From metagenomics to bacterial therapy.

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RESISTANCE OF THE MOUSE'S INTESTINAL TRACT TO EXPERIMENTAL SALMONELLA INFECTION

I. FACTORS WHICH INTERFERE WITH THE INITIATION OF INFECTION BY ORAL INOCULATION

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Described below are observations which seem to account, in large part at least, for the normal resistance of the mouse's intestinal tract to infection with Salmonella enteritidis introduced by mouth, the natural route of infection. Thus inoculated, about 10^8 microorganisms are required to infect 50 per cent of young adult CF-1 mice (1). Their resistance, however, can be sharply reduced by the oral administration of a single, large dose of streptomycin, for during the following 24 hours, <10 microorganisms of the same strain suffice to initiate infection (2, 3). Of the changes in the mouse's enteric microflora resulting from streptomycin treatment, the most consequential was thought to be the elimination of certain obligate anaerobes belonging to the genus Bacteroides (4, 5).
IN VIVO AND IN VITRO ANTAGONISM OF INTESTINAL BACTERIA AGAINST SHIGELLA FLEXNERI

I. CORRELATION BETWEEN VARIOUS TESTS*

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Antagonism against pathogenic bacteria exerted by microorganisms of the normal human body flora has been the subject of numerous studies ever since the time of Metchnikoff’s original ideas on the benefits attributable to the presence of lactobacilli in the intestine. This degree of interest is only natural since, for many different reasons, the ability to control the bacterial flora of patients would be of great value to the physician.

ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES, 2013

Urgent Threats
- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats
- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella Typhi*
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning Threats
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*
Vancomycin-resistant enterococcus (VRE)

- Gram positive bacterium
- Increasing prevalence (<1% to 28.5%)
- One of the most common causes of nosocomial bloodstream infections
- High risk for patients receiving broad spectrum antibiotics
Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT)

Pre-transplant conditioning:
- Total body irradiation
- Cytotoxic chemotherapy
- Prophylactic antibiotic administration

Mucositis – loss of epithelial integrity
Neutropenia
Monocytopenia
High risk of infection – frequent broad-spectrum antibiotic administration

Graft versus host disease
VRE Domination of the GI tract occurs in some patients following allogeneic hematopoietic stem cell transplantation and is associated with VRE bacteremia.

Antibiotic treatment enables VRE Domination of the GI tract in mice.

“Normal” microbiota eliminates persistent VRE

Amp – 1 week

10⁸ VRE

VRE in Fecal Samples

Microbiota composition

Untreated 2 weeks post-infection + Feces

Ubeda et al. (2013) Infection and Immunity
**Clostridium difficile (C. dif)**

- Gram positive bacillus
- Increasing prevalence in hospitalized patients
- One of the most common causes of diarrhea in hospitalized patients
- High risk for patients receiving broad spectrum antibiotics or chemotherapy
Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkstra, Ph.D., and Josbert J. Keller, M.D., Ph.D.
Correlating microbiota components & CDI resistance

Shared microbial taxa associated with *C. difficile* inhibition in murine and human lower GI tracts, as determined by inference.

Protection against *C. difficile* mediated by four commensal bacterial species: *B. intestihominis*, *Blautia hansenii*, *Pseudoflavonifractor capillosus* and *C. scindens*

Secondary bile salt-mediated inhibition of *Clostridium difficile* growth

Loss of microbiota diversity following allo-HSCT is variable
Allo-HSCT patients can be divided into low, intermediate and high microbiota diversity groups.

Transplant-related mortality is markedly reduced in patients with a diverse microbiota following engraftment.

MSKCC Auto-FMT Clinical Trial

Opened: January 2015
PI: Ying Taur, MD, MPH
Site: Memorial Hospital

Enrollment prior to allo-HSCT hospitalization

Collect and store donor feces. Analyze by 16S rRNA gene sequencing

At engraftment: test for presence of Bacteroidetes bacteria by specific 16S PCR

Eligibility: subjects with loss of Bacteroidetes: present (≥1%) in stored feces but not present on engraftment

Exclusion of subjects without pre-transplant Bacteroidetes or with detectable Bacteroidetes upon engraftment, or failure to engraft

Randomization to therapeutic arms (stratified by stem cell source)

Fecal microbiota transplantation with pre-transplant feces

No FMT, routine management

Assessed for C.difficile infection until 1 year post-transplant. Weekly fecal specimen collection while in-hospital, with monthly collection as out-patient.
Microbiota-mediated defense against antibiotic-resistant bacterial infections.

Microbial populations in the gut stimulate antimicrobial mechanisms that reduce the ability of pathogens to colonize the gut.

Complex microbial networks in the gut provide colonization resistance; the indirect and direct mechanisms remain incompletely defined.

Bacterial populations that confer resistance can be defined by metagenomic analyses and include obligate anaerobic bacteria.

Microbiota-mediated modification of bile acids contributes to host resistance to intestinal pathogens.

Microbiota diversity predicts survival following allogeneic hematopoietic stem cell transplantation.

Reconstitution of mucosal bacterial populations following antibiotic therapy using FMT or specific commensal microbes provides an alternative approach to treat and prevent infections in an era of decreasing antibiotic susceptibility.
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