Infektiologische
Konzepte 31. Mai 2012

Kantonsspital Aarau

Infektiöse Diarrhoe

Christoph Fux
Infektiologie & Spitalhygiene
Kantonsspital Aarau
christoph.fux@ksa.ch

Definitionen

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Diarrhoe

Erwachsene: 3 oder mehr Stuhlabgänge von nicht-fester Konsistenz pro Tag Dupont, NEJM, 1993
Kinder: Syndrom von 2-3 Tagen Dauer mit 2-facher oder höherer Frequenz von ungeformten Stühlen JAMA Consensus, 1985

Akut ≤14 Tage

6% in vergangenen 4 Wochen
19/100 Jahre mit Durchfall, 3.3/100 Jahre beim Hausarzt, 0.2/100 Jahre gemeldet

>> Wasser (Cryptosporidien, Noro, ETEC)
>> Nahrung (Noro, Toxine)

Chronisch >1 Monat

Imhoff B et al. CID 2004, Wheeler JG et al. BMJ 1999

Pathophysiologie Dünndarm

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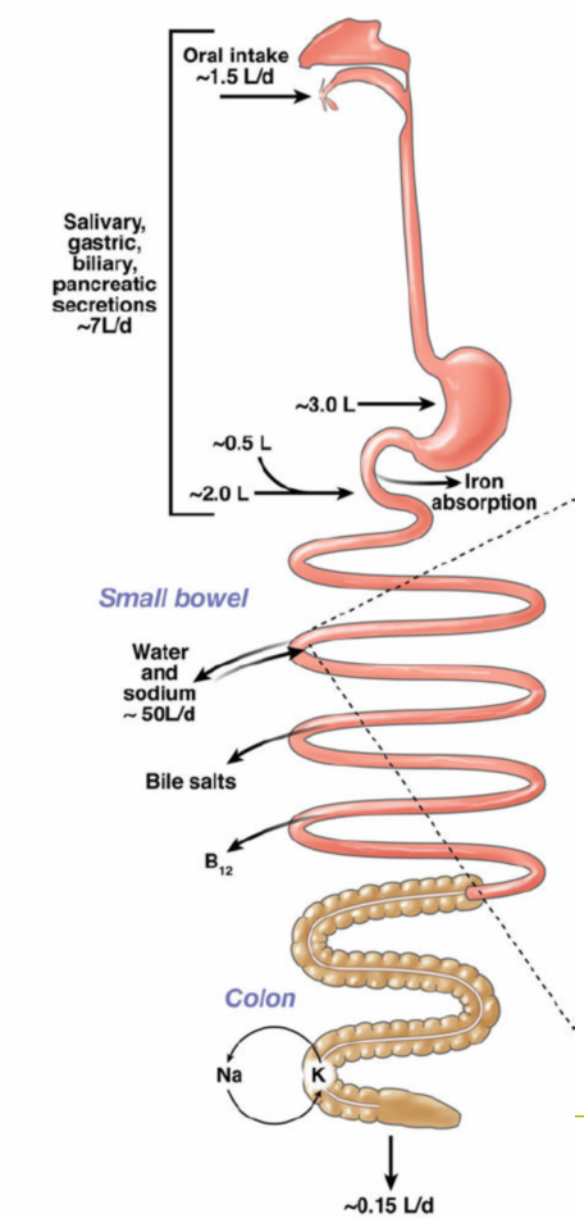

Sekretorisches Enterotoxin

Cholera, S. aureus, B. cereus
ETEC (Hitze-stabil & instabil)

=Reisedurchfall

Cytotoxin

EPEC

Villus-Destruktion

Rotaviren, Noroviren

Cryptosporidien, Mikrosporidien, Cyclospora, Isospora Lamblien

Pawlowski SW et al. Gastroenterology 2009

Pathophysiologie Dünndarm

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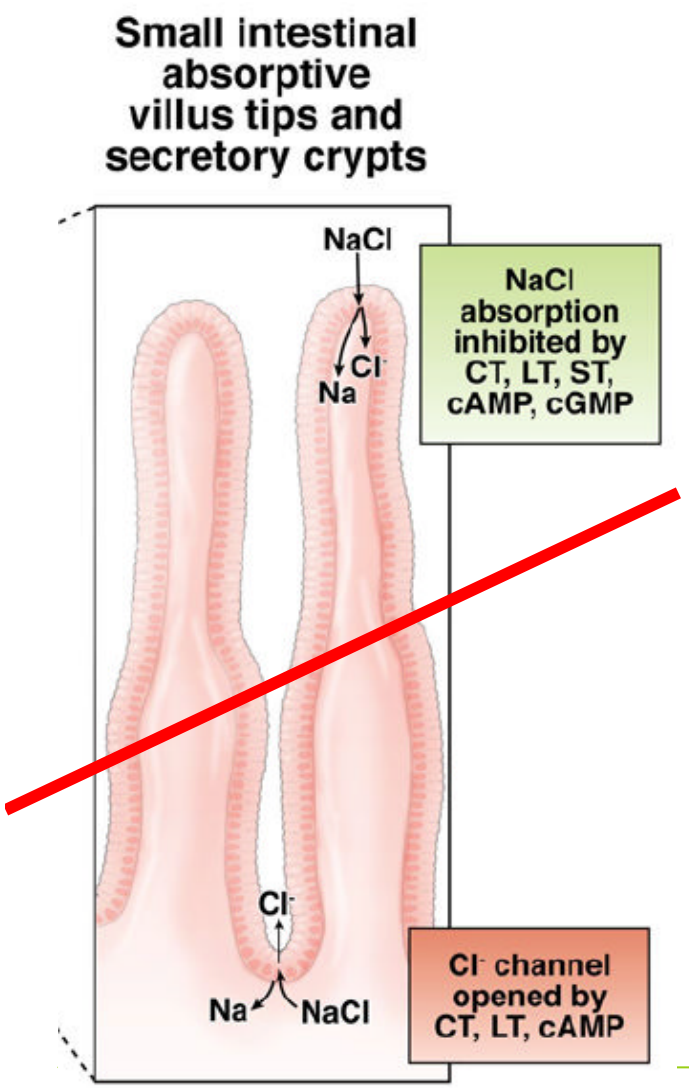

Sekretorisches Enterotoxin

Cholera
ETEC (Hitze-stabil & instabil)

Cytotoxin

EPEC

Villus-Destruktion

Rotaviren, Noroviren

Cryptosporidien
Mikrosporidien, Cyclospora,
Strongyloides
Lamblien

Aeromonas

Pawlowski SW et al. Gastroenterology 2009

Pathophysiologie Kolon

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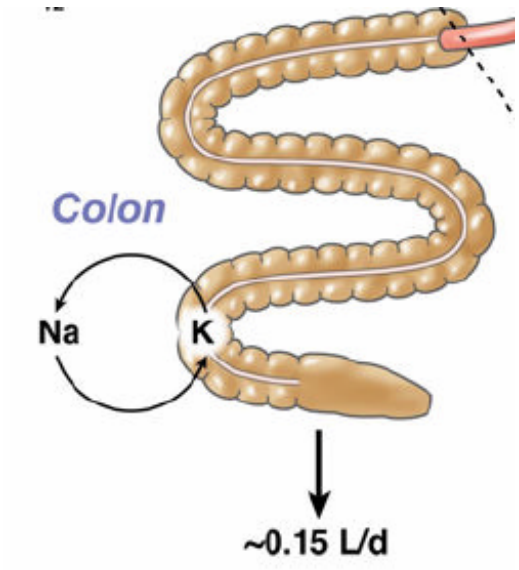

Invasiv-entzündlich
EIEC, EAEC, EHEC
Salmonellen, Shigellen, Yersinien,
Campylobacter
C. difficile
Vibria

Amöben

Enterischer Adenovirus, CMV, MAC

Epidemiologie

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30‘000 Stuhlproben: 5.6% positiv

Campylobacter	2.3%
Salmonella	1.8%
Shigella	1.1%
EHEC O157:H7	0.4%

877 Patienten mit blutiger Diarrhoe

Shigella	15.3%
Campylobacter	6.2%
Salmonella	5.8%
EHEC O157:H7	2.6%

Nahrungsmittel-bedingte Diarrhoe Fälle/100‘000

Salmonellen	17.6	Cryptosporidien	2.8
Campylobacter	13.6	Shiga-toxin+ E.coli	1.9
Shigellen	3.8	Yersinien	0.3

Slutsker L et al. Annals Intern Med 97; Talan D et al. CID 01; CDC MMWR 01;50:1

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Estimates of domestically acquired foodborne illnesses in the United States*

Pathogen	Estimated number of cases per year (mean)	Foodborne (percent)•	Travel-related (percent)	Hospitalization rate (percent)Δ	Death rate (percent)Δ
Bacteria					
Bacillus cereus, foodborne	63,400	100	<1	0.4	0
Brucella spp	839	50	16	55	0.9
Campylobacter spp	845,024	80	20	17.1	0.1
Clostridium botulinum, foodborne	55	100	<1	82.6	17.3
Clostridium perfringens, foodborne	965,958	100	<1	0.6	<0.1
STEC O157	63,153	68	4	46.2	0.5
STEC non-O157	112,752	82	18	12.8	0.3
ETEC, foodborne	17,894	100	55	0.8	0
Diarrheagenic Escherichia coli other than STEC and ETEC	11,982	30	<1	0.8	0
Listeria monocytogenes	1591	99	3	94	15.9
Mycobacterium bovis	60	95	70	55	4.7
Salmonella spp, nontyphoidal	1,027,561	94	11	27.2	0.5
Salmonella enterica serotype typhi	1821	96	67	75.7	0
Shigella spp	131,254	31	15	20.2	0.1
Staphylococcus aureus, foodborne	241,148	100	<1	6.4	<0.1
Streptococcus spp group A, foodborne	11,217	100	<1	0.2	0
Vibrio cholerae, toxigenic	84	100	70	43.1	0
Vibrio vulnificus	96	47	2	91.3	34.8
Vibrio parahaemolyticus	34,664	86	10	22.5	0.9
Vibrio spp, other	17,564	57	11	37.1	3.7
Yersinia enterocolitica	97,656	90	7	34.4	2

ETEC: enterotoxigenic Escherichia coli; STEC: Shiga toxin-producing Escherichia coli.
* All estimates based on United States population in 2006.
• Percentage foodborne among domestically acquired illness.
Δ For laboratory-confirmed illnesses. Unadjusted hospitalization and death rates are presented here. These rates were doubled to adjust for underdiagnosis before being applied to the number of laboratory-confirmed cases to estimate the total number of hospitalizations and deaths. The hospitalization and death rates for atrovirus, norovirus, rotavirus, and sapovirus presented here are the percentage of total estimated illness and were not subject to further adjustment.
Adapted from: Scallan E, Hoekstra RM, Angulo FJ, et al. Foodborne illness acquired in the United States—major pathogens. Emerg Infect Dis 2011; 17:7.

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Parasites					
Cryptosporidium spp	57,616	8	9	25	0.3
Cyclospora cayetanensis	11,407	99	42	6.5	0
Giardia intestinalis	76,840	7	8	8.8	0.1
Toxoplasma gondii	86,686	50	<1	2.6	0.2
Trichinella spp	156	100	4	24.3	0.2
Subtotal	232,705				
Viruses					
Astrovirus	15,433	<1	0	0.4	<0.1
Hepatitis A virus	1566	7	41	31.5	2.4
Norovirus	5,461,731	26	<1	0.03	<0.1
Rotavirus	15,433	<1	0	1.7	<0.1
Sapovirus	15,433	<1	0	0.4	<0.1
Subtotal	5,509,597				
Total	**9,388,075**				

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„Relativ“ sauber...

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Notwendiges Inokulum für symptomatische Infektion

Shigellen	10^{1-2}
Lamblien	10^{1-2}
Amöben	10^{1-2}
Campylobacter	10^{2-6}
Salmonellen	10^{5}
Cholera	10^{8}

Magensäure tötet 99.9% der Bakterien !!!

Risiko antibiotische Vorbehandlung

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Table 2. Number of *Salmonella* cases and population controls exposed to antimicrobial drugs and the OR of *Salmonella* infection by history of antimicrobial drug use 2 weeks–12 months before infection, Denmark 1997–2005; all *Salmonella* cases, irrespective of susceptibility testing

	No. (%) exposed cases/controls		OR for being exposed to antimicrobial drugs, OR (95% CI)
	cases	controls	
Salmonella Typhimurium (4675)			
exposure to:			
broad-spectrum penicillins	601 (12.9)	3998 (9.2)	1.56 (1.41–1.73)
fluoroquinolones	78 (1.7)	326 (0.8)	2.21 (1.70–2.86)
sulphonamides and trimethoprim	177 (3.8)	1295 (3.0)	1.30 (1.10–1.54)
tetracyclines	64 (1.4)	440 (1.0)	1.32 (1.00–1.74)
Salmonella Enteritidis (12151)			
exposure to:			
broad-spectrum penicillins	1202 (9.9)	9169 (7.8)	1.33 (1.24–1.42)
fluoroquinolones	198 (1.6)	929 (0.8)	2.07 (1.76–2.42)
sulphonamides and trimethoprim	535 (4.4)	4017 (3.4)	1.32 (1.20–1.45)
tetracyclines	194 (1.6)	1402 (1.2)	1.33 (1.14–1.55)
Other *Salmonella* serotypes (5776)			
exposure to:			
broad-spectrum penicillins	719 (12.4)	4592 (8.5)	1.62 (1.47–1.77)
fluoroquinolones	186 (3.2)	387 (0.7)	4.55 (3.78–5.47)
sulphonamides and trimethoprim	317 (5.5)	1815 (3.4)	1.72 (1.51–1.96)
tetracyclines	142 (2.5)	607 (1.1)	2.24 (1.85–2.71)

The ORs are adjusted for sex, age, county of residence, population density, income and schooling.

Koningstein M et al. JAC 2010

Inkubationszeit Infekt

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Stunden

6 12 24 36 48

Tage

1 2 3 4 **5** 6 7

S.aureus

Bacillus cereus

Cl. perfringens

E.coli

Salmonellen

Clostridium difficile

Cholera

Shigellen

Rota

Campylobacter

Aeromonas

Diagnostik

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Entzündlich?

Blut? 3%	EHEC, Shigellen, Amöben O157:H7
Schleim?	Amöben
Krämpfe?	Yersinien, C. difficile
Fokalbefund?	Pseudoappendicitis: Yersinia, Campylobacter Blähungen, Flatulenz, Foetor: Lamblien

Dysenterie:

Shigellen
Campylobacter

Leukozyten im Stuhl
Sens 70%, Spec 50-84%

Lactoferrin, Neopterin, Calprotectin
Sens % Spec 90-100%

Thielman NM et al. NEJM 2004, Slutsker L et al. Ann Intern Med 197, 4Guerrant RL et al. JCM 1992

Diagnostik

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Infektiös?

akut: 1x Stuhl-Bakt (evtl. E.coli Toxin) ambulant
1-3x C. difficile Toxin

Stuhl-Bakt 1.5-5.6% positiv

>1 Woche: 2-3 x SAF Parasiten (1x nativ: Strongyloides)
evt. Cryptosporidien, Cyclospora (IF)
Antigen Amöben, Lamblien

Serologien: Amöben, Strongyloides

Guerrant RL et al.CID 2001

Serologien
Kreuzreaktion

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Antigen / Parasit	Sm1	Sm2	Fh	Eg	Sr	Av	Tc	Ts
Bilharzose								
Fasciolose								
Echinokokkose								
Strongyloidose								
Filariose								
Toxokarose								
Trichinellose								

Behandlung – AB Resistenz

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	E.Coli	Campylobacter	Salmonellen	Shigella
Ampicillin	**50-80**	**66**	**20**	**74**
AmoxyClav		**20**	**3**	**1**
3.Gen Cephalo	**2-19**		**1-5**	**0**
Cotrimoxazol	**30-60**	**100**	**9**	65
Chinolone	**4-30**	**53**	**13**	**1**
Azithromycin		**2**		

Stellinig 05, Ruiz 2007, Streit 2006

Therapie

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Oral Rehydration Solution

Na-Glc Transporter bleibt intakt: sekundäre Wasseraufnahme
1L Wasser mit 4 EL Zucker, ½ KL Salz und ½ KL Back-Soda

Loperamid (Imodium®) + viel Flüssigkeit

1x4mg, 2mg-weise bis 12mg/Tag

Antibiotika

do: Dysenterie
don't: EHEC (mehr Shigatoxin: Niereninsuff.)

Noroxin 2x400mg/d für 3-5 Tage	Heilung 1.7 vs. 2.8d
Levofloxacin 1x500mg/d für 3-5 Tage	Keimelimination 18 vs. 49%
Ciproxin 2x500mg/d für 3-5 Tage	
Azithromycin 1x500mg/d für 3 Tage	

Wiström J et al. Annals Intern Med 1992

Therapie antibiotisch

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Indikation

Hypovolämie
Dysenterie
>6 Stühle/Tag
Dauer >48h
Immuunkompromittierung
>70 jährig

: Hospitalisation

ACE Hemmer und AT Blocker

Hypovolämie: Risiko des Nierenversagen

Blutdrucksenker

Hypovolämie: Kollaps

Antidiabetika

Entgleisung des Diabetes

Antikoagulation

Verminderte Resorption des Vitamin K

Antikonzeption, Lithium, Antiepileptika

Malabsorption

persistierender Durchfall

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1Jahr nach Reisedurchfall: 4% Stuhlunregelmässigkeit

Persistierender bakt. Infekt?

EPEC EAEC. Campylobacter, Salmonella, Tropheryma whippeli

Cryptosporidien, Lamblien?

Zoeliakie

Laktose-, Fruktose-Intoleranz

Entzündliche Darmerkrankung

…

Irritable bowel syndrome

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4-32% nach akuter Gastroenteritis

verlängerte oder verkürzte Passage
Blähungen

Aetiologie

Serotonin-Dysbalance
Entzündung mit Vermehrung Lymphozyten/Mastzellen

Halvorson HA et al. Gastroenterology 06, Thabane M et al. Aliment Pharmo. Ther 07

„Cook it, peel it, boil it or forget it“

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.... 2-3% glauben Ihnen....

95% konsumieren	Eiswürfel
90%	Salate
80%	Leitungswasser / Milchprodukte
55%	Glacé, nicht gares Fleisch
	Meeresfrüchte

Dupont, Ann Intern med 2005; Adachi & Dupont, CID, 2006

Prophylaxe

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Antibiotika

Rifaximin
Quinolone
Bactrim

Impfung

Rota
Cholera
Typhus

Probiotika

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Ziel: Positive Beinflussung der Darmflora

Prebiotika

selektive Wachstumsförderung

Probiotika: Verdrängung? Immunmodulation?

Lactobacillus, Bifidobakterium, Saccharomyces boulardii
(Perenterol®, Enterokokken (Bioflorin®), Strept. Salivarius…

Metaanalyse

52% (35-65%) weniger Antibiotika-assoziierte Diarrhoe
3 statt 6 Tage Antibiotika-assoziierte Diarrhoe
17-30 Stunden kürzere akute Diarrhoe
8% (6-21%) weniger Reisediarrhoe

Cave: invasive Infekte bei Immunsuppression

Sazawal S et al. Lancet Infect Dis 2006; vanNiel CW et al. Pediatrics 2002

Risikofaktor Reisen

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TABLE 3. Travel destinations of travelers who were negative for ESBL-producing strains before the trip and rate of fecal colonization with ESBL-producing *E. coli* strains upon return[a]

Continent or region	No. of travelers	No. (%) of travelers positive for ESBL-producing isolates
Africa	25	1 (4)
Asia (India excluded)	31	10 (32)
Central America	6	0 (0)
India	8	7 (88)
Middle East	14	4 (29)
North America	2	0 (0)
South America	1	0 (0)
Southern Europe	16	2 (13)

[a] The rate of acquisition of ESBL-producing strains was highest for travelers visiting India ($P < 0.001$). Three participants visited more than one continent, and therefore, the sum of travelers in this table exceeds the actual number of 100.

24/100
neu ESBL+

Tangden T et al. AAC 2010

Risikofaktor Reisen (2)

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Table 1 Travellers colonised with one or more strains of *Escherichia coli* resistant to ciprofloxacin, gentamicin and/or third-generation cephalosporins (3GC) pre- and post-international travel (n=102)

Antibiotic	Percentage (95% CI) of travellers with resistant *E. coli* pre-travel	Percentage (95% CI) of travellers with resistant *E. coli* post-travel
Ciprofloxacin	3.9 (1.2–10.0)	33.3 (24.9–43.0)[a]
Gentamicin	7.8 (3.8–14.9)	40.2 (31.2–49.9)[a]
3GC	2.0 (0.1–7.3)	25.5 (18.0–34.8)[a]
ESBL-positive	2. 0 (0.1–7.3)	21.6 (14.6–30.6)[a]
Any antibiotic	7.8 (3.8–14.9)	49.0 (39.5–58.6)[a]

ESBL=extended-spectrum beta-lactamase

[a] $p<0.0001$

neue *E.coli*-Stämme?

Transfer neuer Resistenzgene?

Kennedy K et al. Eur J Clin Microbiol Infect Dis 2010

Salmonellen (1)

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Typhös vs. nicht typhös

Salmonella typhi & paratyphi
Reservoir: Mensch
binden spezifisch an M-Zellen über Peyer Plaques
induzieren Endozytose
replizieren und überleben in „Salmonella-containing vacuoles“

Vivotif Berna®

po. Tag 1, 3, 5	Protektion 67%
Lebendimpfstoff	Kühlschrank
	Antibiotika
	Ausscheider

1 ½ Jahre Schutz

Typhim Vi®

im. einmalig	Protektion 53-73%

Salmonellen (2)

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Typhös vs. **nicht typhös**

Salmonella enteritidis & typhimurium

Reservori: Nahrungsmittel, Reptilien
>2‘000 Serovare

S. typhimurium sezernieren proinflammatorische Zytokine
metabolisieren exklusiv Ethanolamin, das bei Enteritis freigesetzt wird

Rotaviren

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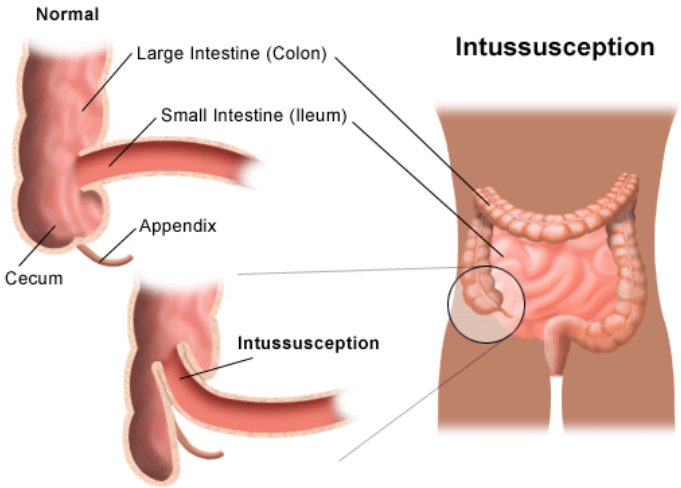
häufigste Gastroenteritis-Ursache bei Kindern

bis 3j. haben alle Rotaviren gehabt
keine bleibende Immunität
Familiäre Exposition: 50% der Kinder infiziert
15-30% der Erwachsenen
Europa: Winterpeak mit Ausbreitung West>Ost

500‘000 Tote pro Jahr
Virusausscheidung 10-21 Tage



Epidemien

39% Restaurant
25% Spitäler & Heime
13% Schulen
10% Feriendestinationen

Richardson S et al. Lancet 1998, Musher DM et al. NEJM 2004

Noroviren

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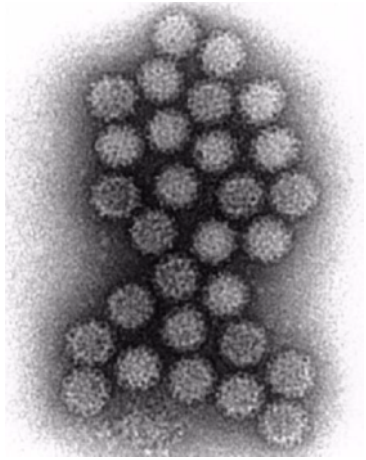

Norwalk-like Virus, „winter vomiting disease“

bis 90% der nicht-bakteriellen Gastroenteritiden
nur serotyp-spezifische Immunität

hoch-kontagiös (Tröpfchen)
Resistenz: Hitze (>60^{0}C), Chlor-Desinfektion
>70% Alkohol

Diagnostik PCR

Kaplan Kriterien

sens 68%, spec 99%

- Erbrechen bei >50% der Betroffenen
- Inkubationszeit 24-48h
- Krankheitsdauer 12-60h
- keine Bakt in Stuhlprobe