THE HUMAN MICROBIOME: THE INFECTION PREVENTIONIST'S BEST FRIEND

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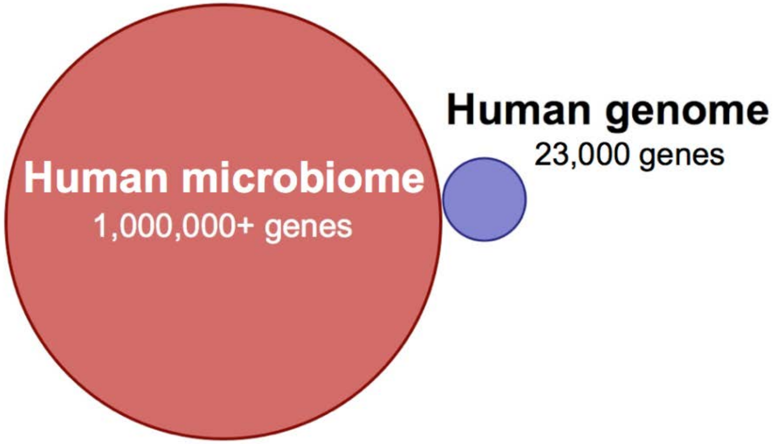
What you will learn

- Describe the new science of human microbiome studies
- Define the terms and techniques used in microbiome science
- Identify important characteristics of the human microbiome
- Identify ways we harm the patient’s microbiome through medicine
- List things we can do to protect the patient’s microbiome

Why study the human microbiome?

- 90% of the cells in the human body are bacteria
  - Some viruses and fungi
  - 3% of body mass
- 99% of the genes in the human body are microbial
- 10,000 unique species, most have never been cultured
- Our microbiome has evolved with us, is in constant interaction with us and contributes to health and disease
- Understanding our microbiome will open up a new world of medicine

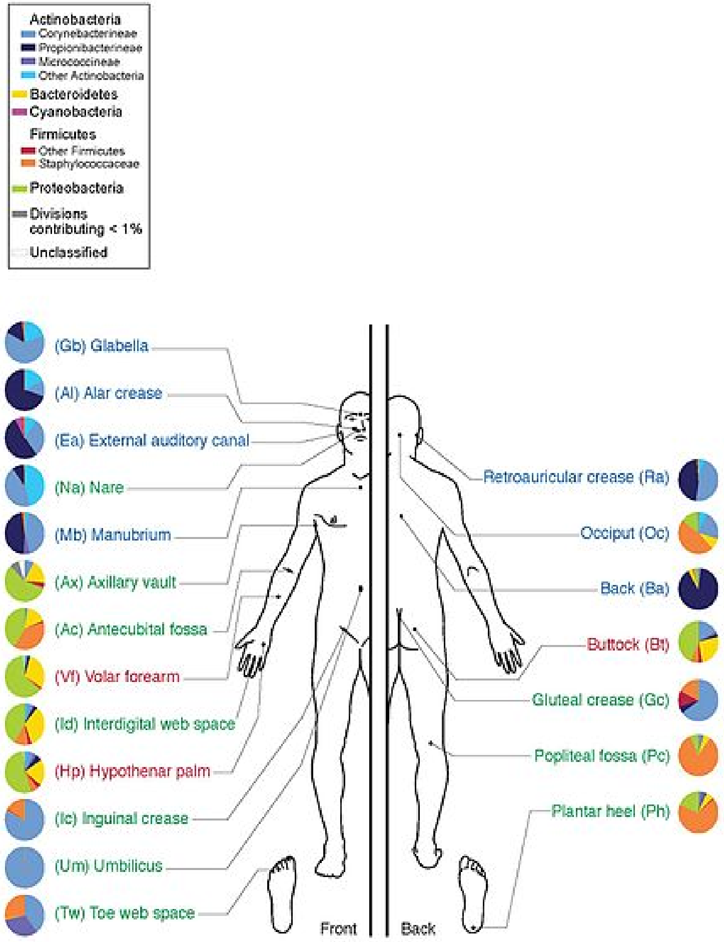


The human microbiome project

- http://www.hmpdacc.org/
- Started in 2008 as a 5-year project
- Modeled on the human genome project that maps every gene on the human chromosome
- Focused on five body sites; mouth, skin, vagina, gut, and respiratory tract
- Uses 16s rRNA and metagenomic sequencing to develop a map of the entire human microbiome

What do we know about the human microbiome?

- It is **like another organ**
- Can be core and transient
- Parts of the body we thought were sterile have a microbiome
- Can change over time
- Differences within the population
- Similarities with race and family
- Relationship to health and disease
- Unstable up to age 2-3, then stabilizes
- Protects us from infection



Human Microbiome Project goals

- Develop a reference set of microbial genome sequences and characterize the normal human microbiome (finished 6/13/2012)
- Explore the relationship between disease and changes in the microbiome
- Develop new technologies and tools for computational analysis
- Establish a resource repository
- Study the ethical, legal and social implications of human microbiome research

Microbial ecology definitions

- **Diversity**; how many different strains live in a community
- **Invasion**; establishment of a foreign organism in a community
- **Metagenomics**; a culture-independent method used for functional and sequence-based analysis of a community
- **Microbiome**; the sum of microbial genes in a community
- **Microbiota**; the sum of the microorganisms in a community
- **Metabolome;** the microbiota's metabolic capability
- **Stability**; the ability of a community to maintain its structure over time
- **Resilience**; the ability of a community to return to its native state after a perturbation
- **Dysbiosis;** disruption of the normal microbiome structure

Ways to study the human microbiome

- The Human Microbiome Project uses new methods to study complex microbial communities and their ecological relationships
  - **Simple metagenomics**; what species are present
  - **Taxonomic diversity**; how many different types and which types of microorganism are present; the community structure, described as alpha, beta and gamma
  - **Functional metagenomics**; the metabolic capability of the population, regardless of the species
- All of these are very important to health

How the human microbiota begins

- The fetus is almost sterile, has a small microbiome
- Most colonization begins at birth
  - Vaginal delivery gives the baby the mother's vaginal and intestinal flora immediately, becomes stable quickly
  - Cesarean delivery deprives the baby of normal flora, acquires normal flora randomly and incompletely, longer period of instability and less colonization resistance
- As the baby encounters new microorganisms, their microbiome matures, depending on their environment
  - Breast-fed babies have very different gut microbiota than formula-fed babies
- The human microbiota is quite mature by about age 2 and remains stable for life

Benefits of the human microbiota

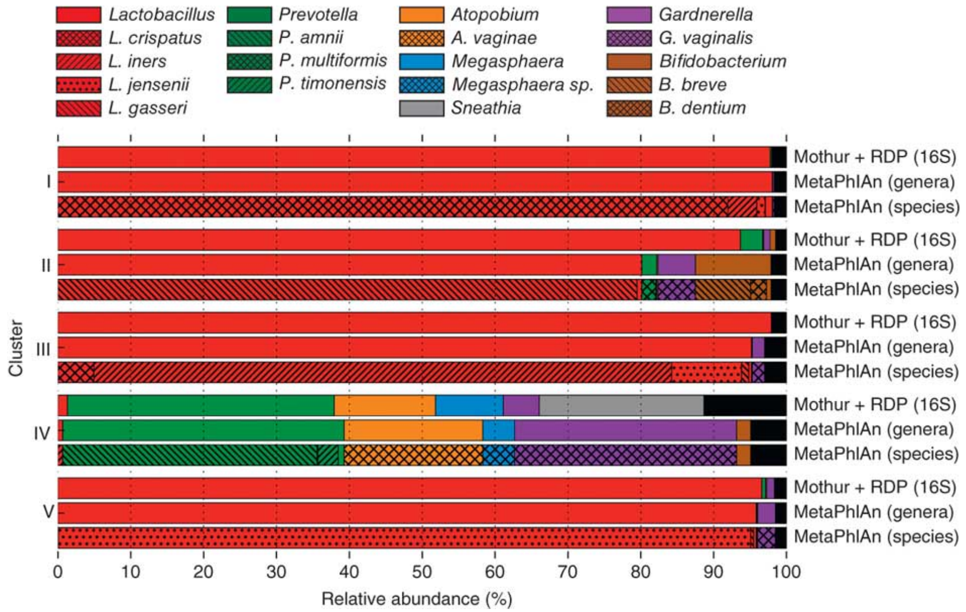
- Protection from infection by competitive exclusion (**colonization resistance**)
  – By occupation of binding sites, receptors
  – By consuming or sequestering essential nutrients from pathogens (siderophores)
  – By production of bacteriocins
- Development of a healthy immune system
  – Normal flora in infancy induce T supressor cells that down-regulate the immune response, producing immune tolerance and avoiding hypersensitivity

Unexpected findings

- Effects on the immune system
  - More, and more types of bacteria are better
- Effects on nutrition
  - Microbiome changes with diet
  - Proposed three human **enterotypes** based on the predominant microbiota
  - Microbiota metabolize nutrients, produce vitamins
- Effects on the neurologic system
  - Proposed neurologic microbiome-gut-brain axis of communication
  - Gut bacteria produce neural signals that may be connected to autism, depression, anxiety, stress

The vaginal microbiota

- The microbiomes of normal and vaginosis patients are drastically different
- The normal microbiome is dominated by *Lactobacillus*
- The vaginal microbiome contributes to the baby's microbiome
- Vaginitis is mostly a disease of dysbiosis



The gut microbiota

- The intestinal microbiome correlates more than others with health and disease (largest microbiota)
- Gut flora have 150 times more DNA and enzymes than human enterocytes
  - Key to nutrition; synthesize vitamins and amino acids, harvest energy
- Three enterotypes
- Pronounced differences in the gut microbiomes of normal humans and those with obesity, malnutrition and inflammatory bowel disease
  - Currently an association; causation is not clear
  - Transplanting normal GI flora into diseased patients cures some diseases

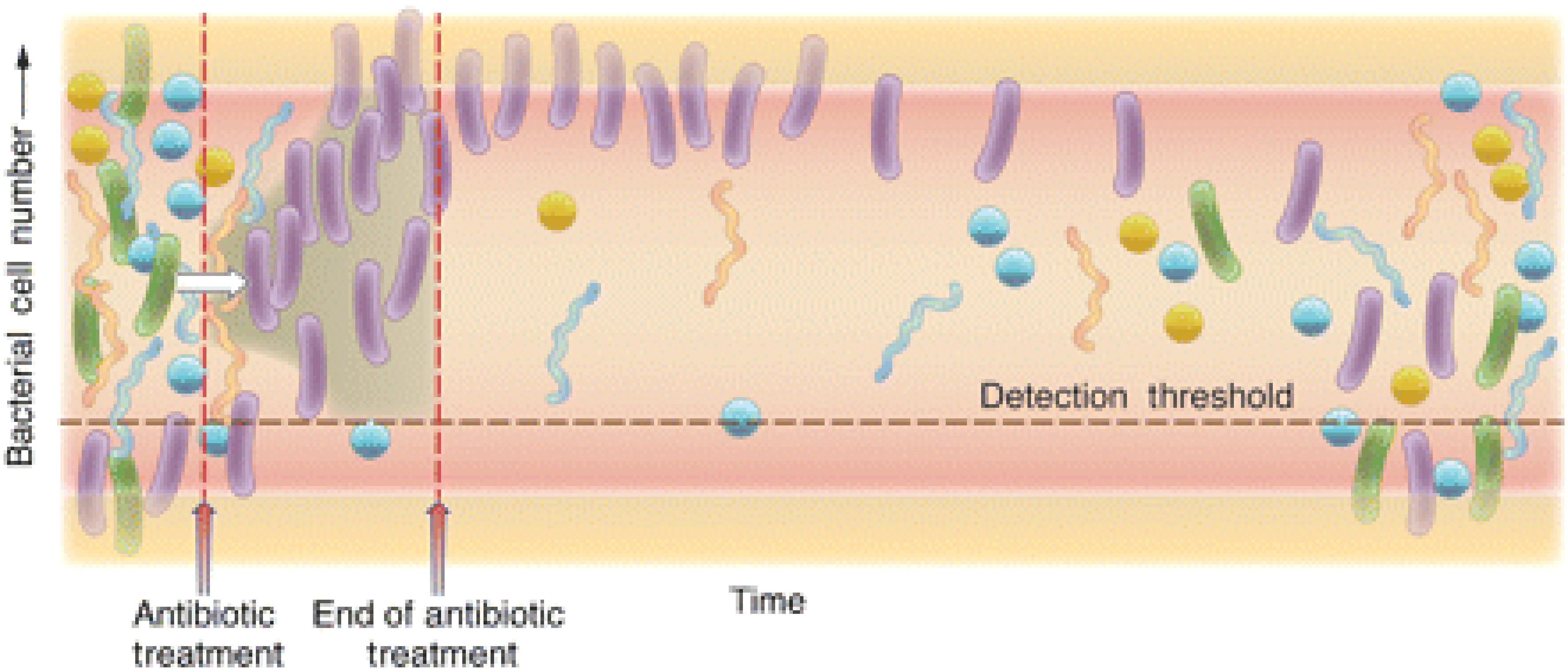
Question

- The effect of an antibiotic on a patient ends:
  1. When the drug level in the patient drops below the minimum inhibitory concentration for bacteria (hours)
  2. When all the antibiotic is metabolized or excreted (days)
  3. When the patient’s insurance pays the bill (weeks)
  4. When the patient’s microbiota returns to normal (months to years, maybe never)

Antibiotics and the microbiome

- The effects of antibiotics on the human microbiome are drastic and long-lasting
  - One dose of antibiotic can change the microbiome for a month, sometimes for 2 years
  - The number of doses and courses matters
    - A study showed that the patients' microbiome recovered after one course of ciprofloxacin but not two
  - Antibiotics kill components of the normal flora
    - Reducing the total number
    - Reducing the susceptible strains
    - Reducing the population diversity
    - Summarized as **dysbiosis**
  - Some taxa are difficult to recover

Antibiotics and the microbiome



Antibiotics and the microbiome

- The effect is **cumulative**; combinations of antibiotics cause more dysbiosis than monotherapy
- Subclinical antibiotics also do this (antibiotics in our food; how does that happen?)
- Many common infections are caused by dysbiosis or the risk increases with antibiotics
  – Antibiotic-associated diarrhea
  – *Clostridium difficile* colitis
  – Bacterial and yeast vaginitis
  – Foodborne bacterial infections (Salmonella, Shigella, Campylobacter)

Antibiotic resistance and the microbiome

- Exposure of the human microbiome to antibiotics does shifts the community to a more resistant population; increases the prevalence of resistance genes in the population; the **resistome**
  - Resistance genes can be on mobile genetic elements (plasmids) and hide in non-culturable bacteria
  - Macrolide resistant genes persisted in the intestine microbiome for up to 4 years following macrolide treatment
- Antibiotic resistant bacteria do not have an advantage and will not spread in the absence of antibiotics

Example of microbiota management in clinical medicine

- Fecal Microbiota Transplantation (FMT)
  - FDA-approved for *C. difficile* colitis
  - Replace dysbiotic GI microbiota with healthy microbiota through an NJ tube
  - Cures much better, faster and safer than antibiotic
  - Patient improves the same day, has normal GI function in 24 hours

Question

- The most important factor preventing hospital-acquired infections in patients is:
    1. How clean their room is at admission
    2. Handwashing by staff
    3. Giving prophylactic antibiotics for surgery
    4. Daily chlorhexidine bathing
    5. Reducing dysbiosis

What does this mean for infection prevention?

- The dominant belief in infection prevention has been that microorganisms are the threat and the answer to infection is to kill them all
- The answer to multi-drug-resistant pathogens is more, and more powerful antibiotics
- Now, we need to change our paradigm:
  - Cleaner is not necessarily better
  - Antibiotics, disinfectants, hand sanitizer, have unintended consequences
  - Fighting antibiotic resistance with more antibiotics is doomed to fail

What does this mean for infection prevention?

- One of the most important things we can do to reduce the risk of infection in our patients is to support **antimicrobial stewardship** programs in our hospitals
  - Your pharmacist is your friend
  - Optimize antibiotic use to minimize exposure

Who is more susceptible to infection (and allergies)?

Changes in medical practice

- **Reduce antibiotic exposure** to patients
  - Non-therapeutic courses (surgery, dental procedures, empiric use)
  - Shorten the course
  - Look at surgical prophylaxis
- **Target antibiotic treatment** as narrowly as possible (versus "broader is better")
- Discontinue using **antimicrobial** soap for bathing and handwashing
- Discontinue antibiotics in animal feeds

Changes in medical practice

- Consider the role of prebiotics and probiotics
  - **Prebiotics**; functional foods; vegetable fiber that changes the microbiota
    - Asparagus, artichokes, bananas, oatmeal, legumes.
  - **Probiotics**; consuming live good bacteria to displace unwanted species
    - yogurt

Changes in medical practice

- Fecal Microbiota Transplantation (FMT, stool transplant) for microbiota-related enteric disease
  - Accepted for *C. difficile* colitis
  - Antibiotics are not the answer to perturbed intestinal flora, they are the problem
  - Procedure has become mainstream
  - Extremely effective
  - Approved by the FDA, there is a billing code for it
  - Doctors still don’t know about it or recommend it

Human microbiome future directions

- We will better understand the effects of the microbiome on health and disease by comparing healthy controls with disease patient data to identify differences
- We may be able to reverse some diseases by restoring healthy microbiomes
- We will understand the effect of antibiotics on the patient and develop more targeted therapies toward pathogens that protect more of the microbiome

Human microbiome research applications to medicine

- The treatment and prevention of infectious diseases may evolve to include not just using antibiotics and vaccines but using **probiotics** and **prebiotics** to manage the patient's microbiome
- The diagnosis of some diseases may involve **metagenomic microbiome analysis** instead of doing cultures for specific pathogens
  - Stool analysis for microbiome to assess the gut ecology rather than looking for a few pathogens
  - The "normal flora" we ignore in the clinical laboratory may have the answer to the patient's disease, not the "pathogens"

What do physicians need to do?

- Own the patient’s microbiome and protect it as much as you can
- Realize that all antibiotics are toxic
- Do not give antibiotics when not absolutely necessary; consider other approaches
- Use the most narrow spectrum and shortest course you need to cure the infection
- Remember the resistome

Thank you!

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