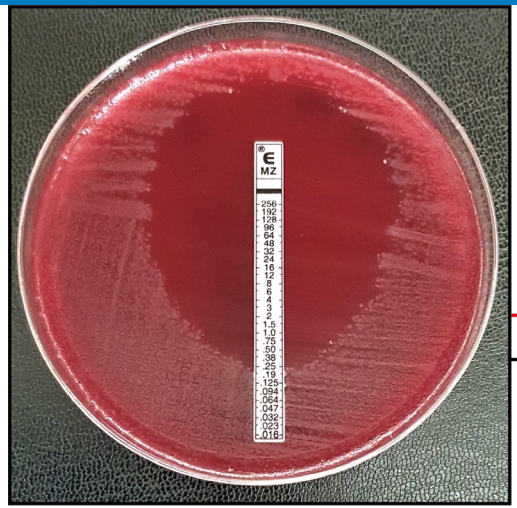
Leiden University Medical Center

LEIDEN DRUG DEVELOPMENT CONFERENCE

The future of anti-infectives

A perspective from the Gram-positive enteropathogen *Clostridioides difficile*



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From *magic bullet* to *magic bully*

- Since the discovery of antibiotics, they have been considered the *magic bullet* (Paul Ehrlich) that would lead to the eradication of infectious diseases

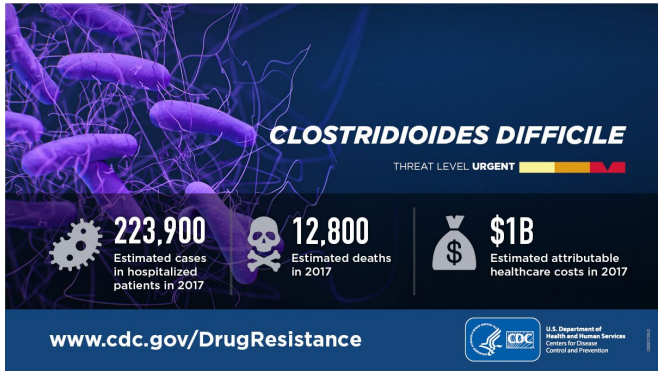
- But resistance was already identified as a problem early on (Alexander Fleming); 5M deaths associated with AMR in 2019
- Collateral damage of *the microbial human*: they affect “the bad” but also “the good”
- Antibiotic paradox: they can cure, but also cause disease

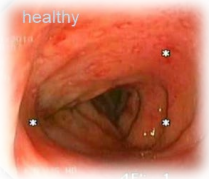
References
- Ehrlich 1911 Folia Serologica
- Fleming 1945 Nobel Lecture
- Murray 2022 Lancet
- O’Neill 2016 amr-review.org
- Yong “I contain multitudes” Vintage Publishing

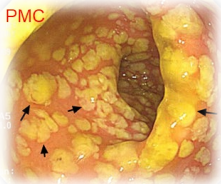
Clostridioides difficile is a Gram-positive enteropathogen in which these aspects come together

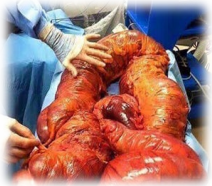
- Cause of infectious diarrhea, toxic megacolon, pseudomembranous colitis
- Toxin-mediated
- **Resistant to many drugs**
  either actively (AMR genes) or passively (endospores)
- Responds to “dysbiosis” of the microbiome
  Antibiotic treatment a risk factor
- Limited treatment modalities
- Frequent relapse, even after initial cure
  with drugs like vancomycin (commonly used)

Good model to look at *some* of the future therapies









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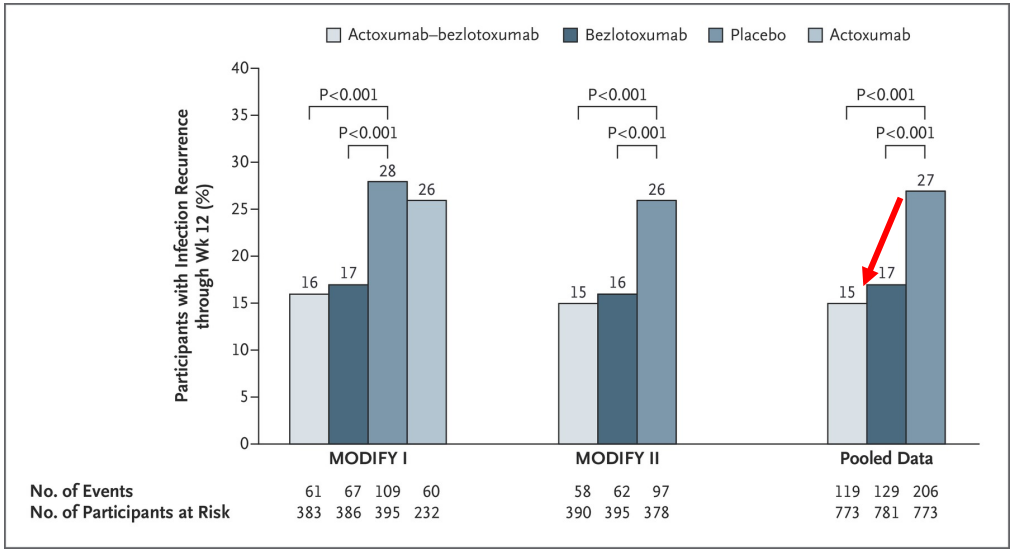
- Leffler and Lamont 2015 NEJM
- Schnizlein and Young 2022 Nat Rev Gastroenterol Hepatol
- Smits 2016 Nat Rev Dis Primer

Bezlotoxumab is a monoclonal antibody indicated to reduce the chance of recurrence

- *C. difficile* infection is a toxin-mediated disease
- Monoclonal antibody targeting toxin A (actoxumab) failed
- Monoclonal antibody targeting toxin B (bezlotoxumab) reduced recurrence
- Host-factors (e.g. HLA variants) affect efficacy



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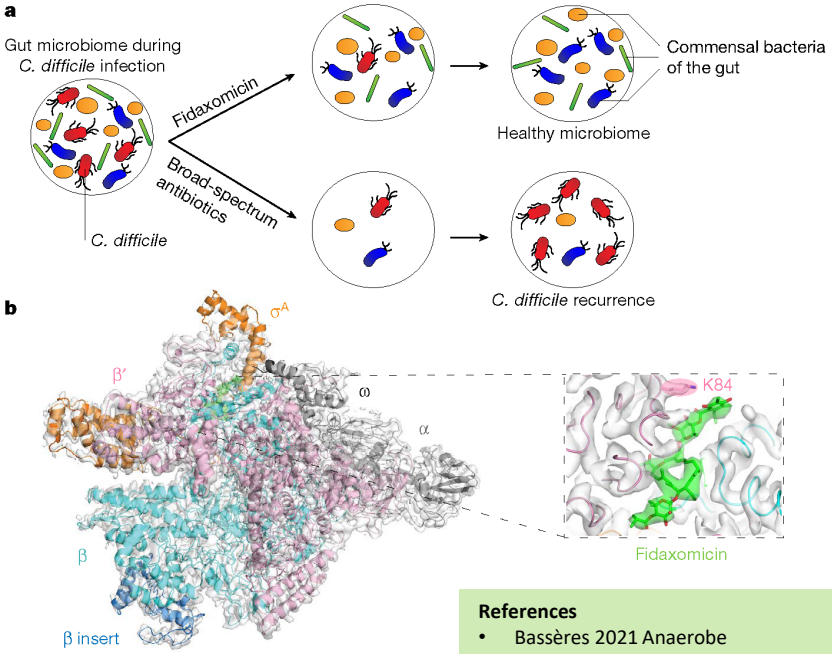
- Cornely 2020 Open Forum Infect Dis.
- Shen 2020 mSphere
- Van Prehn 2021 Clin Microbiol Inf
- Johnson 2021 Clin Inf Dis

Fidaxomicin the first line therapeutic for *C. difficile* infections: a better drug due to narrow spectrum

- Bactericidal macrocyclic antibiotic from the tiacumicin family
- Inhibitor of RNA polymerase
- Minimal systemic absorption
- Lower relapse rate
- Might adhere to spores

- Narrow spectrum of activity
- Recent structural work has identified a key lysine residue responsible for this

- Sporadic resistance reported



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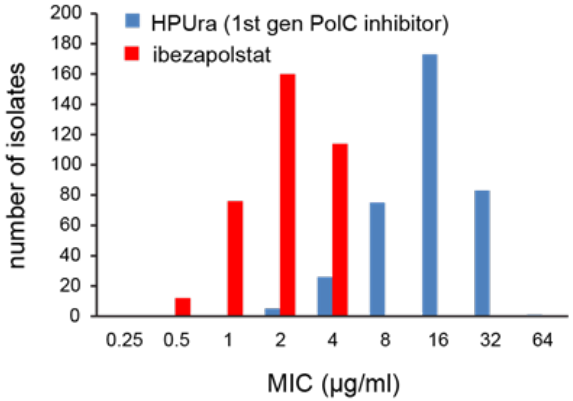
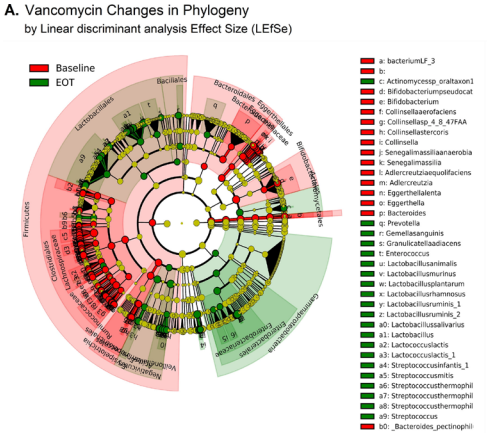
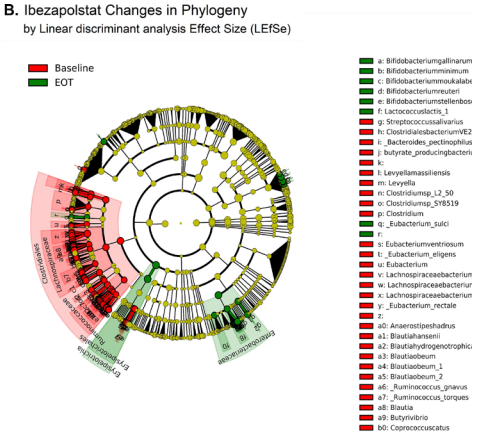
- Fitzpatrick 2022 Lancet Inf Dis
- Schwanbeck 2019 J Antimicrob Chemother
- Freeman 2020 Eur J Clin Microbiol Infect Dis

• Narrow spectrum, *microbiome sparing*, antimicrobials are expected to outperform broad-spectrum antibiotics for CDI

- On the horizon: ridinilazole, ibezapolstat
- Ibezapolstat: first-in-class, targets replicative polymerase PolC of low-[G+C] Gram-positive bacteria (Firmicutes)
- Selected for preferential inhibition of *C. difficile* over other bacteria
- Active against all tested *C. difficile* strains
- Promising results in Phase 2 clinical trials







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- Dvoskin 2012 Antimicrob Agents Chemother
- Van Eijk 2019 Antimicrob Agents Chemother
- Xu 2019 Bioorg Med Chem
- Garey 2020 J Antimicrob Chemother
- Garey 2022 Clin Infect Dis. 2022
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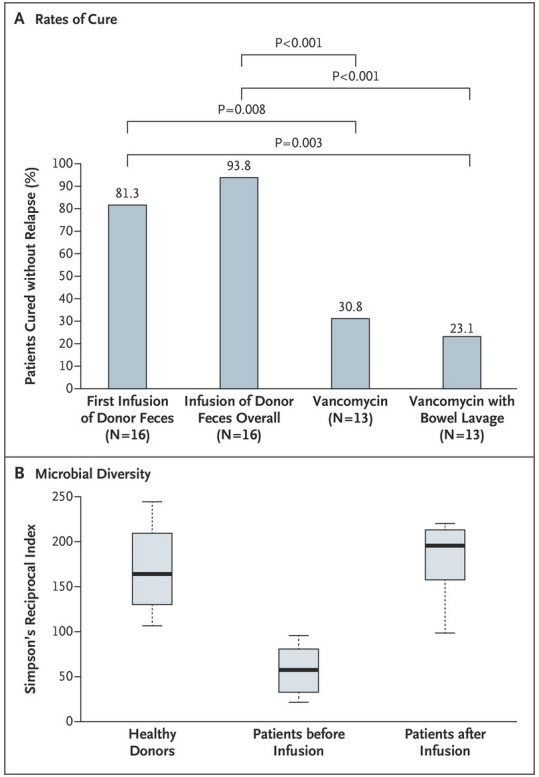
Fecal microbiota transplantation is highly effective for treatment of (recurrent) *C. difficile* infections

- Microbiota replacement therapy (MRT); first RCT in 2013
- Concern for long-term effects and safety of a poorly defined product
- Netherlands Donor Feces Bank offers a carefully screened product; long-term follow-up, registry
- Research into novel therapeutic areas, e.g. decolonization of multidrug resistant bacteria or procarcinogens



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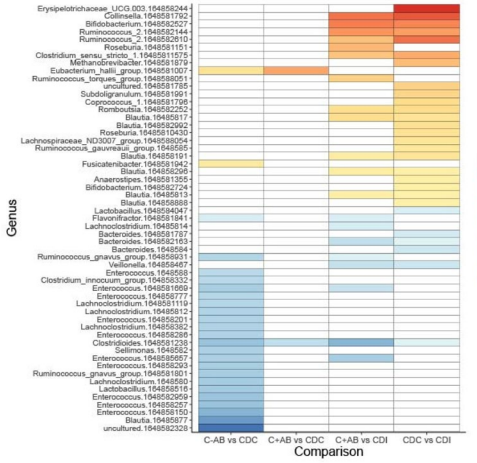
NDFB
Nederlandse Donor Feces Bank

The risks of MRT are more controlled in pharmaceutically produced bacterial preparations, *live biotherapeutic products*

- GMP produced
- Successful Phase 3 trials allow application for Biological License Application with US FDA

- Donor stool derived
  - SER-109 (Seres Therapeutics):
    liquid filled capsule, purified Firmicutes spores (phase 3)
  - Rebyota/RBX2660 (Rebiotix/Ferring) (phase 3):
    enema-based
    RBX7455: capsule, lyophilized bacteriotherapy (phase 1)
- Rationally designed consortium
  (based on microbiota analyses, incl. LUMC)
  - VE303 (Vedanta Bioscience) (phase 2)



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Rebiotix Microbiota Restoration Therapy A FERRING COMPANY

SERES THERAPEUTICS

VEDANTA BIOSCIENCES

A special case of live biotherapeutic product: non-toxigenic *C. difficile* (NTCD)

- Not all *C. difficile* produce toxins
- NTCDs are believed to act through niche-competition

- Effective in *in vitro* and animal models
- Limited evidence from human studies suggest administration can reduce recurrence of CDI
- Best characterized strain licensed to Destiny Pharma (phase 3)

- Production of a unique NTCD strain for human administration
- IMI2 EU-H2020 project: establish a controlled human infection model for *C. difficile* that will allow investigation of these and other interventions in a standardized way

Destiny Pharma

CONTROLLED HUMAN INFECTIONS CENTRE

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- Nibbering 2021 Front Mic
- Oliveira Júnior 2019 Vet Microbiol
- Sambol 2022 PLoS One

The future of (r)CDI anti-infectives: take-home message

- **Monoclonal antibodies** targeting the toxins (bezlotoxumab) have limited success in reducing relapse rates; host-specific differences in efficacy
- (pre)clinical **narrow spectrum drugs** are gaining traction to spare the microbiome and target only pathogen (fidaxomicin, ridinilazole, ibezapolstat)
  - Molecular details of drug binding are necessary
- Microbiome is explored as target for intervention using **live biotherapeutic products** (FMT, LBPs including NTCD)
  - Mostly as adjunctive therapy (next to standard-of-care)
  - Future: engineered LBPs?

- Novel approaches such **controlled human colonization/infection** studies are needed to maximize development