Cl. difficile Infection Diagnosis an therapy

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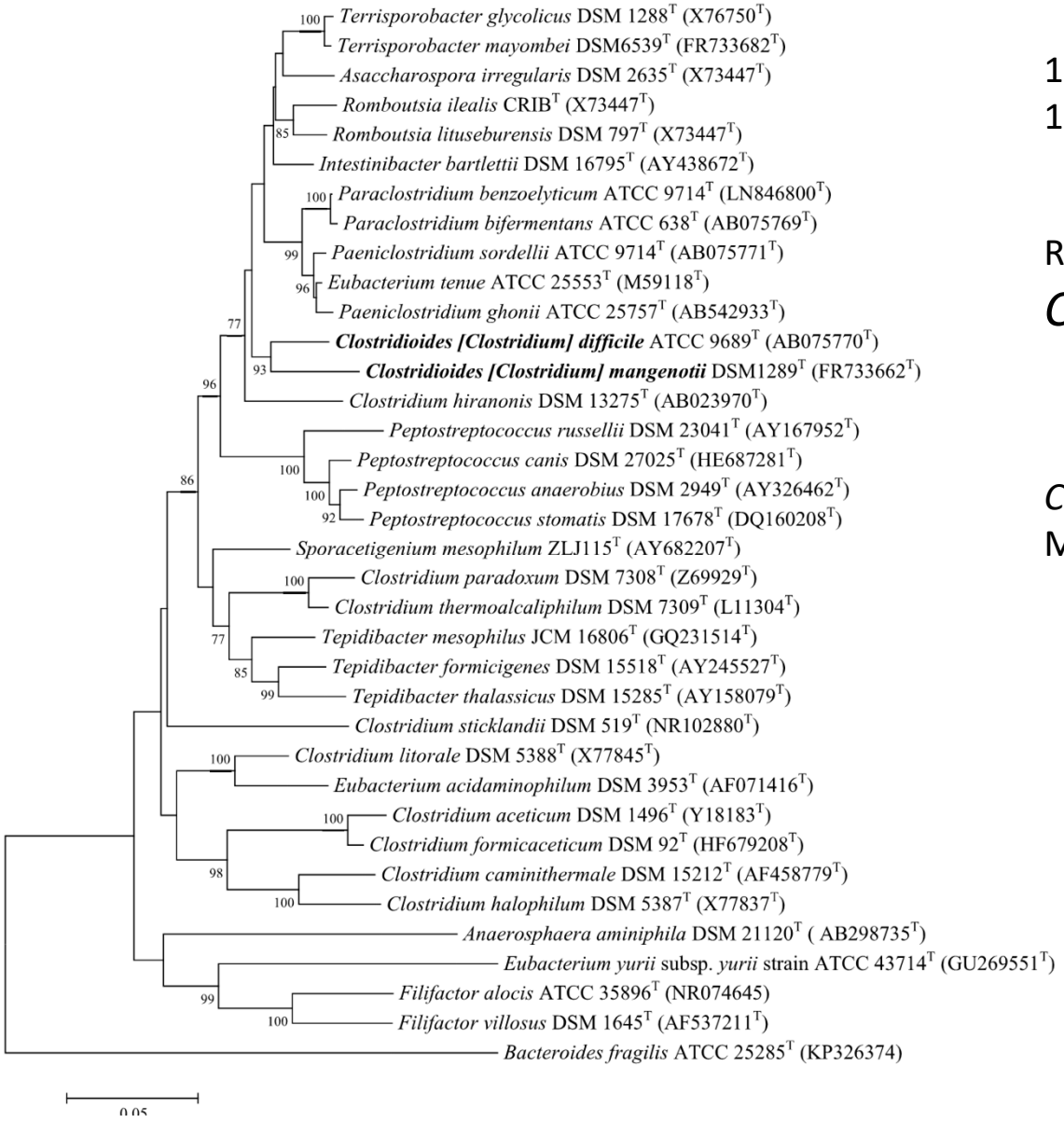
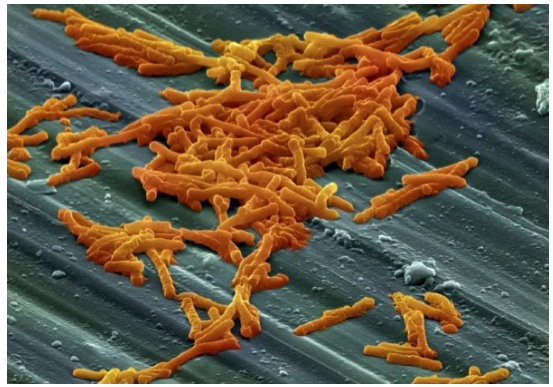


1938: First description
1978: Identified as cause of antibiotic associated colitis

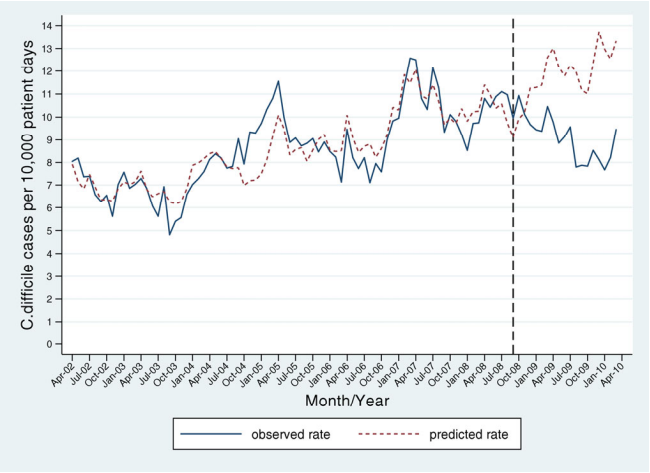
Reclassified 2016:
Clostridium difficile → *Clostridioides difficile*

Cl. difficile strictly anaerobic rods (0.5-1.9 μm – 3-16 μm)
Motile in culture



Lawson, *Anaerobe* 2016; 40:95

Epidemiology

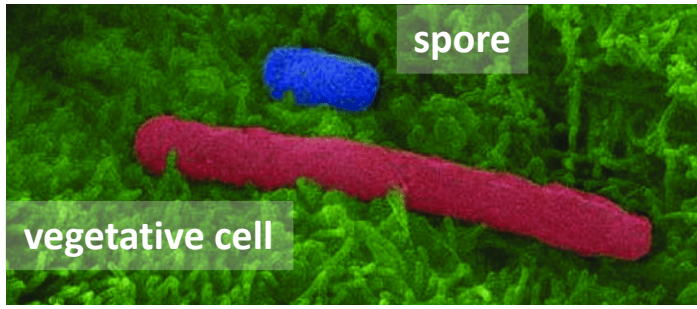


Intervention: public reporting

- 1-3% of healthy adults are colonized
  8-10% of residents of hospitals/ long-term care facilities
- USA/ Canada: 500'000 cases, 29,000 deaths
  → incidence 1996: 31/100,000 2003: 61/100,000
  → mortality 1997: 1.5% 2005: 5.7%
  → most frequent pathogen for healthcare associated infections
- Setting of *Cl. difficile* infection
  - 20% hospital acquired
  - 50% health care associated
  - 30% community acquired

Daneman PLoS Med 2012; e1001268; Samarkos et al. 2018; European J Int Med 50:28

Infectious cycle



- Patient with *Cl. difficile* infection and w/o infection can be sources
  - 10% of all inpatients are *Cl. difficile* carrier

    → 6-fold higher risk for *Cl. difficile* infection (22% vs. 3%)
  - 30% had been in recent contact with carrier
  - 30% had been in recent contact with symptomatic patient
  - Identification of asymptomatic carriers decreased infection from 6.9 to 3 per 10,000 patient days
- Spores are ingested
  - resistant to acid, heat, alcohol, reside for months on surfaces
    → care to avoid transmission from patient to patient
  - Germination in the intestine (signals: bile acids, glycin)
- Two hit hypothesis: infection of a patient with a disrupted microbiota

McDonald, Clin Infect Dis 2018; 66:e1; Zacharioudakis et al., Am J Gastroenterol 2015; 110:
Kong et al, CID 2019; 68:204; Longtin JAMA Intern Med 2016; 176:796

Risk factors for *Cl. difficile* infection

- **Antibiotics**
  - x8-10: during antibiotic therapy until 4 weeks after therapy
  - x3: during the next 3 months.
  - Multiple antibiotics, high cumulative dose, long duration further increase risk
  - Also antibiotic use in previous occupant of hospital bed
- **Older age**
  - >65 years: x5-10 (each year beyond 18y: +2%)
- **Hospitalization/ institutionalization**
  - (only) 30% of cases are community acquired, 82-94% health care exposure
- IBD, gastrointestinal surgery, immunological incompetence (neoplasm, immunosuppressant use), chronic kidney disease

Samarkos et al. 2018; European J Int Med 50:28, Czepiel et al., EJCMID 2019; 38:1211

Most frequent

- Clindamycin
  the first documented
- Fluorochinolones
- Cephalosporin (broad spectrum)
- Penicillin (broad spectrum)
  current leader

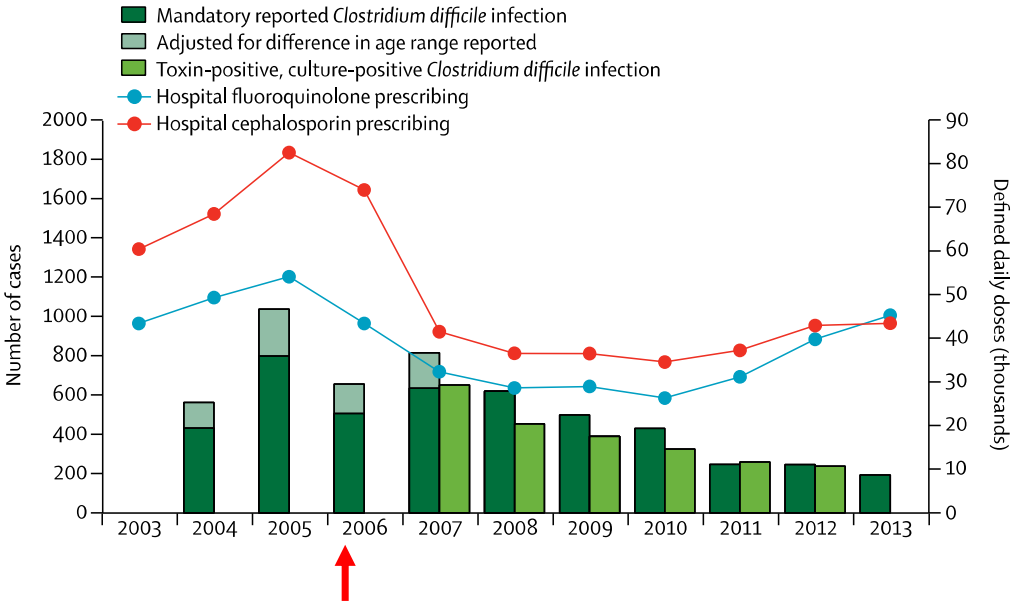
Less (least??) frequent

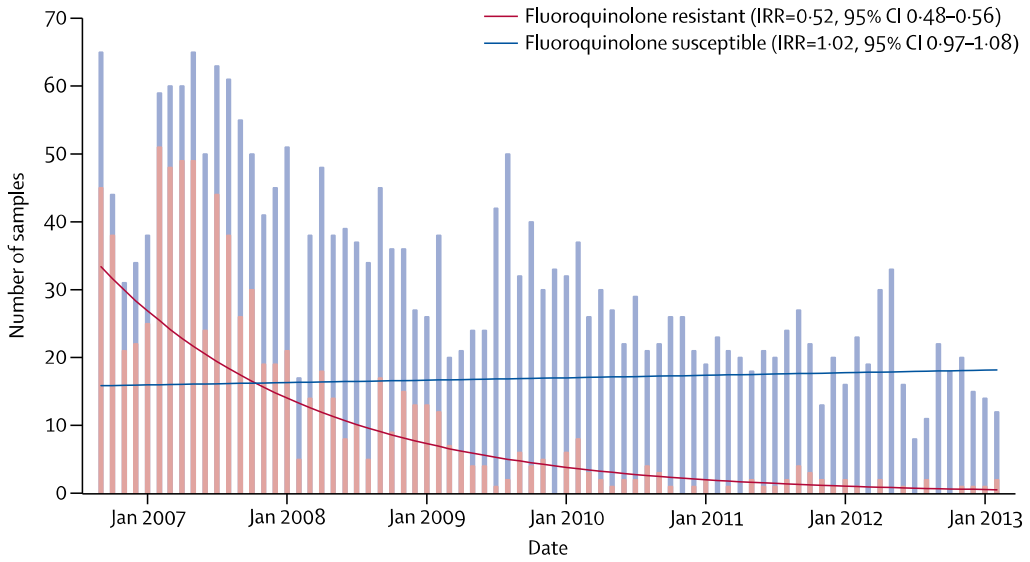
- Aminoglycosides
- Tetracyclines
- Metronidazole
- Vancomycin

Cave: epidemiological limitations preclude strong conclusions

McDonald, Clin Infect Dis 2018; 66:e1

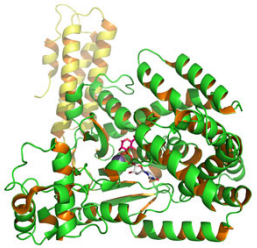
Antibiotic Stewardship



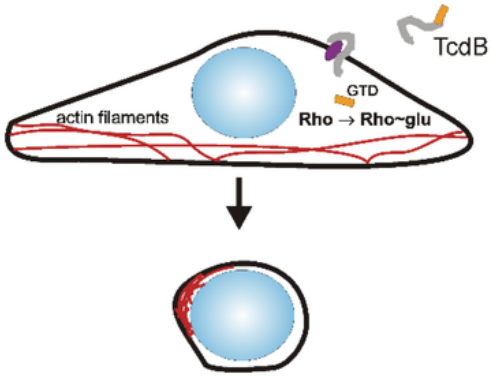


- *Cl. difficile* load decreased by 80% in England (16% increase in other countries)
- Decline was driven by decrease in fluorchinolone resistant strains (cross-correlation >0.88)
- Decline was accompanied by increase in fluoroquinolone susceptible strains
- (in other studies, reduction of cephalosporin usage and reduction of duration has also been successful)

Dingle et al., Lancet Infect Dis 2017; 17:411



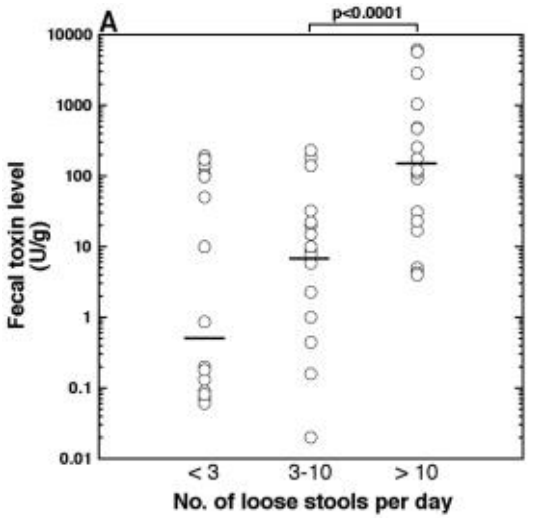
Cl. difficile toxins



- Toxin A, B: enterotoxins → cell retraction (cell cultures)
  → ulcera (colon)
  → colitis, diarrhea
- Toxin B: 10 times more powerful than toxin A
- 10-30% of strains are non-toxinogenic (avirulent)
- NAP1/BI/027: hypervirulent strain (more severe disease)
  - Binary toxin (CDT) → actin depolymerizatoin
  - Fluorochinolone resistant
  - Switzerland 2% of *Cl. difficile* infections in hospitals

glucosylation of Rho GTPases:
cytoskeleton breakdown
pro-inflammatory response

apoptosis



Akerlund et al., J Clin Microbiol 20016; 44:353; Frädrich et al. 2016, Toxins 8:25

Symptoms

- Diarrhea: ≥3 loose stools per 24 hours
- Lower abdominal pain, cramping
- Nausea, anorexia
- Low grade fever (15%)
- Rarely with hematochezia, melena

- Mainly with antibiotics
  - Mainly within 2 weeks of antibiotic therapy, or one month later
  - Rarely later within (10 weeks)
  - 5-10% without antibiotics

Martin Nat. Rev. Gastroentrol 2016; 13:206; McDonald, Clin Infect Dis 2018; 66:e1

Definitions

Clostridium difficile infection =
Diarrhea (≥3 loose stools per 24 hours) + positive test (2-step algorithm)

Non-severe: *Leukocyte count ≤15,000 cells/μl, creatinine ≤132 μmol/l*

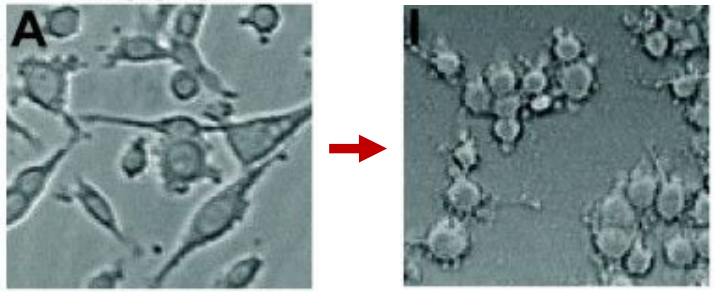
Severe: *Leukocyte count >15,000 cells/μl, creatinine >132 μmol/l*

Fulminant: *Hypotension, shock, ileus, megacolon (>7cm)*

(expert opinion, prospective studies needed)

McDonald, Clin Infect Dis 2018; 66:e1

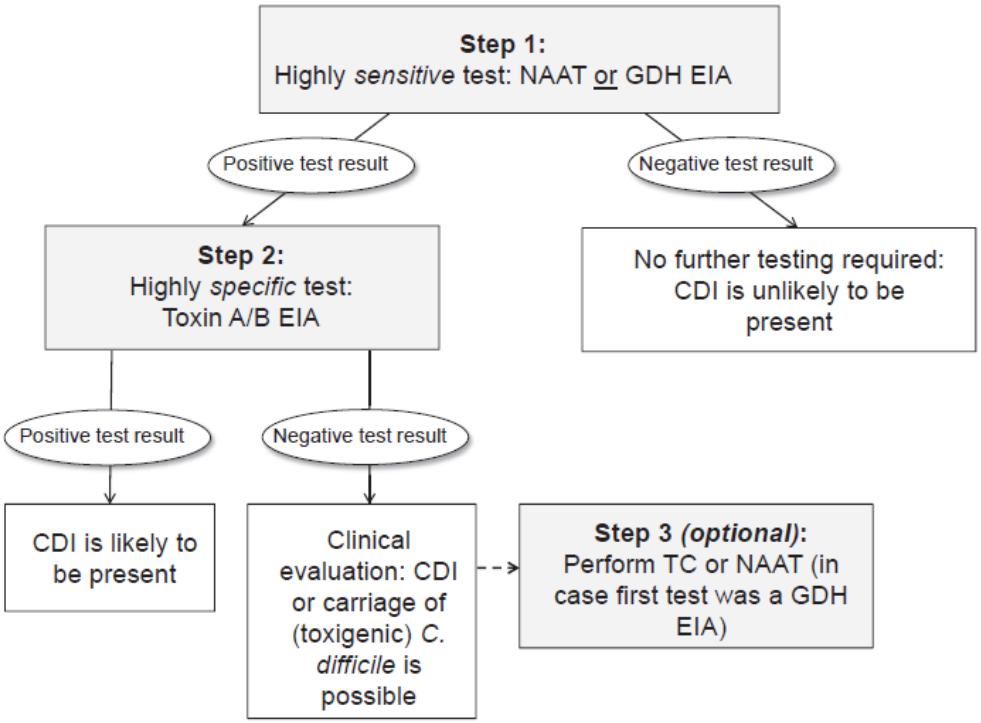
Diagnosis of *Cl. difficile*



- Reference tests
  - CCNA: Cell cytotoxicity neutralization assay (2 days)
    Incubation of cell monolayers with filtered stool for cytopathic effect
    Neutralization with antibodies
  - TC: Toxigenic culture (2 days)
    Anaerobic culture of stool samples on selective media
    Testing for toxin production (CCNA, EIA, NAAT)
- Enzyme immune assay (EIA) for glutamate dehydrogenase (GHD)
  → presence of bacteria
  CCNA: Sens: 80-100%, Spec: 82-95% TC: Sens: 83-100%, Spec: 88-100%
- Nucleic acid amplification test (NAAT) for toxin A+B
  → presence of toxigenic genes
  CCNA: Sens: 83-100%, Spec: 87-98% TC: Sens: 77-100%, Spec: 77-100%
- Enzyme immune assay (EIA) for toxin A+B
  → presence of toxins
  CCNA: Sens: 44-99%, Spec: 87-100% TC: Sens: 29-86%, Spec: 91-100%

Crobach et al., Clin Microbiol Inf 2016; 22:S63

Suggested algorithm



- **How many samples?**
- 1 within 7 days (more only with strong suspicion)

- **Asymptomatic individuals?**
- Usually not (no evidence for benefit)

- **Formed stool?**
- Should not be tested (asymptomatic carrier)
  cave: solid parts of diarrhoeal faeces

- **Should all unformed stool samples be tested in the lab?**
- Yes: for 23% of all *Cl. diff.* positive stool samples no *Cl. diff* test has been requested in UK, 50% in Spain

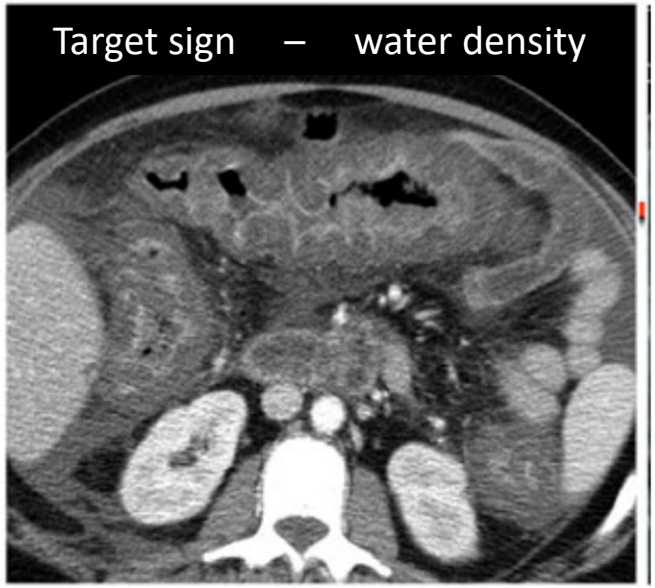
- **Ileus?**
- Rectal swabs (inform microbiology lab)

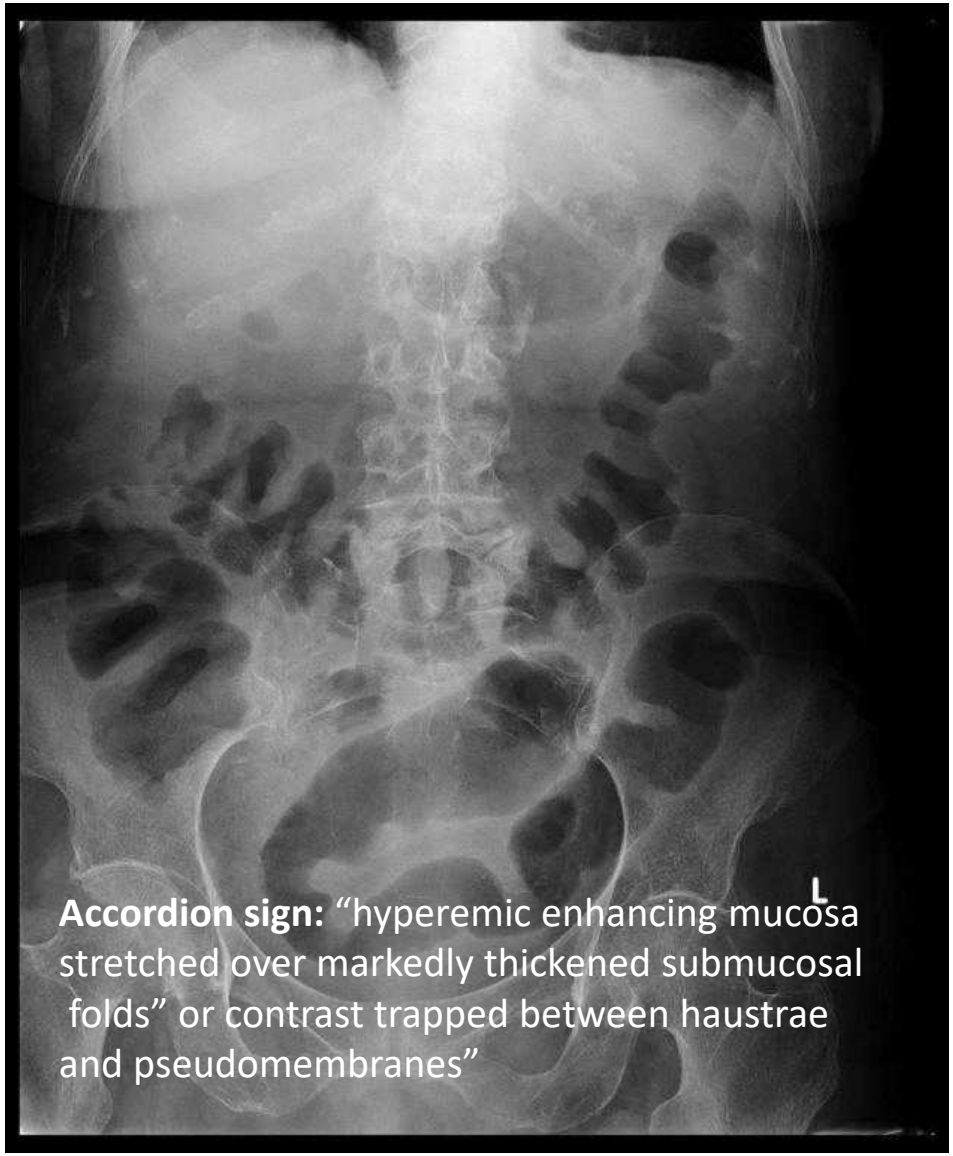
- **Storage?**
- 4°C!! (degrades within 2 hours at room temperature)

Crobach et al., Clin Microbiol Inf 2016; 22:S63

Radiology

- CT-scan (plain abdominal X-ray)
  - Colon dilatation >7cm → toxic megacolon
  - Bowel wall thickening (target sign, halo sign)
  - Free abdominal air

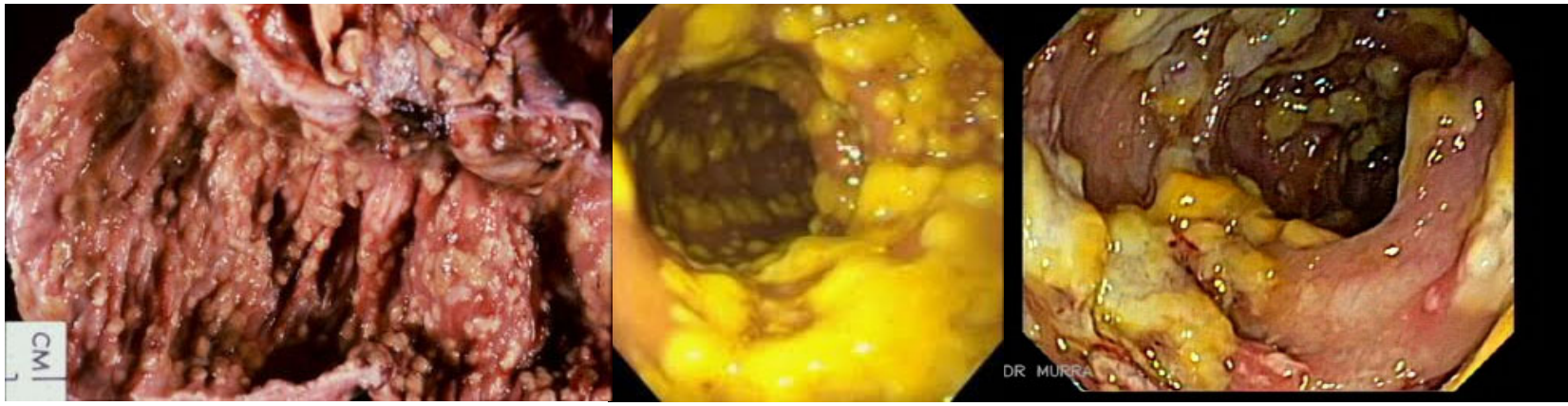




Accordion sign: "hyperemic enhancing mucosa stretched over markedly thickened submucosal folds" or contrast trapped between haustrae and pseudomembranes"

www.radiopaedia.org

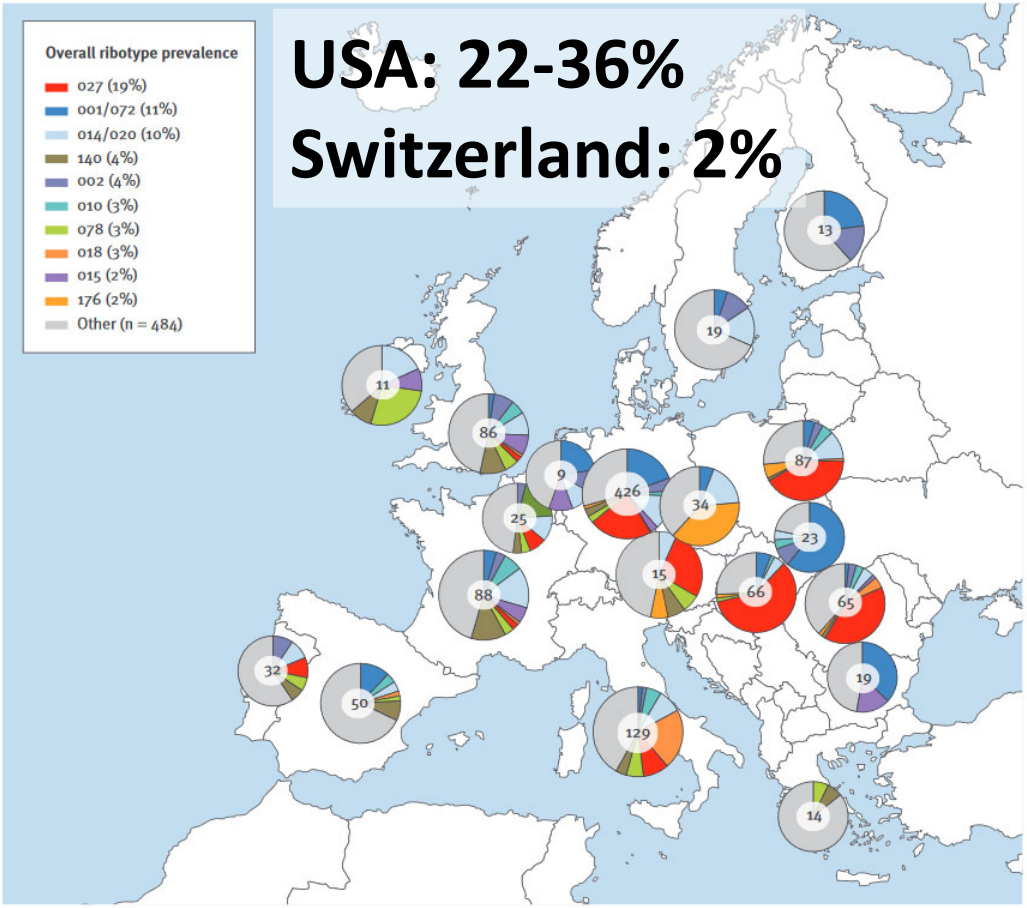
Endoscopy



- Not required
- Consider rectosigmoidoscopy (only) if other diagnoses need to be excluded
- Edema, erythema, friability, inflammation
- Pseudomembranes ”highly suggestive”
  - High sensitivity: 51-89% by endoscopy, 61% by histology
  - Low specificity (1/ 7 *Cl. diff* positive patients in a correlative study)
  - Rectum frequently spared
- Endoscopy/ biopsy not useful in IBD patients (or immune-compromised patients) for *Cl. difficile* detection

Goodhand Aliment Pharmacol Ther 2011; 33:428; Guarner et al., Clin Inf Dis 2012; 54:156

Hypervirulent strain R027



EUCLID 2013; www.eurosurveillance.org

NAP1-Stamm (North American Pulsed field type 1)
NAP1/B1/027
Ribotype 027, R027
Since 2001, USA

Molecular properties:

- More toxin A+B
- Binary toxin (actin depolymerization)
- Hypersporulation

Clinical properties:

- Less susceptible to antibiotics metronidazole, rifampicin, imipenem
- Easier spread in hospitals
- ***Contradictory findings regarding severity of disease***

Fatima et al., 2019, Cureus 11:e3977; Frädrich et al. 2016, Toxins 8:25

Management – isolation?

Schweiz – Hygieneordner Inselspital

- Standardmassnahmen für Patienten ohne Stuhlinkontinenz, mit guter Hygiene
  - Eigenes WC oder eigener Nachtstuhl
- Kontaktisolation für Patienten mit Stuhlinkontinenz und mangelnde Hygiene
  - Isolation für Dauer der Infektion (Symptome?)
- *Cl. difficile* Typ R027 (hochvirulent)
  - Kontaktisolation, Kennzeichen rot
  - Einzelzimmer
  - Handschuhe, Maske, Überschürze, Schutzbrille
  - Kein physischer Kontakt zu anderen Patienten
  - Entisolation nur nach Rücksprache Spitalhygiene
  - Ähnliche Massnahmen werden bei Häufung von *C. diff*. Fällen evtl. für alle Patienten mit C. diff Infektion notwendig

Infectious Diseases Society of America

- Isolation:
  - Single room, dedicated toilet
  - Prioritize isolation for incontinent patients
- Gloves and gowns while caring for patients
- «preemptive contact precautions»
- Continue for 48 hours after resolution of diarrhea

- Hand desinfection: Soap and water preferred over alcohol for removal of spores
- Patients should wash hands and shower
- Antibiotic stewardship

McDonald, Clin Infect Dis 2018

Controversies Europe vs. North America

First non-severe episode

European Society of Clinical Microbiology

Metronidazole 3x500mg p.o.
Vancomycin 4x125mg p.o.
Fidaxomycin 2x200mg p.o.

Infectious Diseases Society of America

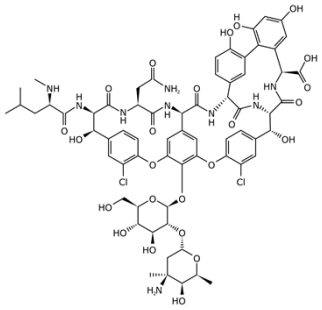
Vancomycin 4x125mg p.o.
Fidaxomycin 2x200mg p.o.

Metronidazole only if access to vancomycin limited

→ Prominent role of metronidazole in Europe vs. no role in North America (since R027 less susceptible to metronidazole).

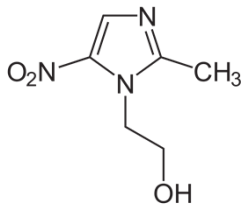
McDonald, Clin Infect Dis 2018

Debast, Clin Microbiol Infect 2013



Vancomycine vs. Metronidazole

in first episode of non-severe *Cl. difficile* colitis



Vancomycine

- Since 1954, WHO essential drug
- Glycopeptide, inhibits construction bacterial cell wall
- Very poorly absorbed (and safe) when swallowed

Metronidazole

- Since 1960, #58 in USA according to frequency
- Forms nitroso radicals under anaerobic conditions which break bacterial DNA

PRO VANCOMYCINE

- More efficient
  multiple RCT since 2000
  e.g. response 73% in 289 patients with metronidazole
  vs. 81% in 266 patients with vancomycine, p=0.02
- Metronidazole is absorbed (what we do not need)
- Metronidazole has side effects
  - Central neurotoxicity (metallic taste, dizziness, headache, confusion, altered speech, nausea, loss of appetite, depression)
  - Peripheral neurotoxixity (numbness, burnin, painful sensation)
  - Carcinogenic in rats and mice

PRO METRONIDAZOL

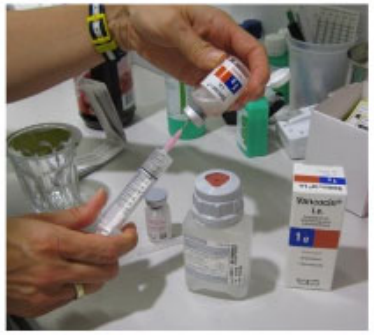
- Lower rates of resistencies (VRE)
- Lower costs

Costs of Clostridioides difficile therapy

- Metronidazole 3x500 mg per day for 10 days : 24 CHF
- Vancomycine 4x125 mg per day for 10 days : 245.50 CHF
- Fidamoxicin 4x125 mg per day for 10 days : 1896.75 Franken
  no limitation by pharmacy, can be prescribed by every physician at Inselspital

AML (Arzneimittelliste) Insel Gruppe	
Mat.Nr.	***Material***
10029113	**VANCOCIN** TS 500 mg i.v. Vial
10026293	**VANCOCIN** TS 1 g i.v. Vial

NICHT - AML
Material
VANCOCIN 125 mg 20 Kps
VANCOCIN 250 mg 20 Kps

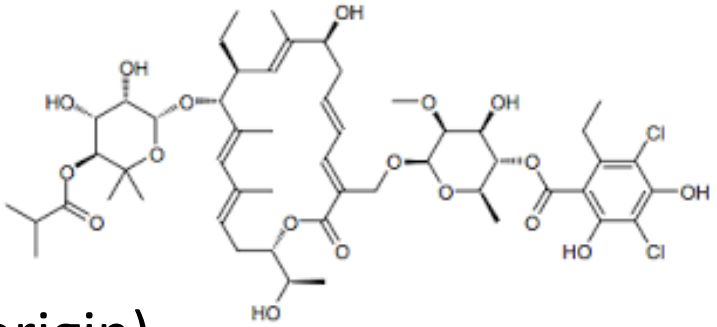


Reconstitution of vancomycine, 500mg in 10ml

- Can be stored in fridge for 2 weeks
- Add honey (bitter taste)
- Use 4x2.5 ml per day (=4x125mg)
- We save 50-270 CHF per 10 day treatment

Dr. Christoph Hanck, personal communication
http://netz.insel.ch/fileadmin/Departemente/DOLS/dols_user/Spitalpharmazie/pdf/ISPI-Handbuch/06_02_06_Vancomycin_orale_Gabe.pdf

Fidaxomicin = Dificlir®



Fidaxomicin

- Makrocykline, from Actinomyces species (bacterial origin)
  Dactylosporangium aurantiacum spp. hamdenesis
- Bactericid - blocks bacterial RNA polymerase
- Only indication: *Cl. difficile* colitis
  - In non-severe disease modestly more effective than vancomycin 71% vs. 61%, OR 1.17 (1.04-1.31)
  - In non-severe disease, lower recurrence compared to vancomycin (15% vs. 25%). lower microbiome alteration?
  - In severe disease, as efficient as vancomycin
  - No experience in fulminant disease
  - 1896.75 CHF for 10 days treatment (vancomycin: 245.50 CHF)

www.compendium.ch, Nelson Cochrane Database Syst Rev 2017; 3:CD004610
Genty et al., Clin Microbiol Infect 2019; 25:987

Treatment

Clostridium difficile infection =
Diarrhea (≥3 loose stools per 24 hours) + positive test (2-step algorithm)

Stop offending antibiotic
→ Higher cure rate (84% vs. 93%), faster resolution of diarrhea (54h vs. 97h)

Non-severe: *Leukocyte count ≤15,000 cell/ml, creatinine ≤132 μmol/l*

America
Vancomycin 125 mg 4x daily p.o. for 10 days
OR Fidamoxicin 200 mg 2x daily p.o. for 10 days
OR Metronidazole 500 mg 3x daily p.o. for 10 days
IF OTHER ALTERNATIVES NOT AVAILABLE

Europe
Metronidazole 500 mg 3x daily p.o. for 10 days
OR Vancomycin 125 mg 4x daily p.o. for 10 days
OR Fidamoxicin 200 mg 2x daily p.o. for 10 days

Severe: *Leukocyte count >15,000 cell/ml, creatinine >132 μmol/l*
As above, no metronidazole

Fulminant: *Hypotension, shock, ileus, megacolon (>7cm)*
Vancomycin 500 mg 4x daily p.o. (or tube) for 10 days
+ Rectal vancomycin (500mg/100ml) if in ileus
+ Metronidazole 500 mg 3x daily i.v.

McDonald, Clin Infect Dis 2018; 66:e1; Mullane et al., Clin Inf Dis 2011; 53:440

Antibiotikarichtlinien Inselspital *Cl. difficile*

Substanzen 1. Wahl
Tagesdosis (Übliche Therapiedauer)[?]

Metronidazol
3x500 mg p.o./i.v.
(10 Tage)

Bei milder Kolitis, erste Episode: Leukozyten <15 G/, Kreatinin < 133 umol/l.

Insel: → Consider: oral application of i.v. vancocin

Vancomycin
4x125 mg p.o.
(10 Tage)

Bei schwerer Kolitis: Leukozytose >15 G/l und Kreatinin > 133 umol/l. Erste Wahl bei Verdacht auf oder Nachweis von Ribotyp 027.

Vancomycin
4x500 mg p.o.

Bei fulminanter Kolitis: Hypotonie, Shock, Ileus oder toxischem Megakolon. Bei Ileus zusätzlich 4x500 mg Vancomycin/d per rectum.

+ Metronidazol
3x500 mg i.v.

Bei Ileus zusätzlich zu Vancomycin p.o. und p.r..

First recurrence

Clostridium difficile recurrence =

- Resolution of symptoms while on therapy
- Reappearance within 2-8 weeks after stopping of antibiotics with positive *Cl. diff*. toxin
- Risk: approx. 25%

Vancomycin 4x125 po, 10 days if metronidazole had been used

+ Vancomycin tapering

- 125mg 4x daily 10-14 days
- 125mg 2x daily 1 week
- 125mg 1x daily 1 week
- 125mg every 2-3 days, for 2-8 weeks

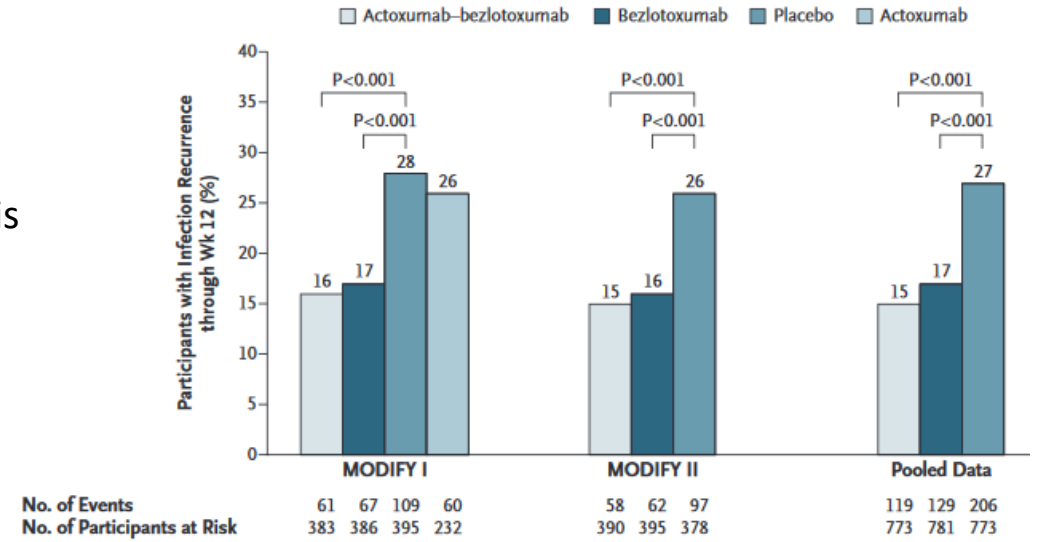
Fidaxomicin 200mg 2x daily for 10 days if vancomycin had been used

Second + third recurrence: Vancomycin tapering, vancomycin → rifaximin, fidamoxicin
Fecal microbiota transplantation.

McDonald, Clin Infect Dis 2018; 66:e1

Anti-toxin antibodies

- Actoxumab (anti-Toxin A) and bezlotoxumab (anti-Toxin B) are fully humanized monoclonal antibodies.
- MODIFY I, MODIFY II trials: total 2655 patients after antibiotic therapy for primary or recurrent *Cl. difficile* colitis
- Study arms: actoxumab i.v. vs. bezlotoxumab i.v. vs. Bezlotoxumab i.v. + actoxumab i.v. vs. placebo
- Beclozumab 17% vs. placebo 28% recurrence (p<0.001) no additional benefit of actoxumab

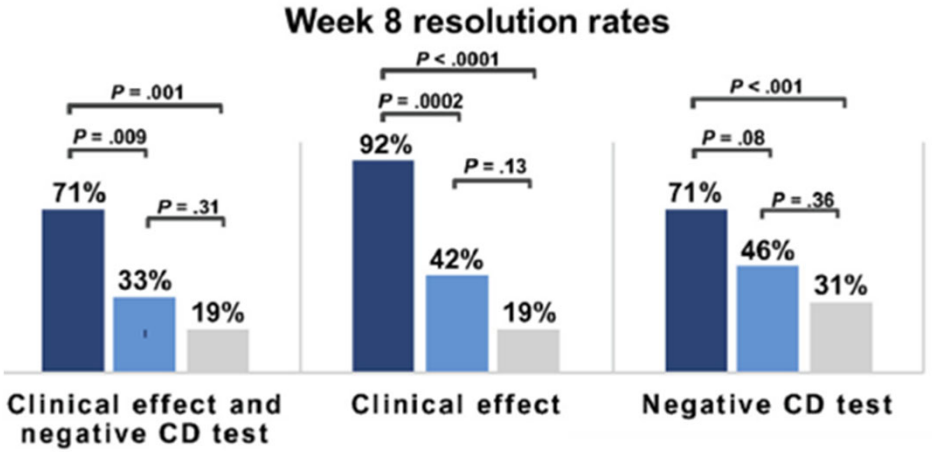


Indikation Schweiz: «Bezlotoxumab (Zinplava) ist indiziert zur Prophylaxe eines Rezidivs einer *Cl. difficile* Infektion bei Patienten > 18 Jahre unter Antibiotikatherapie mit hohem Rezidivrisiko.»

Dosierung: Einmaldosis: 10mg/kg i.v.
Preis: 4342.90 CHF pro 1000 mg

Wilcox et al., 2017, NEJM; 376:305. www.compendium.ch

Fecal microbiota transplantation



Patient with 1 previous treatment fidaxomicin or vancomycin

- 4-10 days vancomycin + FMT
- 10 days fidamoxicin
- 10 days vancomycin

- FMT is more effective than fidamoxicin or vancomycin
- Indicated after 2nd recurrence = 3rd episode
- Higher rates with colonoscopy/ oral tube delivery than enema
- Oral capsules might be equivalent to colonoscopy delivery (96% success in one trial)
- >1 FMT procedures are frequently required

Kao et al., JAMA 2017; 318:1985, Lodberg Hvas, Gastroenterology 2019; 156:1324; Tariy et al., Clin Infect Dis 2019; 68:1351

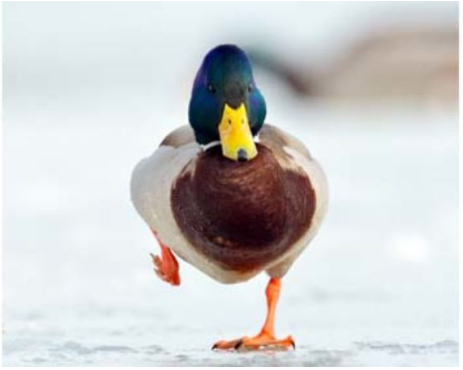
Surgery

- Necessary in only 1% of all cases, 30% of fulminant cases
- Absolut indications: perforation, full-thickness ischemia, abdominal compartment, unstoppable clinical deterioration
- Consider in fulminant colitis (shock, hypotension, ileus, megacolon)
  WBC >25’000… 50’000 per ml? Lactat >2,2…5 mmol/l
  → **don’t call the surgeon too late**
  admittance to surgical vs. medical unit: operation 85% vs. 11%, mortality 13% vs. 39%, p=0.01
- Techniques:
  - Total colectomy with end ileostomy
  - Loop ileostomy vs. antegrade colon lavage (colon sparing)

  Retrospective data favor loop ileostomy over colectomy (mortality 17% vs. 40%)
  → case is open

McDonald, Clin Infect Dis 2018; 66:e1; Sailhamer et al., Arch Surg 2009; 144:433, Ferrada et al., J Trauma Acute Care Surg 2017; 83:36

ENDE



Short update and outlook on clinical IBD-Studies

01.02.2023. Benjamin Misselwitz, Roy Frei

Overview of current studies

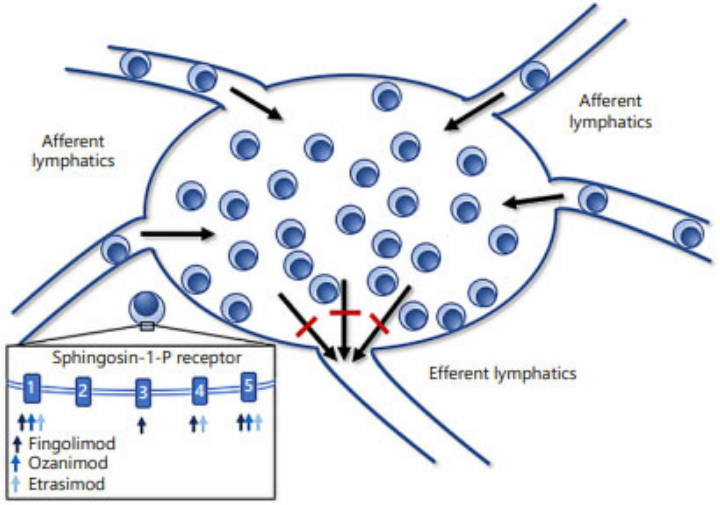
Open studies:

- Arena-1: Etrasimod
- CEC-4-CEL: Transglutaminase 2 Inhibitor
- Nagasin: synbiotic food supplement

Studies opening soon:

- Janssen Duet-CD/Duet UC: Guselkumab/Golimumab
- Abivax: Obefazimod
- Amgen: Efavaleukin
- Falk Gastroparesis: Naronapride/ATI-7505

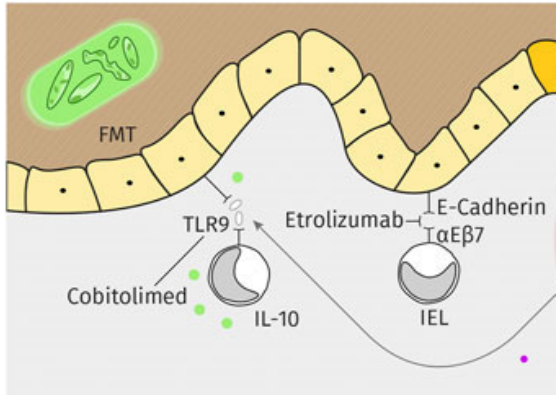
Arena-1: Etrasimod



- Indication: CD
- Medication: Etrasimod
- Mechanism of action:

- Functional sphingosine-1-phosphate receptor 1 (S1P1) antagonist
  → Results in internalization and proteasomal degradation of S1P1
  → Reduced expression of S1P1 on lymphocytes
  → **Reduced T-cell migration out of lymph nodes**
- Key inclusion criteria

- Active CD diagnosed > 6 months



CEC-4-CEL Zöliakie

- Indication: Celiac disease
- Medication: ZED1227 = Transglutaminase 2 Inhibitor
- Mechanism of action:
- Inhibition of transglutaminase 2 with high specificity
- Prevents the formation of deamidated gluten
- Prevents presentation of deaminated peptide to T cells
- Less immune activation
- Key inclusion criteria
- Celiac disease diagnosed > 1 year
- Remaining symptoms despite gluten free diet

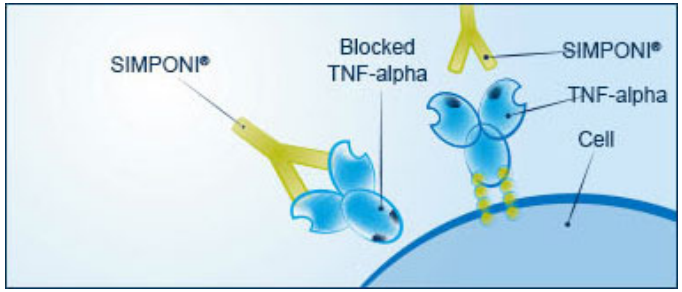
Nagasin

- Indication: CDI
- Medication: synbiotic food supplement
- Mechanism of action:
- Probiotic Lactobacillus, Bifidobacteria and Lactococcus strains
  → Changes (improves?) gut microbiota composition
- Key inclusion criteria:
- Adult patients with diagnosed Cl. difficile infection
- Antimicrobial treatment (Metronidazol, Vancomycin or Fidaxomicin) for Cl. difficile infection

Janssen Duet-CD/Duet UC

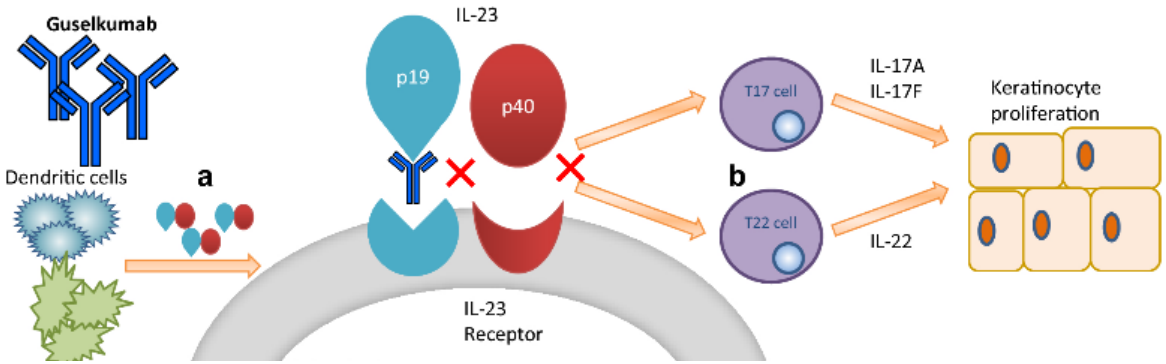
Indication: CD or UC

Medication: Guselkumab + Golimumab



Mechanism of action:

- Guselkumab: Anti-Il-23
- Golimumab: anti-TNF



Abivax

Indication: UC

Medication:

- Obefazimod

Mechanism of action :

- Upregulates the biogenesis of the mRNA inhibitor micro-RNA (miR)-124, which in turn modulates monocyte and macrophage activation

Amgen

Indication:

- CD or UC

Medication:

- Efavaleukin

Mechanism of action:

- IL-2 mutein Fc fusion protein designed to selectively expand Treg with minimal changes in CD4+ conventional T cells (Tcon), CD8+ T cells, or NK cells

Falk Gastroparesis

Indication:

- Moderate idiopathic or diabetic gastroparesis

Medication:

- Naronapride/ATI-7505

Mechanism of action:

- High-affinity 5-HT(4) receptor agonist for gastrointestinal motility disorders
  → Accelerates colonic transit
  → Possibly also accelerates gastric emptying

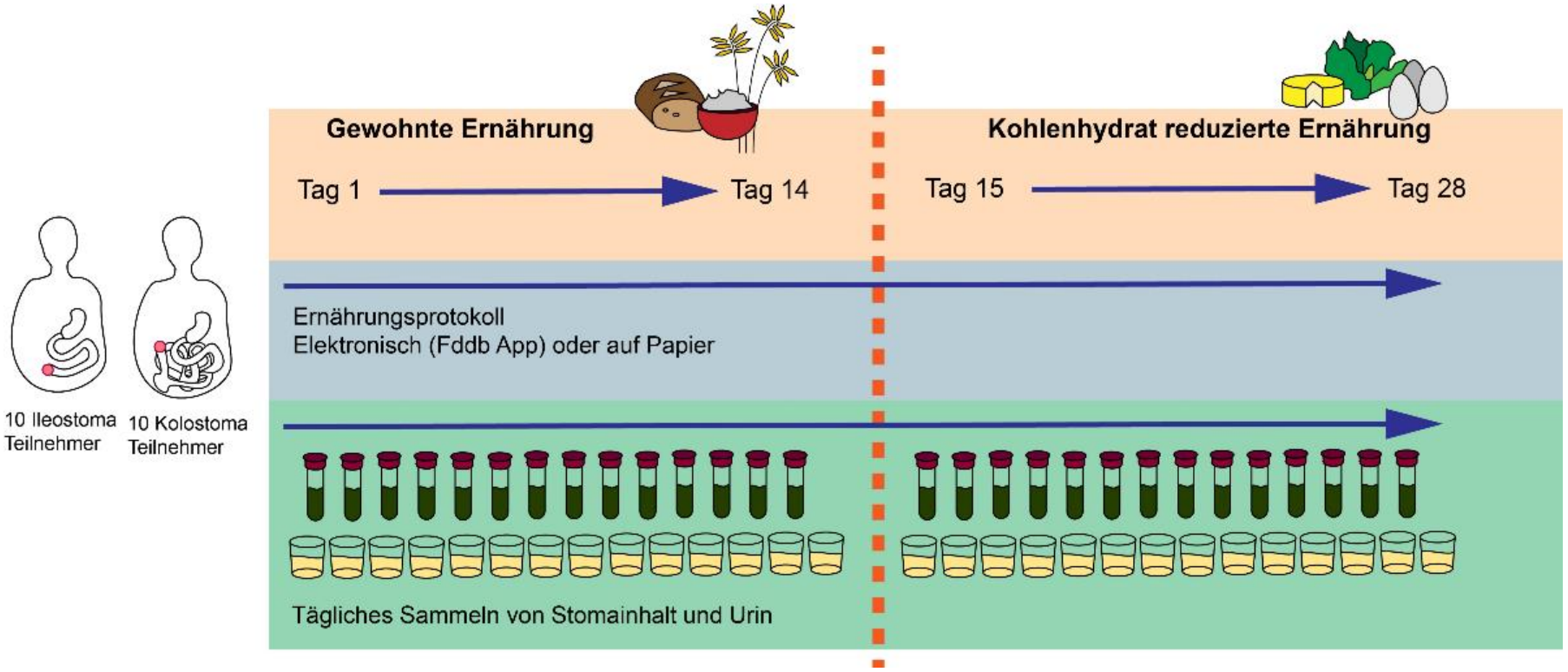
Stoma - studies

To use the stoma as a direct access route to the small and large intestine

Key inclusion criteria

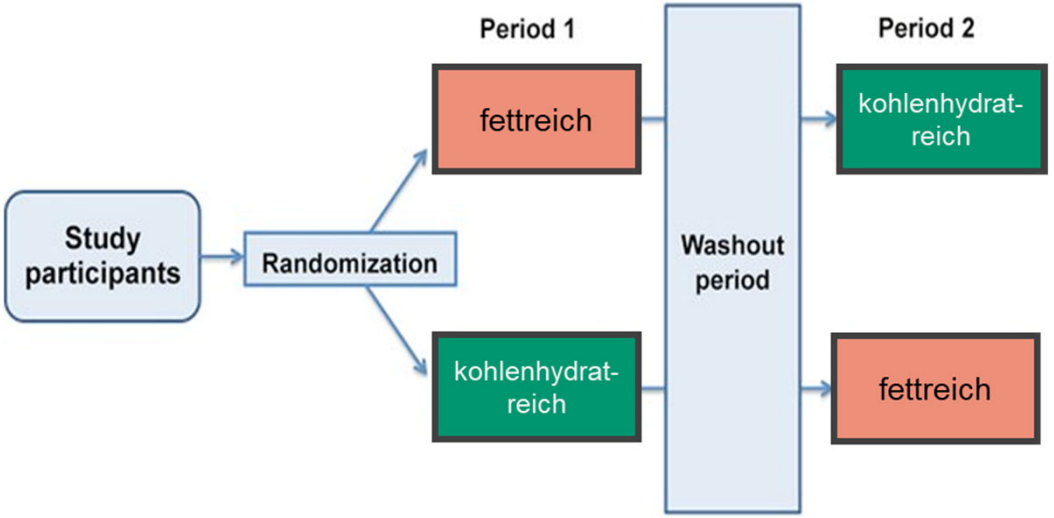
- Ileostomy or colostomy
- Generally good health («happy stoma»)
  but: err on the side of referral

MicroCarb Projekt



NBMISI: Studienaufbau

- **Randomisierte Cross-over-Studie**
- Ziel-Studienpopulation: **50 Ileostoma**- & 20 Kolostoma-Patienten (Stand heute n=17)
- Extensive «multi-omics» Analyse
  → **Bakterien-Metaboliten-Interaktion**
- Anaerobes Kultivieren von Darmbakterien
  → **Bakterien-Bibliothek**
- **Labor-Experimente** mit isolierten Bakterien.



In the following situations please refer patients:

- CD with flare (Etrasimod)
- Celiac disease with symptoms despite gluten free diet (CEC4/ CEL)
- *Cl. difficile* infection under antibiotic treatment
- Happy stoma patients

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Thank you for your attention!