Darmflora Chronisch Entzündlichen Darmerkrankungen & Probiotika - gestern, heute und morgen -

5. Interdisziplinäres Symposium
Darmflora in Symbiose und Pathogenität

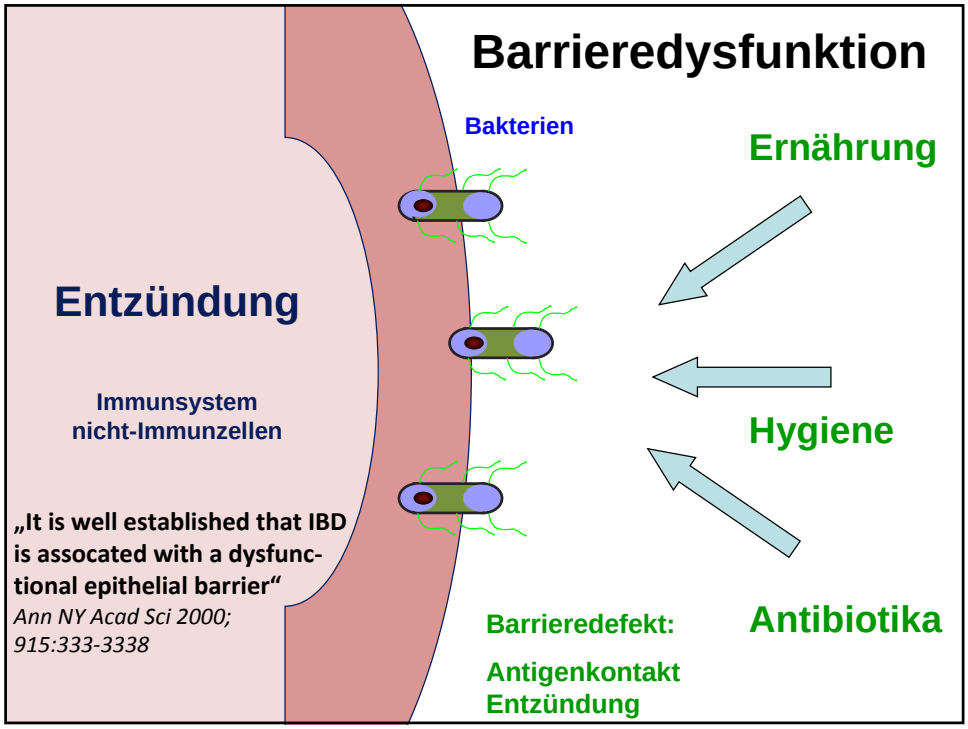
Wolfgang Kruis

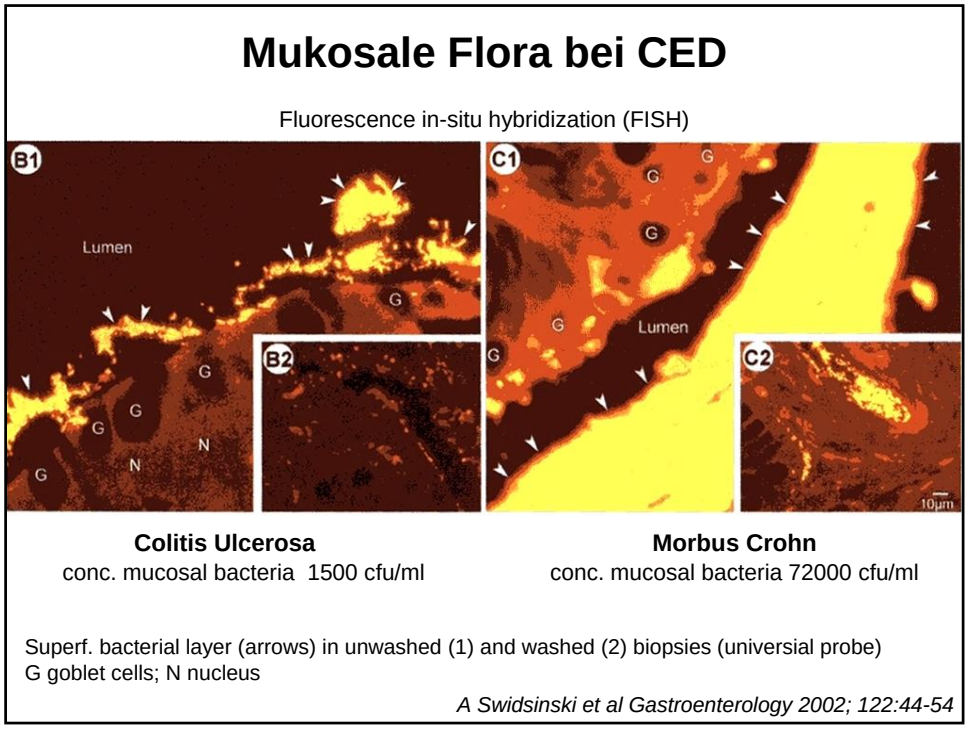
Ev. Krankenhaus Kalk
Universität zu Köln

Erster Fallbericht einer Patientin mit Colitis ulcerosa behandelt mit E coli Nissle

- 20 Jahre alte weibliche Patientin mit chronisch aktiver Colitis ulcerosa (Infektionserkrankung ausgeschlossen)
- 7 Wochen Behandlung mit E coli Nissle (bis zu 200mg/d)
- Nach 5 Wochen wurde Remission erreicht

A Nissle Med Klinik 1918; 2 : 29 - 33





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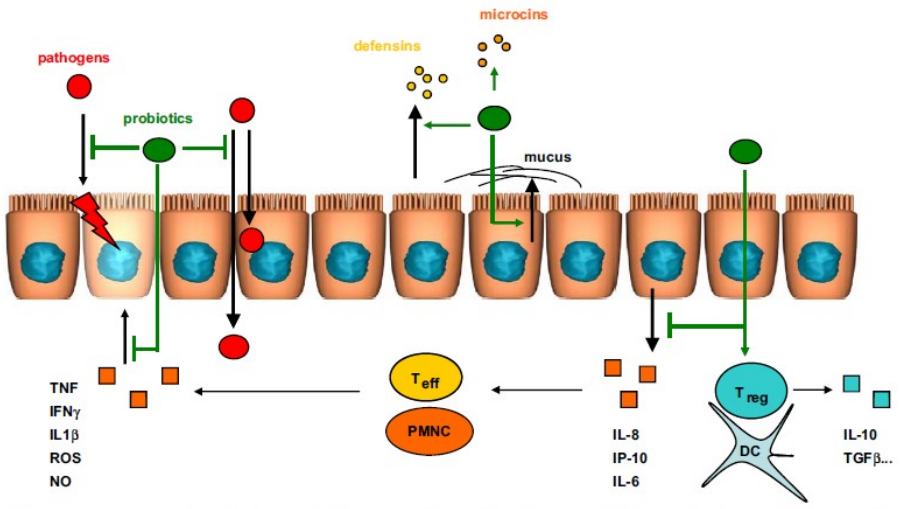
Protektion der Darmmukosa durch Probiotika



G Hörmannsperger & D Haller Int J Med Microbiol 2010;300:63-73

Probiotische Effekte auf Entzündung in Tiermodellen

Animal model	Reference	Probiotic compound	Bacterial structure	Effect
$IL10^{-/-}$	Madsen et al. (2001)	VSL#3	–	Reduced colitis **Enhanced Barrier**
	Jijon et al. (2004)	VSL#3	DNA	Reduced colitis Reduced inflammatory cytokines Systemic effect
	Hormannsperger et al. (2009)	VSL#3	Bacterial surface protein	Regulation of IEC function Intestinal segment specific effect on cecal inflammation
	Kamada et al. (2005)	*E. coli* Nissle	–	Reduced colitis
CD4+ CD62L+ transfer in SCID mice	van der Kleij et al. (2008)	*Lactobacillus reuteri*, *Bifidobacterium infantis* *Bifidobacterium infantis*	–	Reduced colitis Reduction of inflammatory cytokines/enzymes
	Schultz et al. (2004)	*E. coli* Nissle	–	Reduced colitis
TNP^{SAIRE}	Hormannsperger et al. (2009)	VSL#3	–	No effect
DSS	Ukena et al. (2007)	*E. coli* Nissle	Cell surface structures	Reduced colitis
	Vetrano et al. (2008)	*Colifagina* lysed bacteria	–	Reduced colitis, Increased IgA secretion
	Gaudier et al. (2005)	VSL#3	–	No protection
	Kamada et al. (2005)	*E. coli* Nissle	Viable/heat-killed bacteria, bacterial DNA	Reduced colitis
	Foligne et al. (2007)	*Lactobacillus rhamnosus* GG - stimulated IBM-DC	Cell wall components	Reduced colitis Induction of regulatory mechanisms
	Rachmilewitz et al. (2004)	VSL#3/*E. Coli*	Unmethylated DNA	Reduced colitis Systemic effect
	Fitzpatrick et al. (2007)	VSL#3	–	Reduced colitis Reduction of inflammatory cytokines/enzymes
	Kokesova et al. (2006)	*E. coli* Nissle, *Lactobacillus casei*, *E. coli*	–	Reduced colitis
	van der Kleij et al. (2008)	*L reuteri*, *B.infantis*	–	Reduced colitis Reduction of inflammatory cytokines/enzymes
	Geier et al., (2007)	*Lactobacillus rhamnosus* GG	–	No effect
	Geier et al., (2007)	*Lactobacillus fermentum* BR11	–	Reduced colitis
	Schultz et al. (2004)	*E. coli* Nissle	–	Reduced colitis Reduction of inflammatory cytokines
TNBS	Di Giacinto et al. (2005)	VSL#3	–	Reduced colitis Induction of regulatory cells
	Foligne et al. (2007)	*Lactobacillus rhamnosus* LR32 - stimulated IBM-DC	Cell wall components	Reduced colitis Induction of regulatory mechanisms
	Peran et al. (2006)	*lactobacillus fermentum*	–	Reduced colitis Reduction of oxidative stress
DNBS	Shibolet et al. (2002)	VSL#3/ *Lactobacillus rhamnosus* GG	–	No effect
Iodoacetamide	Shibolet et al. (2002)	VSL#3/ Lactobacillus rhamnosus GG	–	Reduced colitis Reduction of inflammatory cytokines/enzymes

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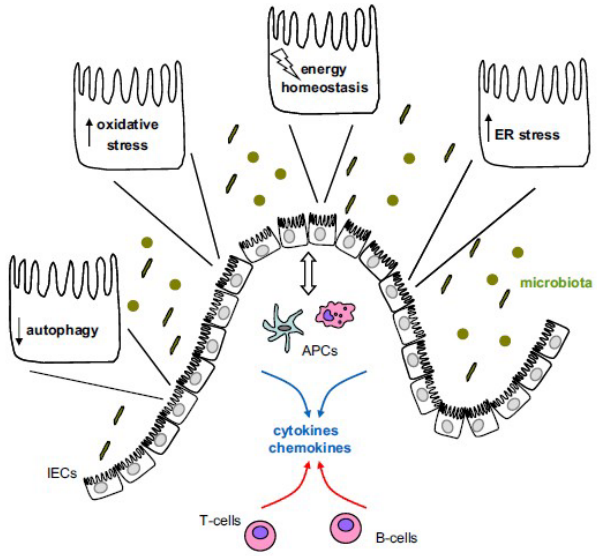
Ziele der protektiven Aktivität von Probiotika an der Darmmukosa (?)



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CED
Therapiestudien mit Probiotika

Disease	Reference	Probiotic compound	Study design	Outcome
Pouchitis	Pronio et al. (2008)	VSL#3	PC, 31	Effective prevention
	Gionchetti et al. (2007)	VSL#3	23	Induction of remission
	Laake et al. (2005)	Bifidobacteria and *Lactobacillus* fermented milk product	61	Reduced histopathological inflammation and disease symptoms during intervention
	Mimura et al. (2004)	VSL#3	R, PC, 36	Maintenance of remission
	Gosselink et al. (2004)	*Lactobacillus rhamnosus* GG	Retrospective, controlled, 117	Delay of pouchitis onset
	Gionchetti et al. (2003)	VSL#3	R, PC, 40	Effective prevention
	Gionchetti et al. (2000)	VSL#3	R, PC, 40	Maintenance of remission
Ulcerative colitis	Soo et al. (2008)	VSL#3	15	Induction of remission
	Furrie et al. (2005)	*Bifidobacterium longum*, Synergy 1	R, PC, 18	Induction of remission
	Bibiloni et al. (2005)	VSL#3	32	Induction of remission
	Cui et al. (2004)	Bifidobacteria, BIFICO	R, PC, 30	Maintenance of remission
	Kruis et al. (2004)	*E. coli* Nissle	R, 222	Equivalent to 5-ASA
	Tursi et al. (2004)	VSL#3	R, 90	Better than 5-ASA or balsalazide in induction of remission
	Kato et al. (2004)	*Bifidobacterium breve/bifidum, Lactobacillus acidophilus*-fermented milk	R, PC, 20	Induction of remission
	Guslandi et al. (2003)	*Saccharomyces boulardii*	24	Induction of remission
	Ishikawa et al. (2003)	Bifidobacteria	R, PC, 21	Maintenance of remission
	Venturi et al., (1999)	VSL#3	Open, 20	Maintenance of remission
	Rembacken et al. (1999)	*E. coli* Nissle	R, 120	Equivalent to 5-ASA
	Kruis et al. (1997)	*E. coli* Nissle	R, 120	Equivalent to 5-ASA
Crohn's Disease	Fujimori et al. (2007)	Bifidobacteria, Lactobacilli, Psyllium (=prebiotic)	Open, 10	Significant reduction of CD severity
	Guslandi et al. (2000)	*Saccharomyces boulardii*	R, 32	Better than 5-ASA alone in maintenance
	Malchow (1997)	*E. coli* Nissle	PC	Maintenance of remission

R=randomized, PC=placebo controlled, no=number of study participants.

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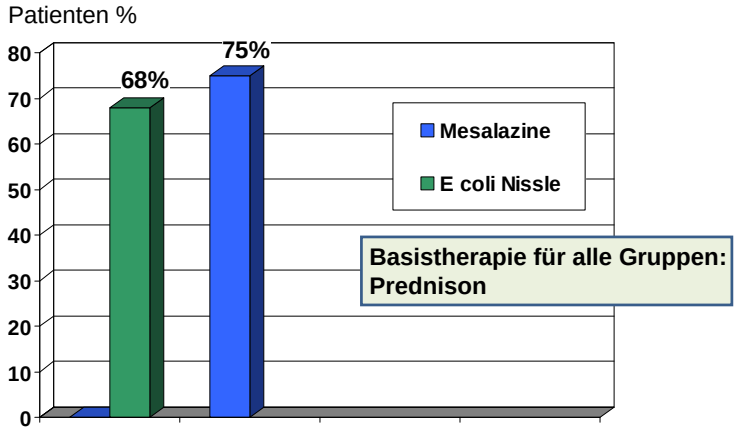
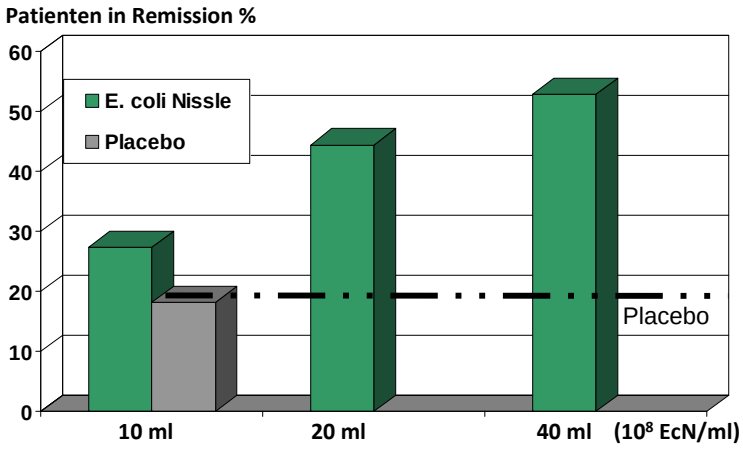
Colitis ulcerosa
Induktion einer Remission



BJ Rembacken et al Lancet 1999; 354:635-639

Einläufe mit E coli Nissle bei aktiver distaler Colitis ulcerosa



H Matthes et al DDW, 2006

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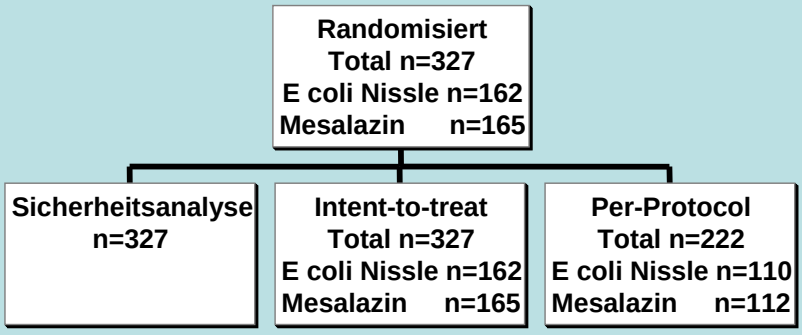
Remissionserhaltung bei Colitis ulcerosa mit *E. coli* Nissle

Prospektiv, doppelblind; Studiendauer 12 Monate
Gruppe I *E. coli* Nissle (Mutaflor ®); 1 x 200mg/d
Gruppe II Mesalazin (Salofalk ®); 3 x 500mg/d

Patienten



W Kruis et al Gut 2004;53:1617-23

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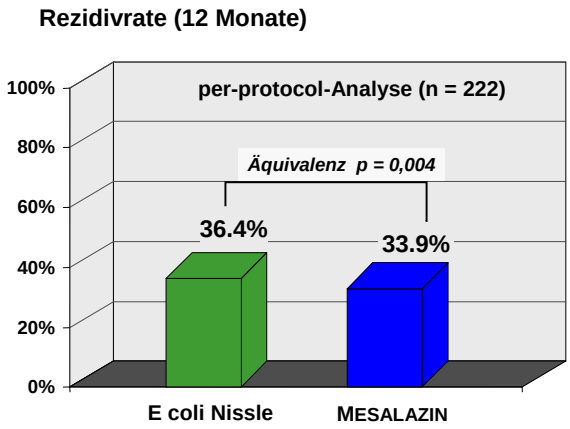
Colitis ulcerosa
Rezidivverhütung mit *E. coli* Nissle



W Kruis et al Gut 2004;53:1617-23

Erhaltung der Remission bei Colitis Ulcerosa

Leitlinien der
European Crohn´s Colitis Organisation (ECCO)
Journal of Crohn's and Colitis (2008) 2, 24–62

Probiotika

ECCO statement 6l

***E. coli* Nissle is an effective alternative to 5-ASA for maintenance [EL1b, RG A]**

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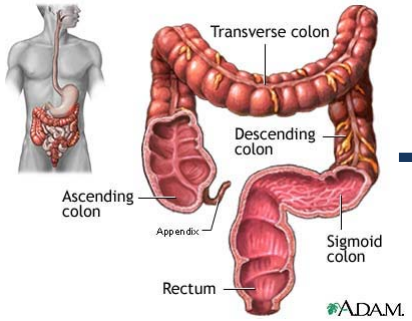
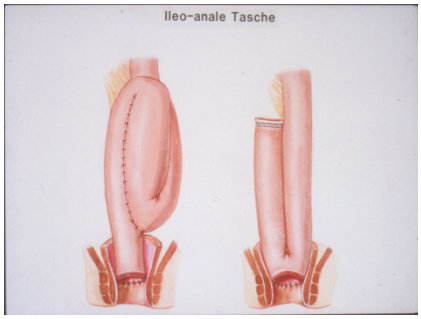


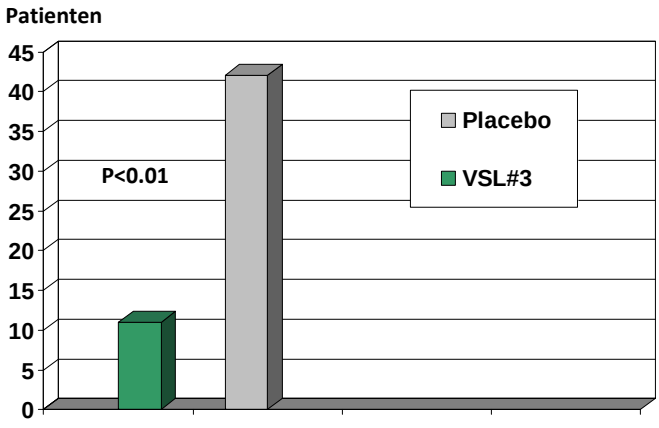
Pouch-Anlage mit ileoanaler Anastomose



Bis zu 50% der Patienten erleiden eine Pouchitis – Behandlung?

Probiotika zur Vermeidung und Therapie der chronischen Pouchitis

Primäre Prävention einer Pouchitis mit Probiotika



P Gionchetti et al. Gastroenterology 2000; 118:A190

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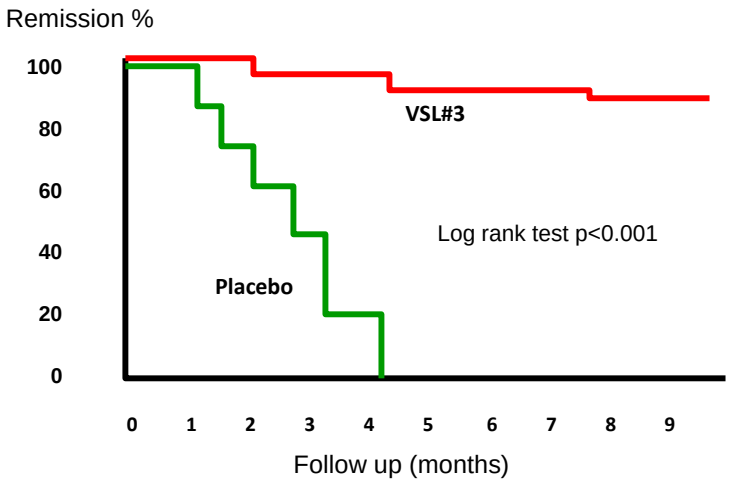
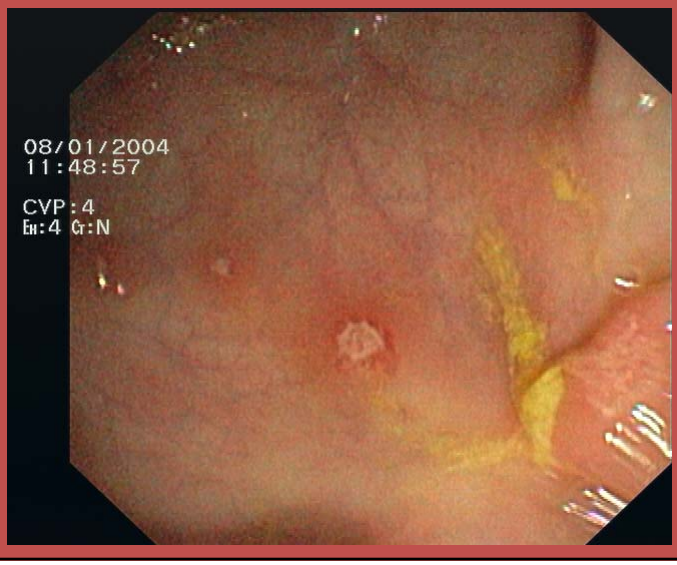
Probiotika zur Remissionserhaltung bei chronischer Pouchitis



P Gionchetti et al Gastroenterology 2000; 119:305

Morbus Crohn: Aphte, Erosion, Ulcus



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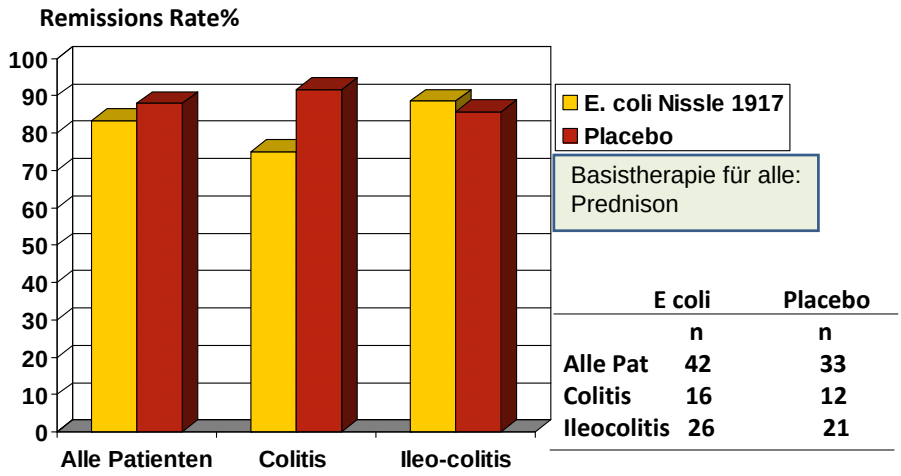
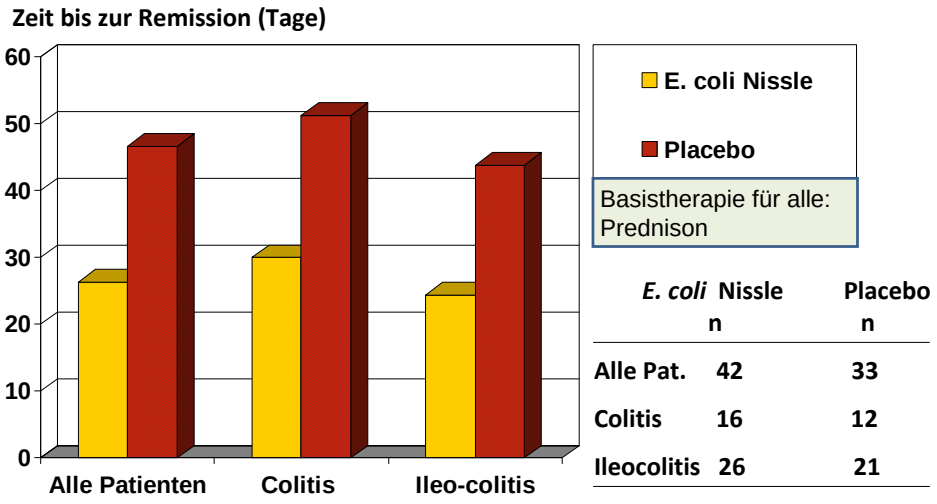
Morbus Crohn: Induktion einer Remission mit *E coli Nissle*



	E coli n	Placebo n
Alle Pat	42	33
Colitis	16	12
Ileocolitis	26	21

HA Malchow J Clin Gastroenterol 1997; 25:653-658

Morbus Crohn: Induktion einer Remission mit *E coli Nissle*



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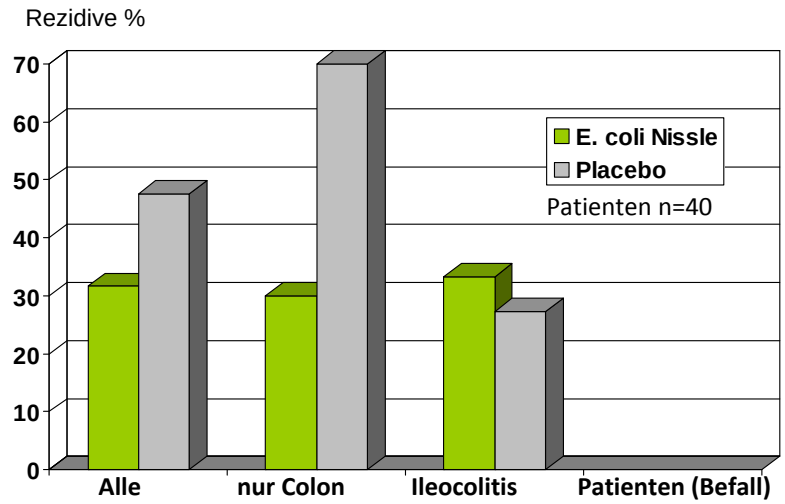
Morbus Crohn
Remissionserhaltung mit E. coli Nissle 1917



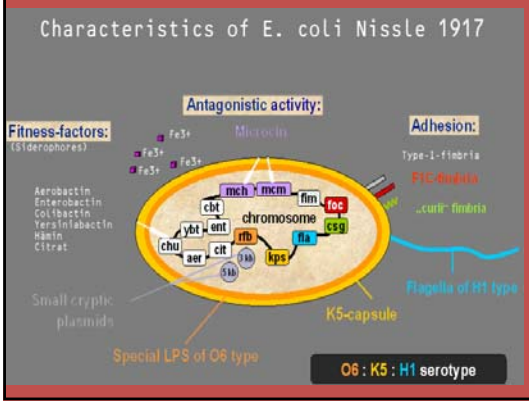
HA Malchow J Clin Gastroenterol 1997; 25:653-658a

Probiotika bei CED

Indikation	Studienlage	Präparat
<u>Morbus Crohn</u>		
-- Induktion der Remission	-+ (Zeit bis Remission?)	*E. coli* Nissle
-- Erhalt der Remission	-+ (Kolon? Kombiniert?)	*E. coli* Nissle
<u>Colitis ulcerosa</u>		
-- Induktion der Remission	- (oral) +(rektal)	*E. coli* Nissle
-- Erhalt der Remission	++	*E. coli* Nissle
<u>Pouchitis</u>		
-- Primäre Prävention	++	VSL#3
-- Remissionserhaltung	++	VSL#3

Therapie der CED mit Probiotika
Pharmazeutika - Nutrizeutika

Pharmazeutika
(Medikamente)



Nutrizeutika
(Nahrungsmittel)

Darmflora
Chronisch Entzündlichen Darmerkrankungen & Probiotika
- gestern, heute und morgen -

- Probiotika sind in verschiedenen Indikationen bei CED (Rezidivprophylaxe Colitis ulcerosa, Pouchitis) als Monotherapie wirksam und stellen dort eine „Ersatz-“ (Alternativ-) Behandlung dar.
- Weitere Grundlagenforschung und klinische Studien müssen zukünftig das Prinzip der probiotischen Therapie sichern und ausbauen helfen.

Beachte:

In choosing a probiotic strategy, clinicians should adhere to …..selection from a reputable supplier, with appropriate documentation of contents and shelf life; anticipation of strain-specific effects; avoidance of cocktails without documentation of the activities of each ingredient with absence of interstrain antagonism; and published evidence of efficacy from clinical trials.

F Shanahan & SM Collins Gastroenterol Clin North Am. 2010 ;39:721-6

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