# *Przeszczepianie flory jelitowej w celu zwalczania infekcji bakteriami wielolekoopornymi u pacjentów hematologicznych*

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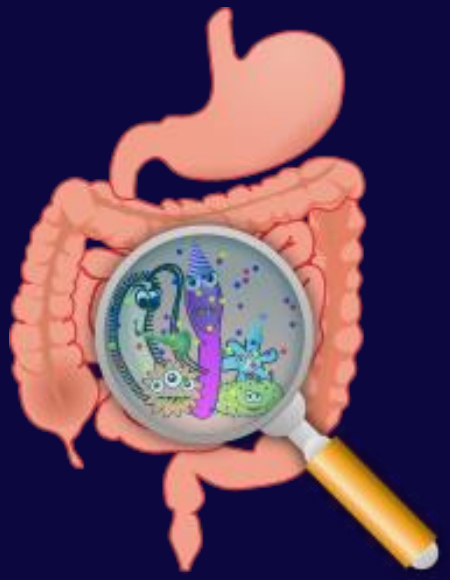
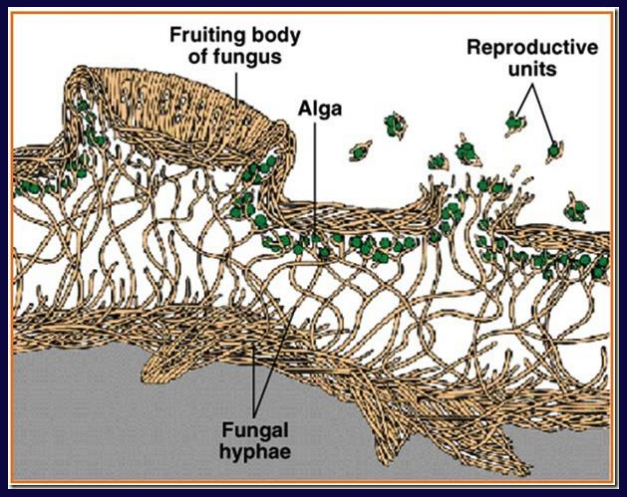
# Gut microbiome as a complex tissue

- about $10^{14}$ bacterial cells in our body—
  - 10x more than the roughly $10^{13}$ human cells —and 95% of these bacterial cells reside in the GI tract;
- The total surface of GI tract: 400 $m^2$
  - 2 tennis courts
- Gut microbiota weight can reach up to 1-2 kg
  - Only about 30 % of the GI microbiota is detectable by culture-based techniques;
  - Detailed sequencing studies suggest that 15,000–36,000 different bacterial species are known to inhabit the human GI tract, with each individual hosting roughly 500–1,500 species, although only a small subset of these are prevalent.

# Humans vs. Lichens

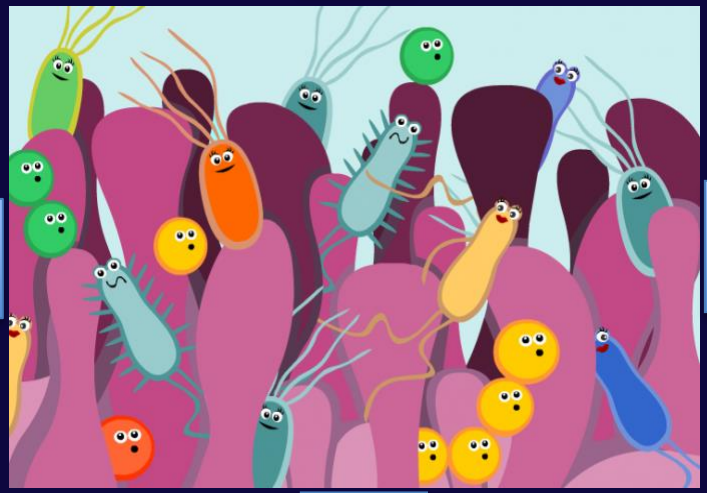




IMMUNE SYSTEM DEVELOPMENT

NUTRITION

METABOLISM

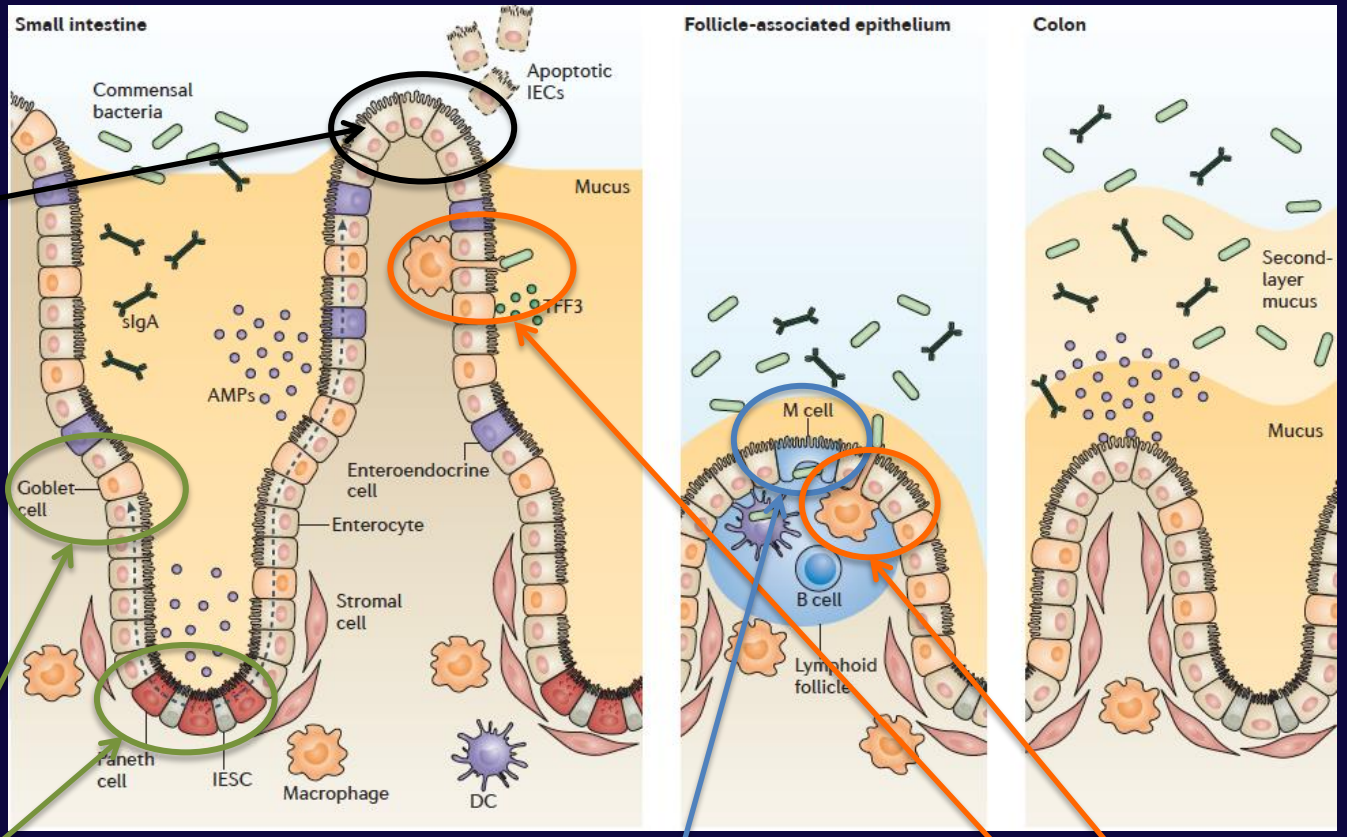


HOST DEFENCE

COLONIZATION PROTECTION

# Simplified interactions between gut mucosa and commensal bacteria

IECs express PRRs (TLR, NOD, RLR) for recognision of bacterial ligands and endogenous signals



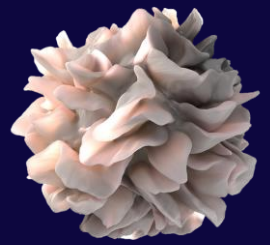

Secretion of mucus and antibacterial peptides

sampling of antigens and microorganisms for presentation to themucosal immune system

**Subepithelial macrophages** sample luminal contents through transepithelial dendrites

*Peterson and Artis. Nature Rev. Immunol, 2014; 14:141*

# Impact of gut microbiota on myeloid cells



- In response to commensal bacteria, intestinal endothelial cells produce cytokines via PRR signaling, promoting the development of DCs and macrophages with tolerogenic properties,
  - including specialized TGFβ-producing CD103+CD11b+ DCs within the GI tract that can induce Foxp3-expressing regulatory T cell (Treg) expansion;
- Upon recognition of bacteria, DCs carry antigenic material and live bacteria to secondary lymphoid tissues, including mesenteric lymph nodes and Peyer's patches, and present them to adaptive immune cells.
  - This induces the differentiation of Treg cells and gut-homing properties on T cells for the recruitment of recirculating mature cells to the original site of antigen encounter at the intestinal lamina propria;
- Commensal bacteria induce secretion of indoleamine dioxygenase from myeloid cells – enzyme degrading tryptofan, needed for activation of T cells and increases number of T regs;

# Impact of commensal bacteria on T cells

Commensal bacteria mediate:

- Intestinal immune tolerance by producing short chain fatty acids (acetate, propionate and butyrate) through the fermentation of undigested carbohydrates. These have been shown to induce colonic regulatory T cells through upregulation of gut-homing molecules and Foxp3.
- A subset of bacteria from the order Clostridiales has been identified as important for induction of colonic Treg cells, potentially by upregulating TGF-β to support Foxp3 induction.
- In contrast, pathogen-associated stimuli cause inflammatory responses via IL-1 and IL-6 induction, resulting in subsequent Th1 and Th17 activation .

# Impact of commensal bacteria on B cells

- Commensals have recently been shown to regulate B-cell development within intestinal lymphoid system;
- Intestinal endothelial cell secretion of cytokines induces B-cell class switching to IgA in a T cell-independent as well as T cell-dependent manner.
- IgA produced by local plasma cells is transported by intestinal endothelial cells across the epithelial barrier into the intestinal lumen to act as another important line of defense against microbes.

# Beneficial effects of anaerobic bacteria

- Anaerobes with identified beneficial functions include *Lactobacillus rhamnosus , Bacteroides thetaiotamicron, Bacteroides fragilis, Bifidobacterium infantis, Faecalibacterium prausnitzii, Clostridium XIVa group bacteria, and Barnesiella spp.*
- These bacteria have been noted to regulate protective host functions such as:
  - **increasing tight junction strength,**
  - **decreasing intestinal permeability,**
  - **enhancement of epithelial repair,**
  - **increasing mucus production from goblet cells, and**
  - **secretion of antimicrobial peptides from epithelial cells.**

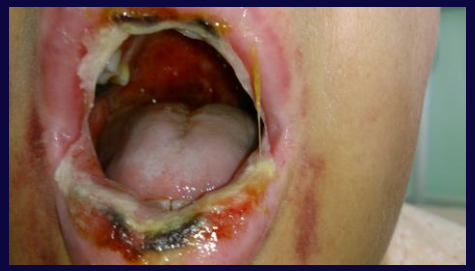
**Anaerobic commensal bacteria contribute to maintaining stability and preventing overgrowth or infection with pathogenic bacteria.**

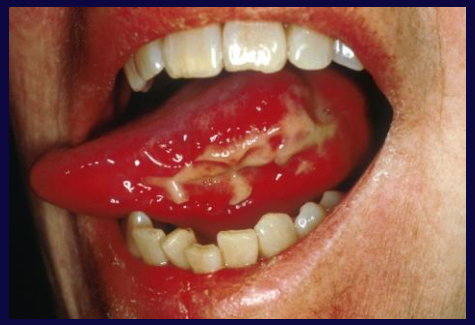
- antibiotic administration to mice prior to pathogen exposure markedly increase host susceptibility to infection.
  - Antibiotic induced susceptibility to Salmonella or Shigella infections was found to be associated with a loss of obligate anaerobic bacteria belonging to the Bacteroides genus;

- normal flora prevents intestinal colonization by exogenous bacteria in humans, leading to the **concept of 'colonization resistance'**.
  - Analysis of the human fecal flora demonstrated that many antibiotics, particularly those with an anaerobic spectrum, resulted in marked expansion of Enterococcus and Enterobacteriaceae in the intestinal tract;

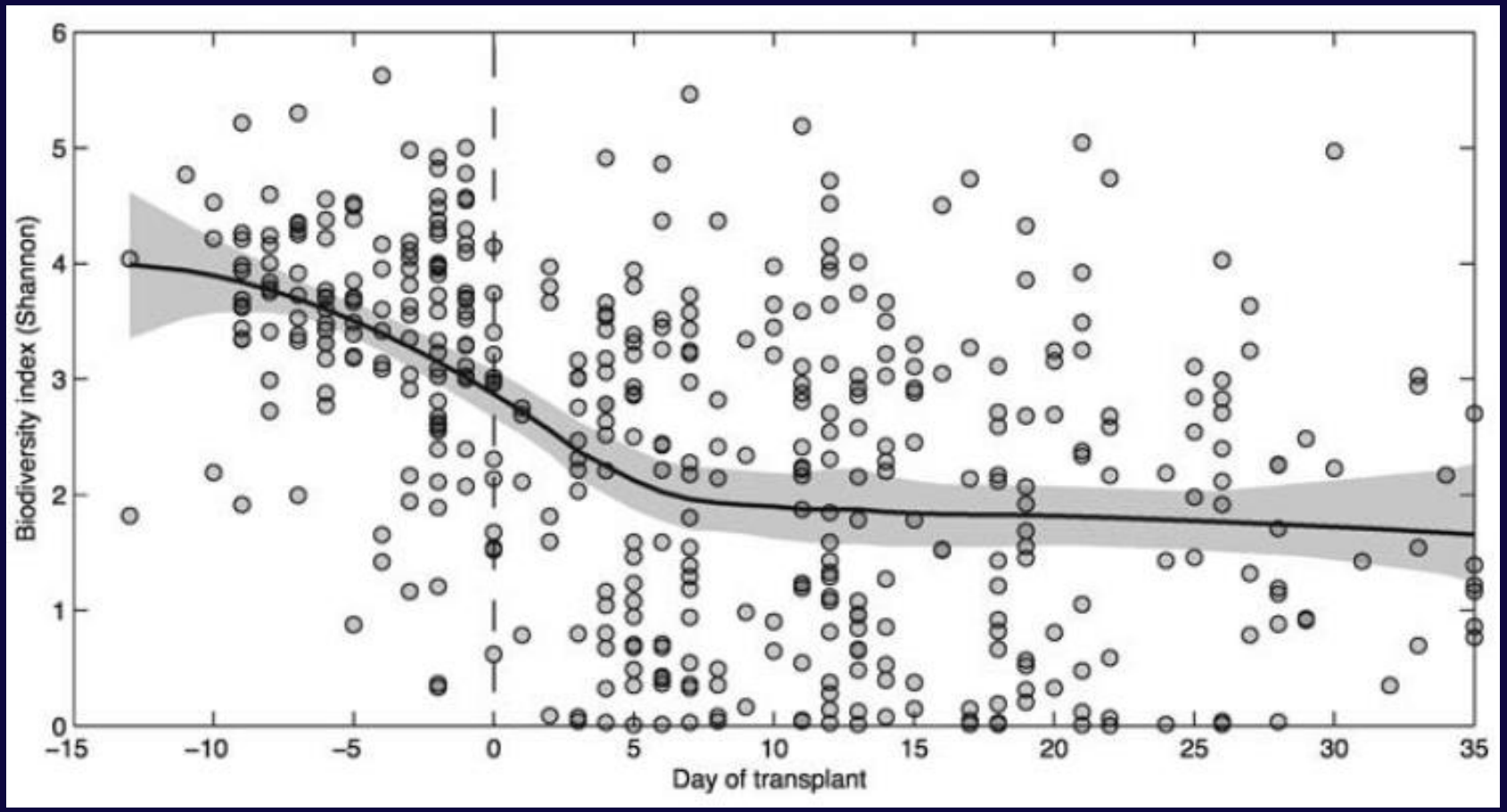
# Bacterial infections after alloSCT

- Mucosal barrier injury is a frequent complication of allo-HSCT and enables commensal microbes to invade underlying tissues and the bloodstream;
- As a result, systemic bacterial infections are frequent during the early transplant period;
- Vancomycin-resistant Enterococcus (VRE), viridians-group Streptococcus, and aerobic gram-negative bacteria are the most common causes of bloodstream infection following alloSCT.
- Why some patients develop bacteremia while others do not is unclear.





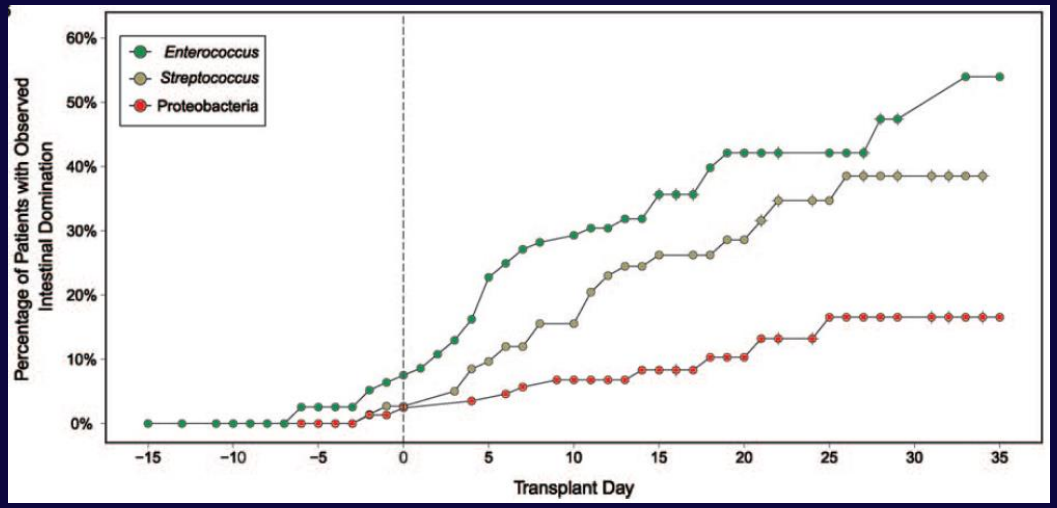
# Loss of Microbial Diversity Following Allo-HSCT




Taur et al. Clin Infect Dis 2012;55:905

# Development of bacterial domination after alloSCT

- In some patients, the microbiota remained relatively diverse, experiencing only mild fluctuations in composition. In these patients, the genus *Blautia* was frequently an abundant inhabitant and appeared to be associated with diminished antibiotic administration.
- Other patients demonstrated marked changes in composition, with transitions from a relatively diverse microbiota to a simpler one with fewer members.
- In many instances, the microbial composition became dominated by a single bacterial taxon.




Proportion of patients with observed intestinal domination by **Enterococcus**, Staphylococcus and/or Proteobacteria

Taur et al. Clin Infect Dis 2012;55:905

# Clinical predictors of intestinal domination

| Predictor | *Enterococcus* Domination | | *Streptococcus* Domination | | Proteobacteria Domination | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Age, years | 1.00 (.98–1.04) | .790 | 0.99 (.97–1.03) | .681 | 1.00 (.95–1.05) | .978 |
| Female sex | 0.84 (.42–1.64) | .611 | 1.07 (.50–2.27) | .852 | 1.12 (.33–3.78) | .854 |
| Underlying diagnosis (leukemia vs other) | 3.22 (1.60–6.94) | .001 | 0.71 (.32–1.51) | .375 | 0.66 (.18–2.19) | .498 |
| Prior antibiotics (14 days)[a] | 1.49 (.77–2.94) | .237 | 1.03 (.48–2.17) | .945 | 1.31 (.39–4.44) | .651 |
| Conditioning regimen (myeloablative or reduced intensity vs non-myeloablative) | 1.01 (.44–2.84) | .977 | 0.61 (.25–1.75) | .329 | 0.98 (.22–9.25) | .983 |
| T-cell depleted graft | 0.81 (.40–1.61) | .551 | 0.91 (.39–2.00) | .812 | 1.07 (.29–3.62) | .910 |
| Stem cell source (cord vs other) | 1.22 (.55–2.52) | .607 | 0.54 (.19–1.34) | .196 | 1.36 (.36–4.69) | .633 |
| Fever[b] | 1.68 (.78–3.74) | .182 | 0.90 (.36–2.39) | .826 | 1.28 (.30–6.34) | .747 |
| Antibiotics[b] | | | | | | |
| Vancomycin | 2.12 (.67–10.21) | .222 | 0.95 (.33–3.77) | .938 | 5.17 (.52–707.15) | .192 |
| Metronidazole | 3.38 (1.65–6.73) | .001 | 1.94 (.81–4.30) | .131 | 1.73 (.41–6.03) | .426 |
| Fluoroquinolones[c] | 1.09 (.49–2.24) | .832 | 1.19 (.51–2.60) | .677 | 0.09 (.00–.75) | .020 |
| Beta-lactam[d] | 1.64 (.74–3.99) | .232 | 1.69 (.62–5.64) | .319 | 1.23 (.27–7.50) | .800 |

Finding that metronidazole is strongly associated with Enterococcus domination supports the notion that anaerobic bacteria contribute to colonization resistance.

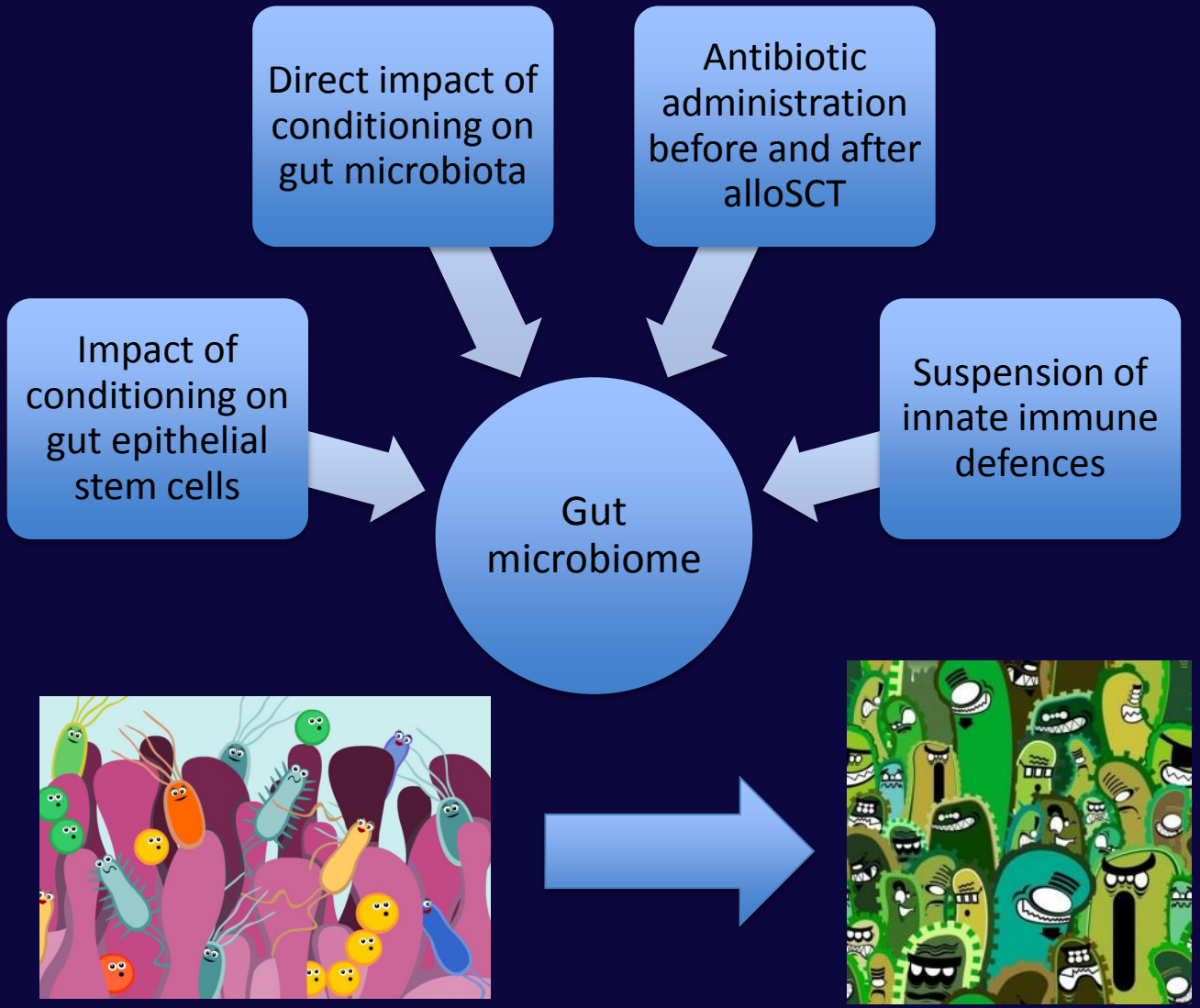
Taur et al. Clin Infect Dis 2012;55:905

# Association of intestinal domination with bacteremia

| | VRE Bacteremia | | Gram-negative Bacteremia | |
|---|---|---|---|---|
| Dominating Taxon[b] | HR (95% CI) | *P* | HR (95% CI) | *P* |
| *Enterococcus* | 9.35 (2.43–45.44) | .001 | 1.35 (.25–5.08) | .690 |
| *Streptococcus* | 0.21 (.00–1.75) | .184 | 0.82 (.09–3.65) | .823 |
| Proteobacteria | 0.75 (.01–6.14) | .837 | 5.46 (1.03–19.91) | .047 |

Taur et al. Clin Infect Dis 2012;55:905

# Possible mechanisms altering the gut microbiome in alloSCT setting



# Impact of gut colonization with MDR bacteria on the outcomes of alloSCT (Medical University of Warsaw)

- For 3 consecutive years (2010-2012), we monitored the gut colonization status before alloSCT in 115 patients;
- Patients colonized with MDR bacteria (N=35) have been called „colonized" and remaining (N=85) – „non-colonized";

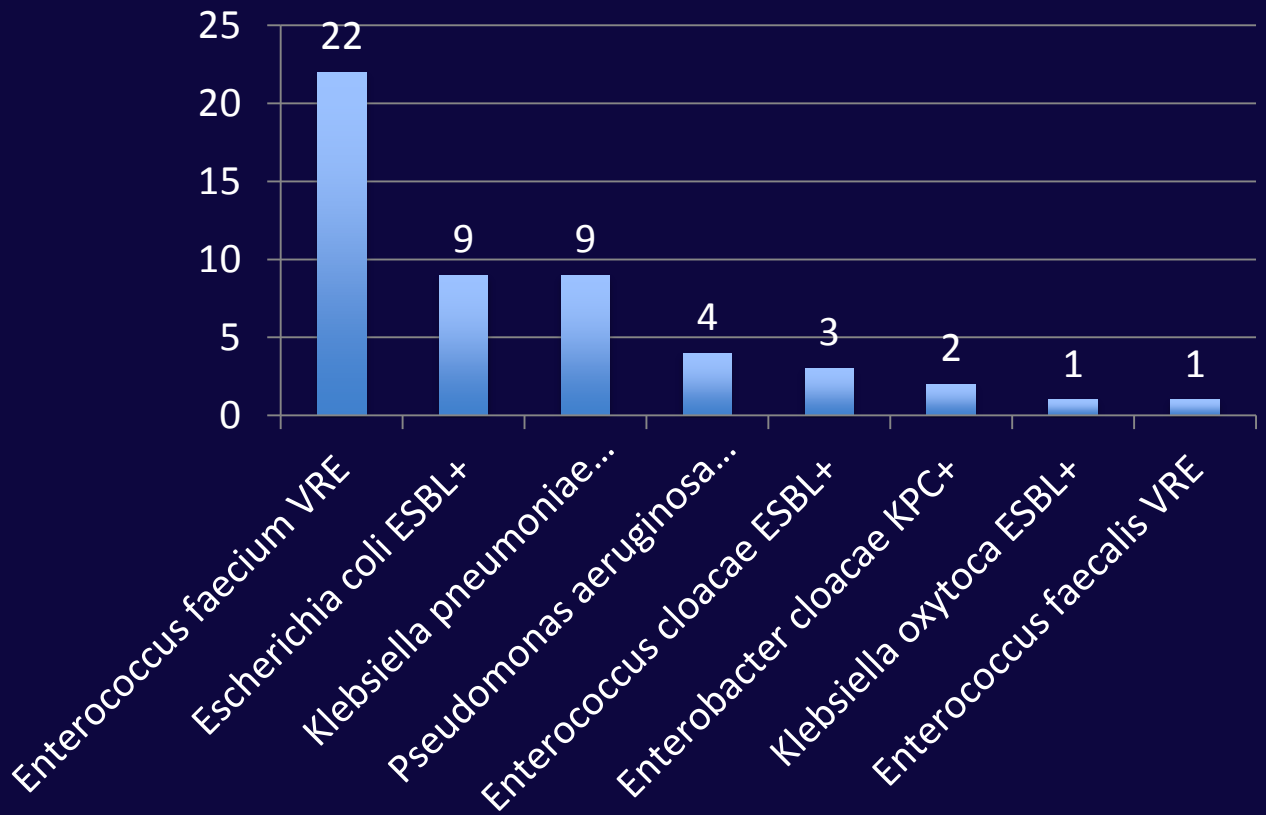
➢ We expected that „colonized" patients will develop more infections and infection-related mortality than „non-colonized";

➢ However, we anticipated also impact on GvHD resulting from alteration of gut microbiome

# Impact of gut colonization with MDR bacteria on the outcomes of alloSCT (Medical University of Warsaw)

| Characteristics | All (N=115) | Not colonized (N=80; 69%) | Colonized (N=35; 31%) | p |
|---|---|---|---|---|
| Gender: males | 53% | 55% | 49% | 0.525 |
| Age at alloSCT | 47 (18-78) | 47 (18-65) | 48 (20-78) | 0.306 |
| Time from diagnosis to alloSCT | 9.5 (.2-212) | 9.7 (0.2-121) | 9 (0.5-212) | 0.733 |
| Hematological diagnosis | | | | |
| AML | 44% | 47% | 40% | 0.565 |
| ALL | 10% | 7% | 14% | |
| MPD | 8% | 7% | 9% | |
| MDS | 10% | 9% | 11% | |
| lymphoma | 11% | 11% | 11% | |
| MDS/MPD | 5% | 7% | 0 | |
| other | 12% | 11% | 14% | |
| Disease stage (according to EBMT score) | | | | |
| Early | 36% | 39% | 29% | 0.618 |
| Intermediate | 21% | 21% | 20% | |
| Late | 27% | 24% | 34% | |
| unknown | 16% | 15% | 17% | |
| EBMT score | 4 (1-7) | 4 (1-7) | 4 (1-6) | 0.536 |
| Conditioning: myeloablative | 58% | 60% | 54% | 0.567 |
| Cell source: PBSCT | 97% | 96% | 35 (100%) | 0.484 |
| WBC at alloSCT ($x10^9$/L) | 3.8 (.1-119) | 3.9 (0.1-79) | 3.2 (0.3-119) | 0.796 |
| ANC at alloSCT($x10^9$/L) | 2.0 (0-74) | 2.0 (0-74) | 1.3 (0-31) | 0.459 |
| Stem cell donor | | | | |
| MRD | 38% | 40% | 34% | 0.802 |
| MUD | 48% | 47% | 49% | |
| mMUD | 14% | 13% | 17% | |
| Donor female to male recipient | 32% | 37% | 20% | |
| MTX for GvHD prophylaxis | 79% | 79% | 79% | 0.893 |

# Impact of gut colonization with MDR bacteria on the outcomes of alloSCT - frequency of colonizing MDR bacteria




Objaśnienia: ESBL - Extended-Spectrum Beta-Lactamases; KPC - Klebsiella Pneumoniae Carbapenemase; MBL – Metallo - Beta – Lactamase; VRE – Vancomycin – Resistant – Enterococci

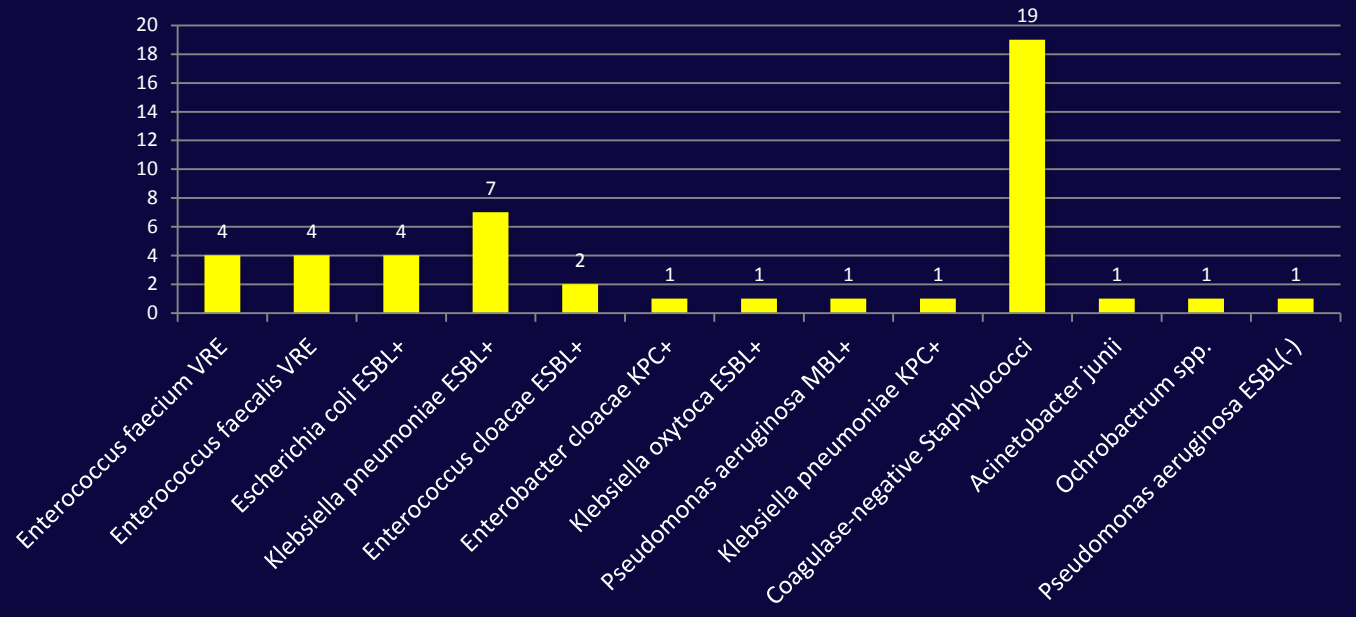
# Impact of gut colonization with MDR bacteria on the outcomes of alloSCT - results

| Parameter | All (N=115) | Not colonized (N=80; 69%) | Colonized (N=35; 31%) | p |
|---|---|---|---|---|
| ANC >0.5 x $10^9$/L (days) | 18 (11-46) | 18 (11-46) | 18 (11-29) | 0.581 |
| PLT >20 x $10^9$/L (days) | 13 (0-83) | 13 (0-83) | 13 (0-57) | 0.322 |
| Mucositis | 58% | 56% | 63% | 0.555 |
| grade III-IV | 24% | 24% | 26% | 0.751 |
| aGvHD (%) | 50% | 46% | 60% | 0.461 |
| aGvHD grade II-IV | 29% | 22.5% | 43% | 0.049 |
| GI aGvHD | 20% | 15% | 31% | 0.070 |
| cGvHD | 51% | 51% | 49% | 0.978 |
| extensive cGvHD | 17% | 19% | 14% | 0.891 |

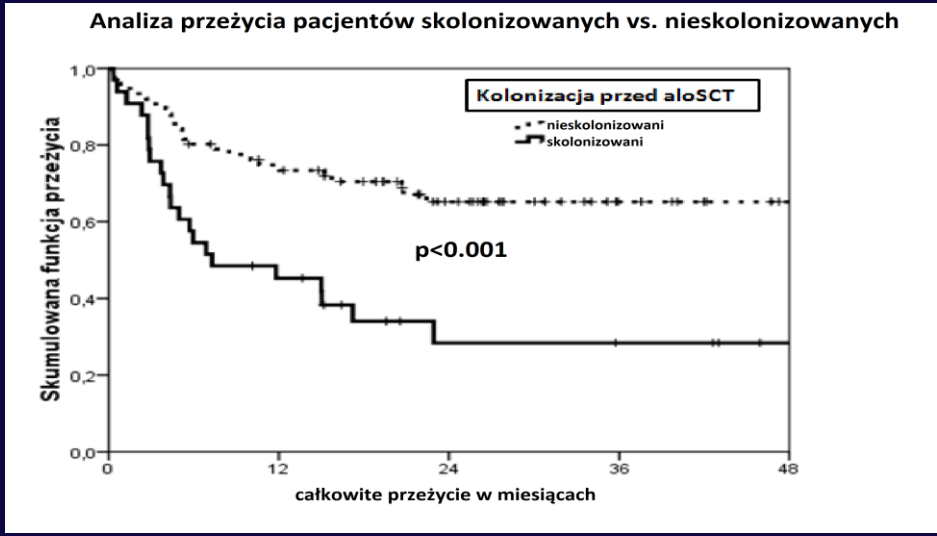
# Impact of gut colonization with MDR bacteria on the outcomes of alloSCT - results

| Parameter | All(N=115) | Not colonized (N=80; 69%) | Colonized (N=35; 31%) | p |
|---|---|---|---|---|
| Blood culture done | 73% | 69% | 83% | 0.541 |
| No. of blood collections/patient | 2.8 (0-18) | 2.6 (0-18) | 3.2 (0-18) | 0.350 |
| At least 1 positive blood culture | 30% | 21% | 40% | 0.049 |
| At least 1 positive blood culture with MDR bacteria | 16% | 10% | 29% | 0.036 |

Pathogens identified in blood cultures taken after alloSCT



# Impact of gut colonization with MDR bacteria on the outcomes of alloSCT - results

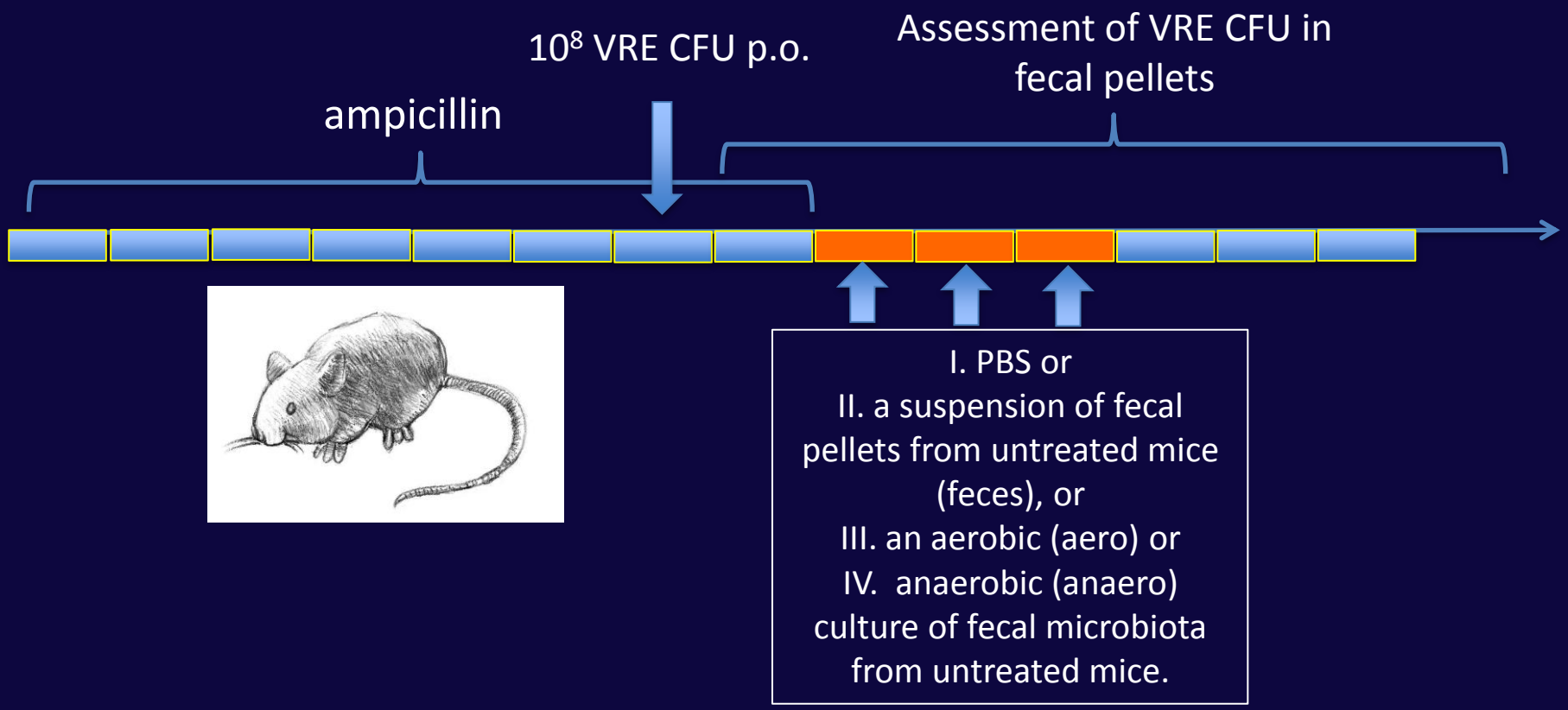



| Parameter | All(N=115) | Not colonized (N=80; 69%) | Colonized (N=35; 31%) | p |
|---|---|---|---|---|
| Cause of death | | | | |
| Infection (including those with GvHD) | 11% | 5% | 26% | 0.004 |
| other | 11% | 10% | 14% | |
| unknown | 20% | 19% | 23% | |
| OS at 3 months | 87% | 91% | 77% | <0.001 |
| at 12 months | 67.8% | 76% | 48% | |
| at 24 months | 57.1% | 67% | 32% | |

# THESIS:

# REGENERATION OF HEALTHY GUT MICROBIOME MAY LEAD TO ERADICATION OF COLONIZING PATHOGENIC BACTERIA

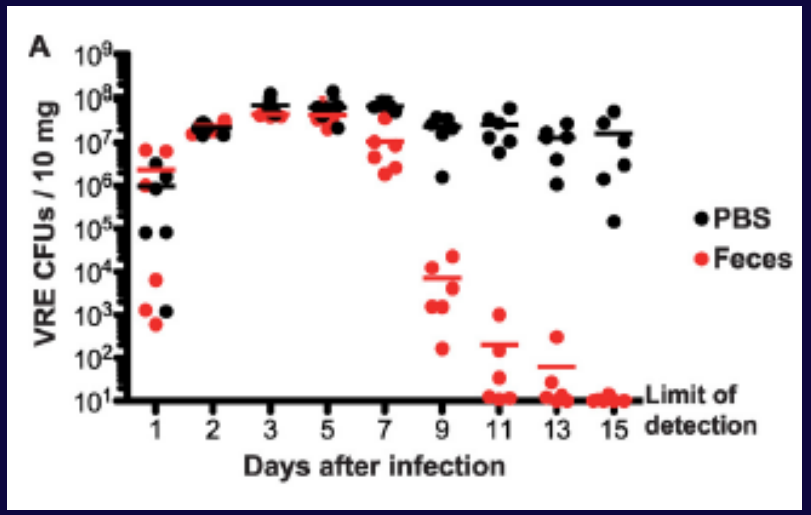
# Commensal anaerobic bacteria suppress VRE colonization in antibiotic - treated mice.




Ubeda et al. Inf Immunity 2013;81:965

# Commensal anaerobic bacteria suppress VRE colonization in antibiotic-treated mice

- Untreated mice rapidly and completely eliminate orally administered VRE from the intestine, while mice that have been treated with ampicillin become dominated by VRE;
- Once dominated, mice continue to harbor large numbers of VRE in the colon;

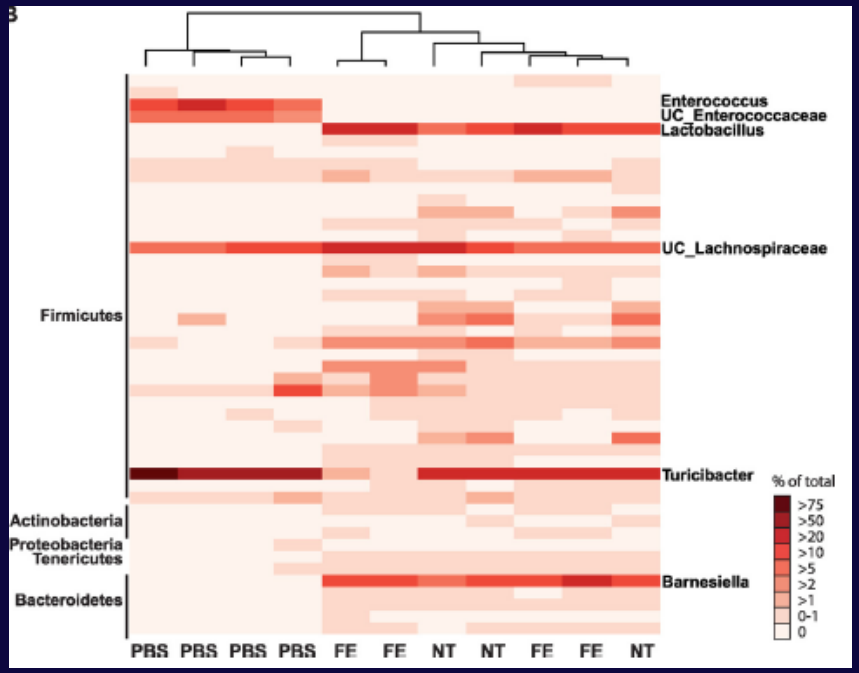



- After feces transplantation, VRE colonization was reduced to undetectable levels within 15 days, with reduction in the density of VRE within 7 days of fecal transfer

Ubeda et al. Inf Immunity 2013;81:965

# Commensal anaerobic bacteria suppress VRE colonization in antibiotic-treated mice

- Composition of the microbiotas of PBS and fecal transplant (FE) mice was analyzed 15 days following infection and compared with that of the microbiotas of untreated mice (NT).
- Hierarchical clustering was used to cluster samples by their microbiota composition at the genus level.
- Each column represents one mouse. Each row represents one genus. The most predominant phyla (left) and genera (right) are indicated.

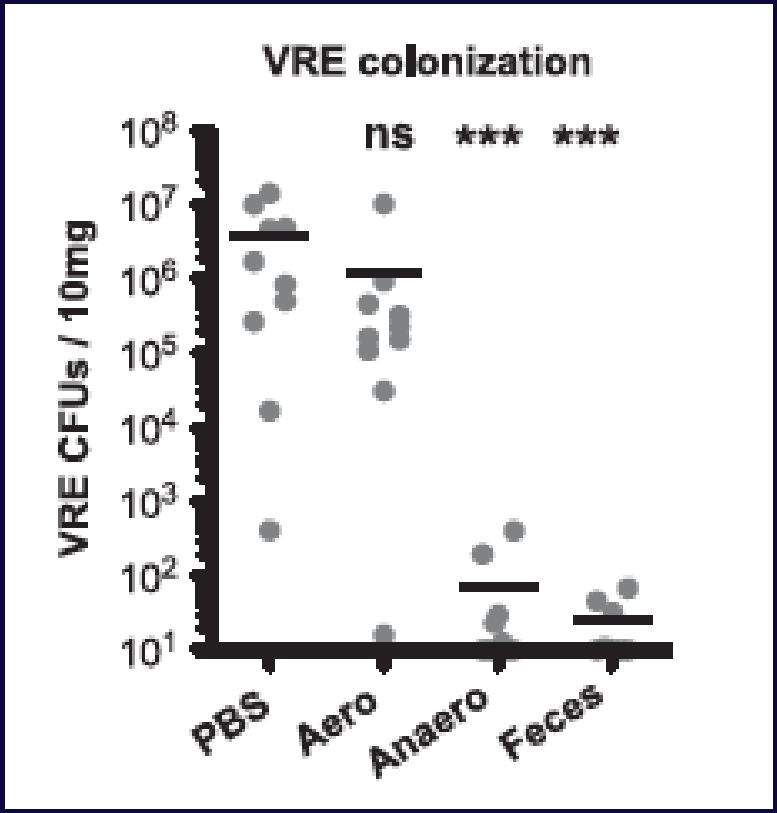



Untreated and reconstituted mice had similar gut microbiome, while VRE-dominated mice were distinct

Ubeda et al. Inf Immunity 2013;81:965

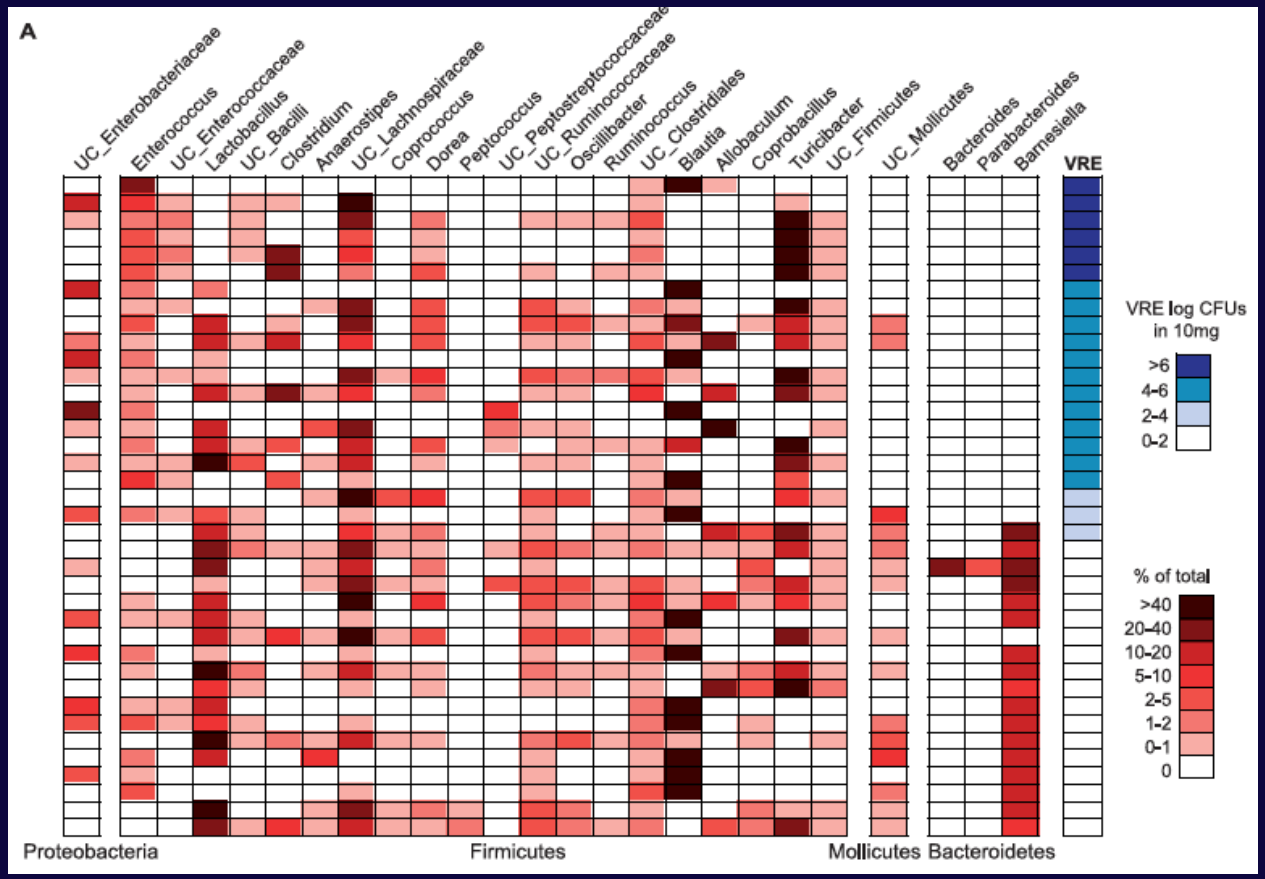
# Commensal anaerobic bacteria suppress VRE colonization in antibiotic-treated mice.

While aerobically cultured fecal pellets did not eliminate VRE, **anaerobically cultured bacteria were as effective as unfractionated feces at reducing the density of VRE colonization**




Ubeda et al. Inf Immunity 2013;81:965

# Reconstitution with Barnesiella correlates with VRE clearance.




While reconstitution of mice with bacterial taxa varied from mouse to mouse irrespective of VRE density, clearance of VRE was markedly enhanced in mice recolonized with bacteria belonging to the Barnesiella genus

Ubeda et al. Inf Immunity 2013;81:965

# Similar observations in murine model have been made according to eradication of Gram (–) bacteria from the gut

- Administration of a diverse microbiota to chronically infected mice can lead to clearance of Salmonella typhimurium from the gut lumen, suggesting that some components of the normal flora either displace S. typhimurium or create an inhospitable environment */Endt et al. PLoS Pathog 2010; 6:e1001097./.*
- Recent studies using the murine Salmonella typhimurium model of intestinal infection demonstrated that bacteria belonging to the Porphyromonadaceae family are associated with resistance to intestinal infection, suggesting that this subset of obligately anaerobic bacteria belonging to the Bacteroidetes phylum provides colonization resistance against at least some pathogenic Gram-negative bacteria */Ferreira et al. PLoS One 2011; 6:e20338./.*

The NEW ENGLAND JOURNAL of MEDICINE

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Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

# Restoration/regeneration of healthy gut microbiome cures Clostridium difficile colitis

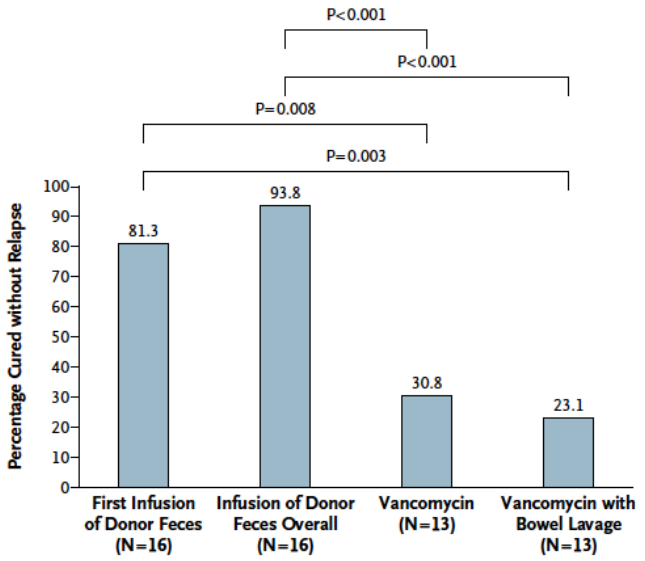



**Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.**

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

**Table 2. Adverse Events in 16 Patients in the Infusion Group.***

| Adverse Event | On Day of Infusion of Donor Feces | During Follow-up |
|---|---|---|
| | *no. of events* | |
| Belching | 3 | 0 |
| Nausea | 1 | 0 |
| Vomiting | 0 | 0 |
| Abdominal cramps | 5 | 0 |
| Diarrhea | 15 | 0 |
| Constipation | 0 | 3 |
| Abdominal pain | 2 (associated with cramping) | 0 |
| Infection | 0 | 2† |
| Hospital admission | NA | 1‡ |
| Death | 0 | 0 |
| Other adverse event | 1§ | 1‡ |

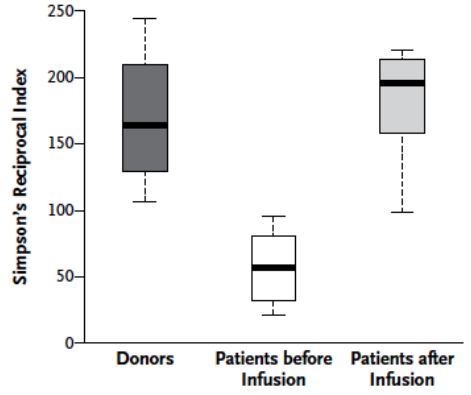



**Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.**

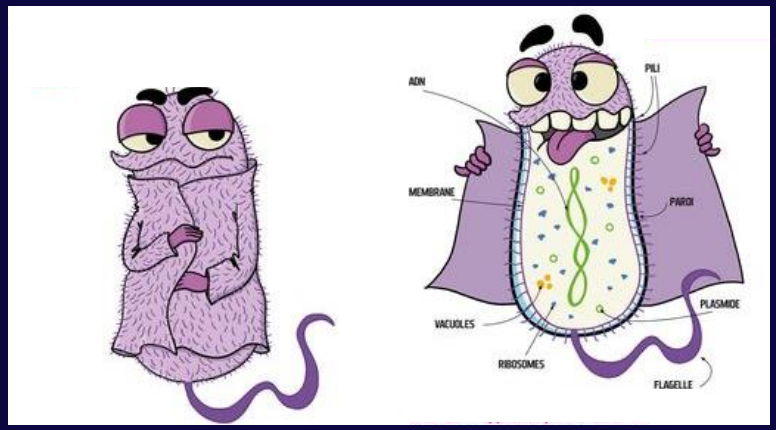
Microbiota diversity is expressed as Simpson's Reciprocal Index of diversity in fecal samples obtained from nine patients before and 14 days after the first infusion of donor feces, as compared with their donors. The index ranges from 1 to 250, with higher values indicating more diversity. The box-and-whisker plots indicate interquartile ranges (boxes), medians (dark horizontal lines in the boxes), and highest and lowest values (whiskers above and below the boxes).

# Stool Transplantation to Reduce Antibiotic Resistance Transmission (START)

ClinicalTrials.gov Identifier: NCT02461199

Prospective Observational Study of Fecal Microbiota Transplantation Used to Eradicate Gut-colonizing Multidrug-resistant Bacteria in Patients With Blood Disorders

# Methods –detection of colonization




- Cultures of rectal swabs, done using standard microbiological techniques;
- Ability of isolates to produce extended spectrum beta-lactamases (ESBL) and carbapenemases is detected by phenotypic methods (MBL, KPC, OXA-48), Rapidec Carba NP biochemical assay (bioMerieux, France) and/or by Gene-Xpert qualitative real-time PCR (qPCR) method (Cepheid, USA).

# Methods: fecal microbiota preparation

- **DONOR of feces**: 21 years old, healthy, non obese (BMI – 21) unrelated female donor who underwent thorough clinical examination and antimicrobial testing – negative results of:
  - anti-HAV IgM and IgG, HBsAg, anti-HBc,HBV DNA; anti-HCV, HCV RNA, anti-HIV, HIV RNA, syphilis (serology), anti-CMV IgM and IgG, anti-EBV IgM and IgG,
  - stool examination for parasites, GDH antigen and toxin A/B of Clostridium difficile (EIA/ELISA or equivalent), enteropathogenic flora (classical culture).

100 g of stool blended with 100 ml sterile physiological saline and passed 3 times through metal sieves to remove particulate material under sterile conditions.
Stored frozen in 50 ml aliquots at -80oC.

# Methods: fecal microbiota transplantation

- After obtaining informed consent, the day before FMT procedure, the bowel lavage was performed with the oral laxative drug containing macrogols and sodium sulfate;
- The patient was fasting for at least 12 hours and treatment with a proton pump inhibitor was introduced twice daily to neutralize gastric acid;
- The following day, 100 ml sample of fecal microbiota suspension was thawed and within following two hours infused to the patient's small intestine via naso-duodenal tube;
- The FMT has been repeated on the subsequent day.

# Methods: Inclusion and exclusion criteria

**Eligibility**

- Ages Eligible for Study: 18 Years and older
- Genders Eligible for Study: Both

**Study Population:**

- Patients with blood disorders treated in the Department of Hematology, Oncology and Internal Diseases, with positive gut colonization status with MDR bacteria, who consent for fecal microbiota transplantation.

**Inclusion Criteria**:

- Age >18 y
- Carrier status of MDR bacteria in stool: Klebsiella pneumoniae resistant to carbapenems, Pseudomonas aeruginosa resistant to carbapenems, Enterococcus faecalis VRE, Enterococcus faecium VRE, Enterobacter cloacae KPC+ or other MDR species documented by at least two stool cultures;
- Blood neutrophil count > 500/uL on the day of fecal microbiota transplantation

**Exclusion Criteria**:

- Inability to obtain informed consent and lack of consent;
- Blood neutrophil count <500/uL on the day of fecal microbiota transplantation or expected decrease to the mentioned number within 2 consecutive days;
- Intensive, myelosuppressive chemotherapy (e.g. DHAP, ICE, ESHAP, HD-Cy, HD-Ara-C, DA, conditioning before allogeneic stem cell transplantation, BEACOPP) planned within 2 consecutive days;
- Patients up to 1 month after hematopoietic stem cell transplantation;
- Clinical signs of mucositis;
- Severe liver failure;
- Patients undergoing intensive antimicrobial treatment.

# Methods: outcomes

Primary Outcome Measures:

- Eradication of gut colonizing bacteria as proven by at least two negative stool cultures.
  - [ Time Frame: 2 weeks to 6 months after fecal microbiota transplantation ] [ Designated as safety issue: No ]

Secondary Outcome Measures:

- Eradication of gut colonizing bacteria as proven by PCR.
  - [ Time Frame: 2 weeks to 6 months after fecal microbiota transplantation ] [ Designated as safety issue: No ]
- Incidence of infective episodes
  - [ Time Frame: from day "0" (day of FMT) to 6 months after fecal microbiota transplantation ]

# START – patients' characteristics

| ID | Gender | Age | Diagnosis | Gut colonization status |
|---|---|---|---|---|
| HS | Male | 43 | Plasma cell leukemia | K. pneumoniae MBL NDM; E. coli ESBL |
| ZM | Male | 51 | Myeloma | K. pneumoniae MBL NDM; E. coli ESBL |
| PZ | Male | 58 | CNS Diffuse large B cell Lymphoma | K. pneumoniae MBL NDM; E. coli ESBL |
| LJ | Male | 69 | Myeloma | P. aeruginosa MBL; K. Pneumoniae carbamenem res. |
| OA | Female | 37 | Acute Myelogenous leukemia | K. Pneumoniae carbapenem res |
| SM1 | Female | 54 | Acute Myelogenous leukemia | C. difficile 2 relapse, colonization with E.cloacae (reduced ssceptibility to carbapenems) and Stenotrophomonas maltophilia |
| MT | Female | 76 | Diffuse large B cell Lymphoma | Acinetobacter ursigii MBL, K. pneumoniae ESBL, E.coli ESBL, K. pneumoniae carbapenem res. |
| SM2 | Female | 54 | Acute Myelogenous leukemia | E.cloacae (reduced susceptibility to carbapenems); |
| JE | Male | 56 | cGvHD after alloSCT | K. pneumoniae MBL, E. coli ESBL |
| PZ | Male | | Lung cancer | K. pneumoniae MBL |

# START - Results

| ID | Gut colonization status | Stool culture after 1 week | Stool culture after 1 month | PCR at 1 month |
|---|---|---|---|---|
| HS | K. pneumoniae MBL NDM; E. coli ESBL | Positive but E. coli ESBL eradicated | Positive but E. coli ESBL eradicated | Positive |
| ZM | K. pneumoniae MBL NDM; E. coli ESBL | negative | negative | Positive |
| PZ | K. pneumoniae MBL NDM; E. coli ESBL | negative | negative | negative |
| LJ | P. aeruginosa MBL; K. Pneumoniae carbamenem res. | negative | negative | negative |
| OA | K. pneumoniae carbapenem res | positive | negative | NA |
| SM1 | C. difficile 2 relapse, ADDITIONAL indications: colonization with E.cloacae (reduced ssceptibility to carbapenems) and Stenotrophomonas maltophilia | Negative | negative (for Stenotrophomonas) Positive (for Clostridium and E. Cloacae) | NA |
| MT | Acinetobacter ursigii MBL, K. pneumoniae ESBL, E.coli ESBL, K. pneumoniae carbapenem res | negative | negative | NA |
| SM2 | E.cloacae (reduced susceptibility to carbapenems); | negative | negative (but new VRE detected) | NA |
| JE | K. pneumoniae MBL, E. coli ESBL | positive | NA | NA |
| PZ | K. pneumoniae MBL | NA | NA | NA |

# FUTURE?

From: **Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing Clostridium difficile Infection**

JAMA. 2014;312(17):1772-1778. doi:10.1001/jama.2014.13875

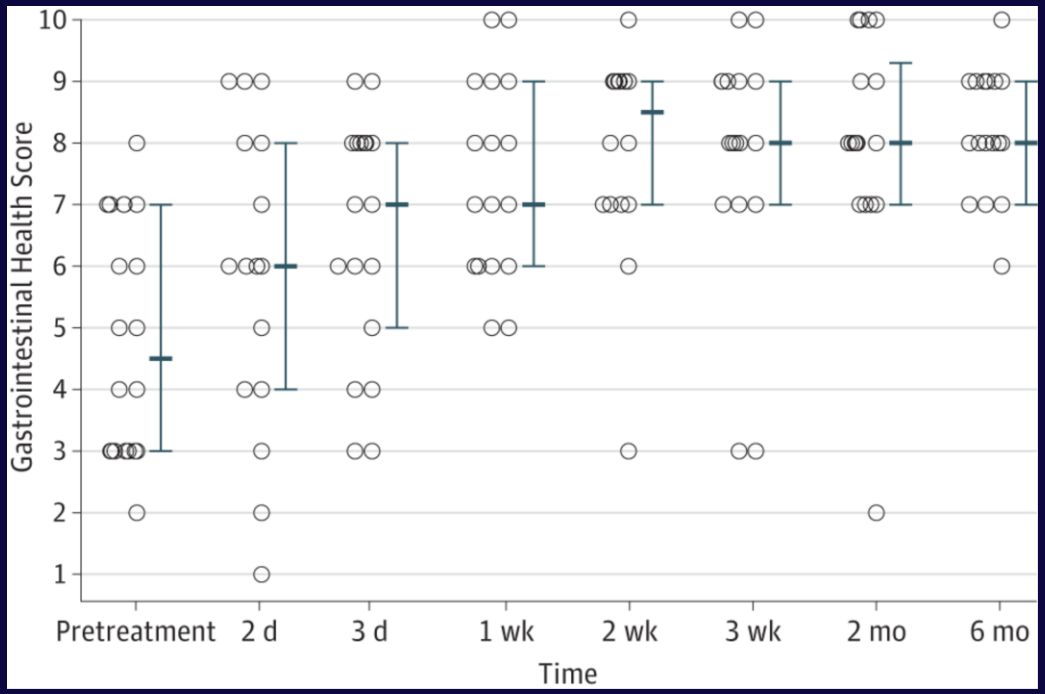



Figure Legend:

Self-reported Gastrointestinal Health Status Over Time in the Study PopulationShown are individual scores of subjective gastrointestinal well-being over time (black circles); medians (horizontal bars) are shown with interquartile ranges (error bars). Scores reported using a standardized questionnaire with a scale of 1 to 10, with 1 indicating the least well. The n = 18 at 3 weeks and 6 months; at all other time points, n = 20.

# Conclusions and future plans

- Gut colonization with MDR bacteria adversely affects outcomes of alloSCT not only by increasing infection-related mortality but also aGvHD
  - Clinical trial with FMT for prophylaxis and treatment of gut aGvHD

- Fecal microbiota transplantation is a promising method of elimination of gut-colonizing MDR bacteria
  - Clinical trial planned

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- Anonymous, honorary stool donors
- Brave patients
- Healthy gut flora !!!


# Sanitas non olet

(Health does not smell)