für die Stuhlbank abgefroren

biologische Therapie Faecotherapie

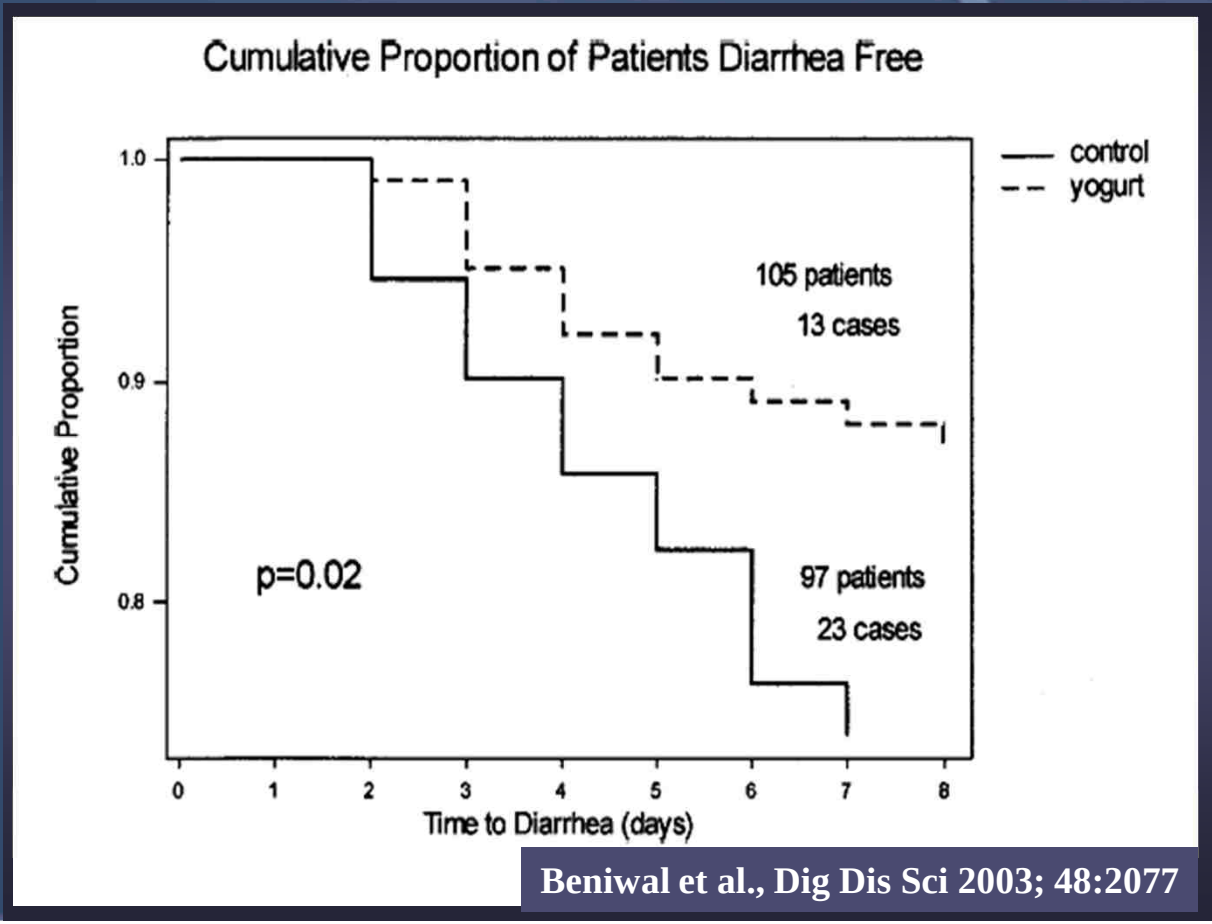
- **Intervention**

Einbringen der Donorstuhlsuspension

1. 10 min. vor Instillation Gabe von 20 mg Domperidon
2. fraktionierte Instillation (jeweils 100 ml im Abstand von 5 Minuten) der Donorstuhlsuspension via nasoduodenaler Sonde
3. danach Okklusion der Sonde
4. 60 min. nach Instillation erneute Gabe von 20 mg Domperidon

Prophylaxe mit Präbiotika
- essen Sie mehr Joghurt ! -

- 227 g Joghurt vs. Placebo zur Prävention der AAD



Beniwal et al., Dig Dis Sci 2003; 48:2077

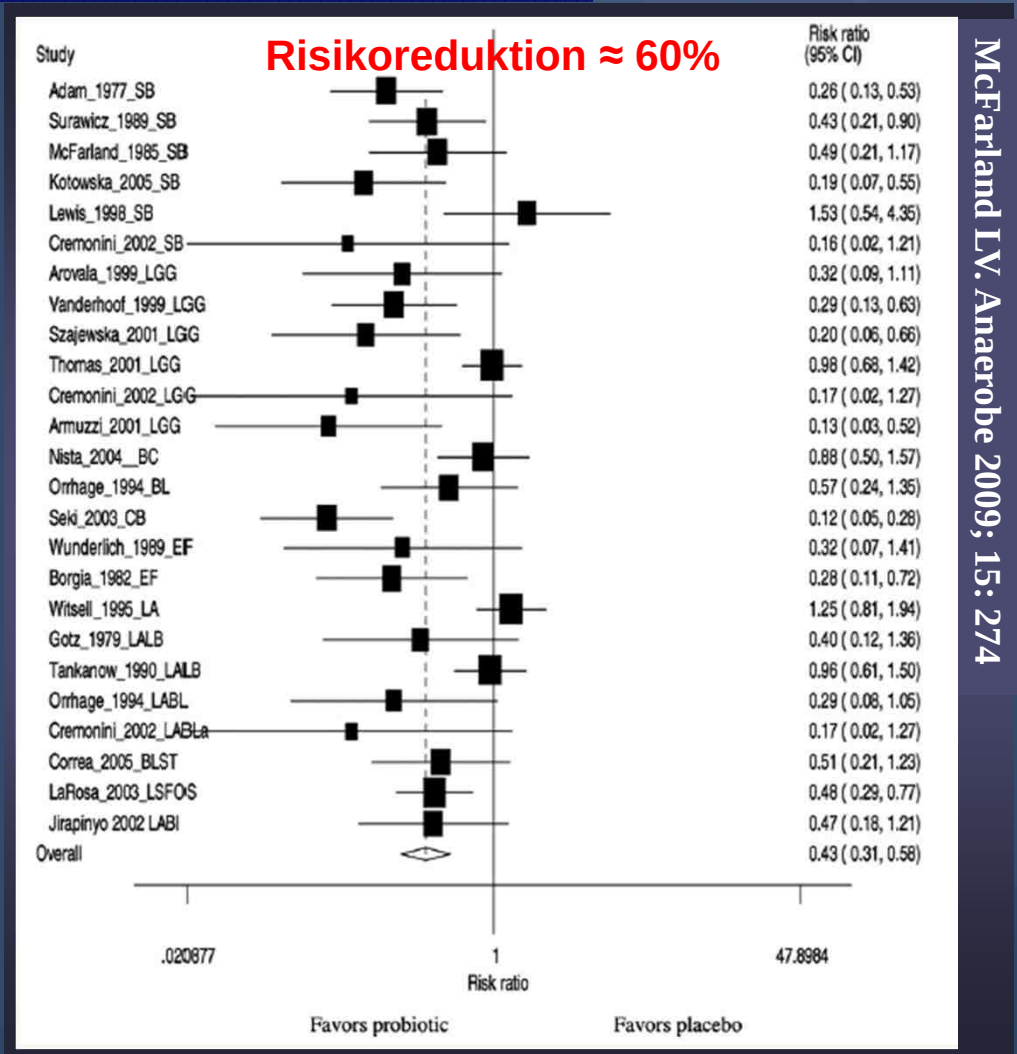
Prophylaxe mit Präbiotika - essen Sie mehr Joghurt ! -

- 2 x 100 g Lactobacillus Emulsion vs. Placebo zur Prävention der AAD

	Probiotic	Control	P value*
Diarrhoea			
Yes	7 (12)	19 (34)	0.007
No	50 (88)	37 (66)	
No of patients	57†	56†	
C difficile toxin			
Positive	0	9 (17)	0.001
Negative	56 (100)	44 (83)	
No of patients	56‡	53‡	

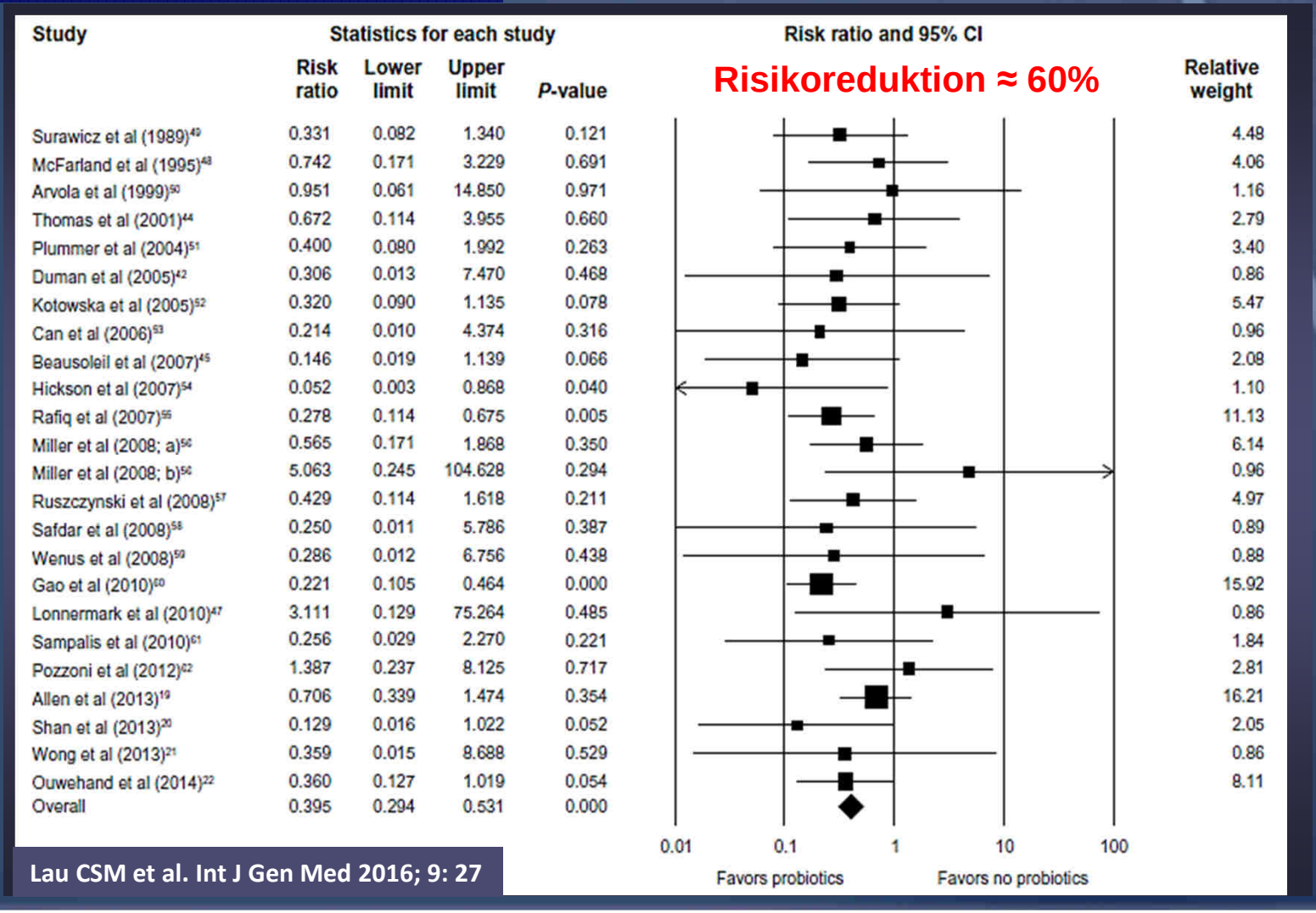
Hickson M et al., BMJ 2007; 348: 80

CDAD-Prophylaxe
- Meta-Analyse -



McFarland LV. Anaerobe 2009; 15: 274

CDAD-Prophylaxe
- Meta-Analyse -



Lau CSM et al. Int J Gen Med 2016; 9: 27

biologische Therapie die Zukunft

- „echte“ Bacteriotherapie

Targeted Restoration of the Intestinal Microbiota with a Simple, Defined Bacteriotherapy Resolves Relapsing *Clostridium difficile* Disease in Mice

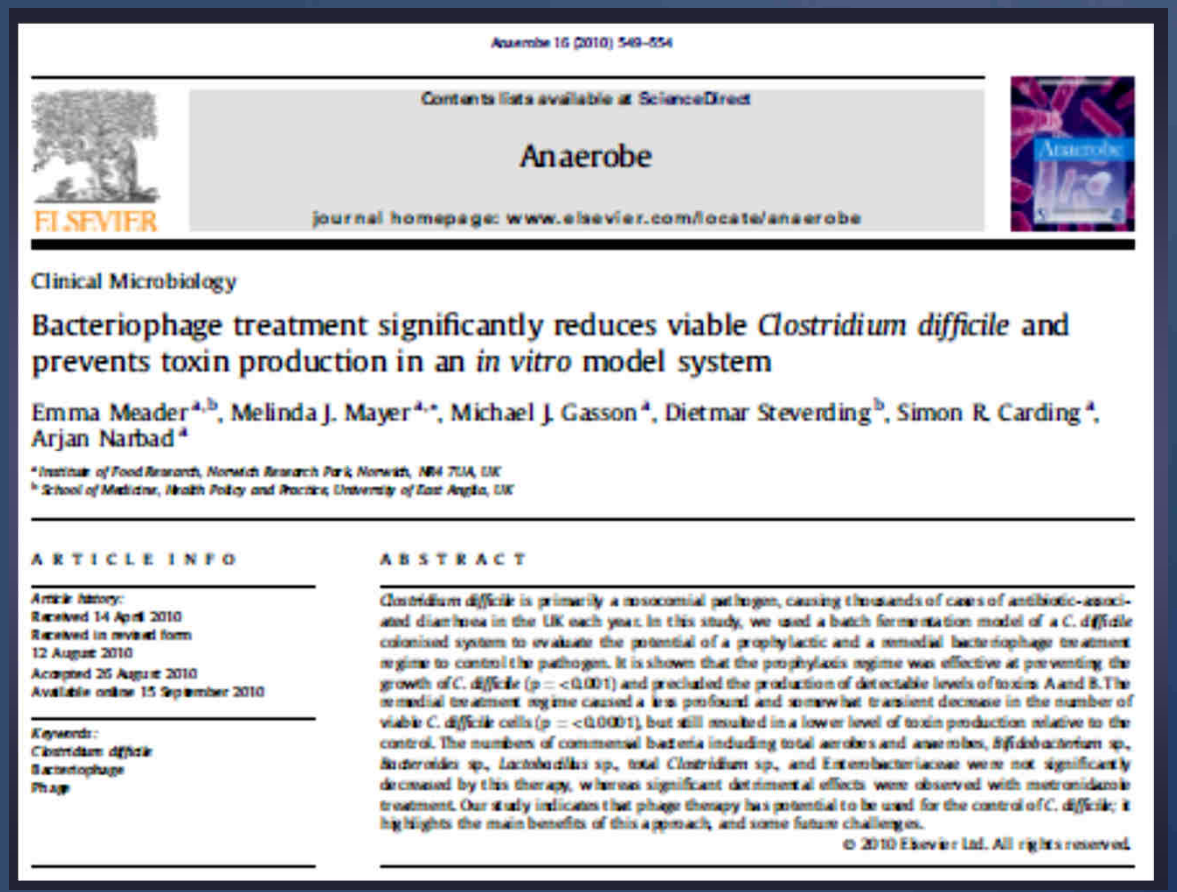
Abstract

Relapsing *C. difficile* disease in humans is linked to a pathological imbalance within the intestinal microbiota, termed dysbiosis, which remains poorly understood. We show that mice infected with epidemic *C. difficile* (genotype 027/BI) develop highly contagious, chronic intestinal disease and persistent dysbiosis characterized by a distinct, simplified microbiota containing opportunistic pathogens and altered metabolite production. Chronic *C. difficile* 027/BI infection was refractory to vancomycin treatment leading to relapsing disease. In contrast, treatment of *C. difficile* 027/BI infected mice with feces from healthy mice rapidly restored a diverse, healthy microbiota and resolved *C. difficile* disease and contagiousness. We used this model to identify a simple mixture of six phylogenetically diverse intestinal bacteria, including novel species, which can re-establish a health-associated microbiota and clear *C. difficile* 027/BI infection from mice. Thus, targeting a dysbiotic microbiota with a defined mixture of phylogenetically diverse bacteria can trigger major shifts in the microbial community structure that displaces *C. difficile* and, as a result, resolves disease and contagiousness. Further, we demonstrate a rational approach to harness the therapeutic potential of health-associated microbial communities to treat *C. difficile* disease and potentially other forms of intestinal dysbiosis.

Citation: Lawley TD, Clare S, Walker AW, Stares MD, Connor TR, et al. (2012) Targeted Restoration of the Intestinal Microbiota with a Simple, Defined Bacteriotherapy Resolves Relapsing *Clostridium difficile* Disease in Mice. PLoS Pathog 8(10): e1002995. doi:10.1371/journal.ppat.1002995

biologische Therapie die Zukunft

- **Phagentherapie**



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Clinical Microbiology

Bacteriophage treatment significantly reduces viable *Clostridium difficile* and prevents toxin production in an *in vitro* model system

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Bacteriophage
Phage

ABSTRACT

Clostridium difficile is primarily a nosocomial pathogen, causing thousands of cases of antibiotic-associated diarrhoea in the UK each year. In this study, we used a batch fermentation model of a *C. difficile* colonised system to evaluate the potential of a prophylactic and a remedial bacteriophage treatment regime to control the pathogen. It is shown that the prophylaxis regime was effective at preventing the growth of *C. difficile* ($p = <0.001$) and precluded the production of detectable levels of toxins A and B. The remedial treatment regime caused a less profound and somewhat transient decrease in the number of viable *C. difficile* cells ($p = <0.0001$), but still resulted in a lower level of toxin production relative to the control. The numbers of commensal bacteria including total aerobes and anaerobes, *Bifidobacterium* sp., *Bacteroides* sp., *Lactobacillus* sp., total *Clostridium* sp., and Enterobacteriaceae were not significantly decreased by this therapy, whereas significant detrimental effects were observed with metronidazole treatment. Our study indicates that phage therapy has potential to be used for the control of *C. difficile*; it highlights the main benefits of this approach, and some future challenges.

Faecotherapie alles wird gut ?

- **Tumorgenese/-wachstum ↑**

Baxter *et al. Microbiome* 2014, **2**:20
http://www.microbiomejournal.com/content/2/1/20

Microbiome

RESEARCH Open Access

Structure of the gut microbiome following colonization with human feces determines colonic tumor burden

Nielson T Baxter[1†], Joseph P Zackular[1†], Grace Y Chen[2] and Patrick D Schloss[1*]

Conclusion: Our results suggest that the initial structure of the microbiome determines susceptibility to colonic tumorigenesis. There appear to be opposing roles for certain Gram-negative (Bacteroidales and Verrucomicrobia) and Gram-positive (Clostridiales) bacteria in tumor susceptibility. Thus, the impact of community structure is potentially mediated by the balance between protective, butyrate-producing populations and inflammatory, mucin-degrading populations.

Faecotherapie alles wird gut ?

- **Transfer von Resistenzsignaturen !!!**

Pathogens **2014**, *3*, 238-248; doi:10.3390/pathogens3020238

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pathogens

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www.mdpi.com/journal/pathogens

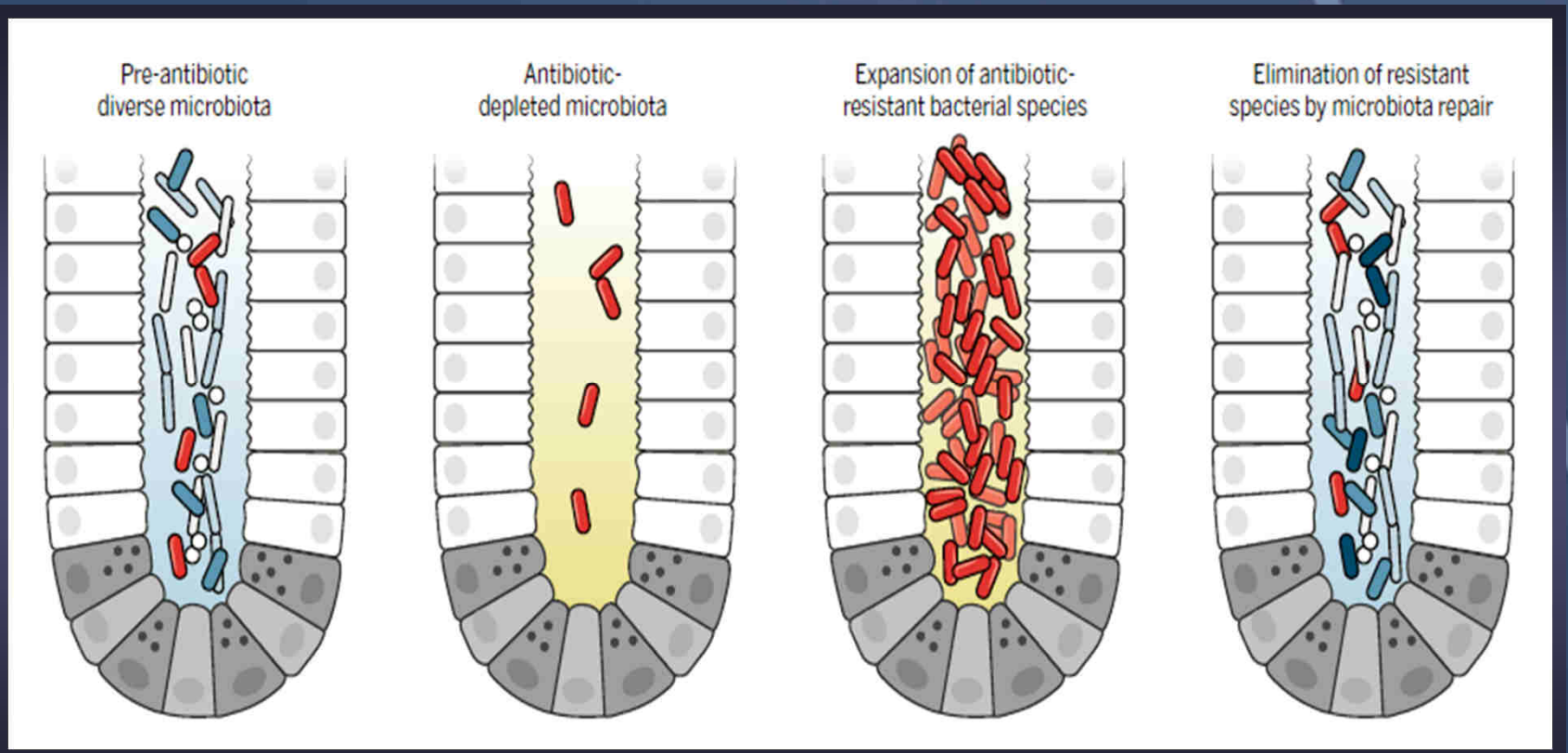
Review

Integrons in the Intestinal Microbiota as Reservoirs for Transmission of Antibiotic Resistance Genes

Anuradha Ravi [1], Ekaterina Avershina [1], Jane Ludvigsen [1], Trine M. L'Abée-Lund [2] and Knut Rudi [1,*]

Faecotherapie alles wird gut !

- **Verdrängung von MRE**



Pamer EG. Science 2016; 352: 535

Take-home messages

- die Faecotherapie ist immer noch eine experimentelle Therapie !
- nach Evidenz-basierten Maßstäben ist nur die rezidivierende CDI eine sichere Indikation !
- Langzeiteffekte für Rezipient und Umwelt sind (noch) ungeklärt !