Defining the Microbiome: A collection of microbes or microorganisms that inhabit an environment
- Inhabitants: Prokaryotes/Bacteria (largest component), Viruses, Eukaryotes
- Diversity: There is significant microbial diversity in body sites and between individuals.
  - By understanding the role of microbiota shifts, we may predict an individual’s ‘health status’
- Human Microbiome: 1:1 Cellular ratio between mammal and microbial cells, 3 lbs of Bacteria in intestines!

Symbiotic Relationships – The Host and Microbes

- **Host-Microbial Mutualism**: Analyzing the benefits conferred by microbes to humans
  - Production of beneficial metabolites (SCFA, \(2^9\) Bile acids, NT, Choline) and Eliminate harmful (Choline)
    - Mammals are less capable of producing SCFA, such as acetate, propionate, and butyrate
      - Butyrate is the ‘essentially’ the only energy source for colonocytes
    - 90% of Serotonin (5-HT) is made in the gut. Regulation of synthesis is by gut bacteria
    - Choline, a component of red meats, can be linked to the regression of cardiovascular disease. The intestinal bacteria are capable of ‘fixing’ these potentially harmful metabolites
  - Vitamin Synthesis – gut bacteria produce some vitamins, like VitD and VitK
  - Resistance against invading pathogens
  - Maturation of mucosal immune system and immune cells: As proven by studies evaluating the effectiveness of the immune system in gnotobiotic mice, its strength is derived by gut microbiome.

- **Host-Microbial Dysbiosis**: Maladaptation of the gut microbial community, leading to constitutive inflammation
  - Host Genetics: Mutations in genes involved in the inflammatory pathways
  - Lifestyle: Diet and Stress – the western diet (\(\uparrow\)Fat, \(\downarrow\)Fiber) has been tied to underlying inflammation
  - Early Colonization: Though not necessarily lasting until adulthood, birthing procedures play a role
  - Medical Practices: Vaccination administration, antibiotic (abx) use, and hygiene, medications
    - Many prescription medications affect the microbiome. As predicted, drug classes like PPIs exhibit a strong influence on the microbiome due to their alteration of the digestive environment (pH), though there are others related to cardiac health that may be surprising (Statins, ACE-I, etc)
    - Main Rx Offenders: Broad spectrum abx (beta-lactams, fluoroquinolones, tigecycline, cleocin)
    - Favorable Perturbations: Rifaximin – Used to tx Traveler’s Diarrhea, this drug inhibits RNA polymerase, specifically decreasing inflammation and promoting beneficial bacteria

- **The Role of Host-Microbe Relationships**
  - Recent studies have been showing the significant role the gut microbiome plays in: mood disorders, sleep, stress, chronic disease states, allergies, and much more.

Methods of Studying the Microbiome
- Culture Techniques: Predominantly obligate anaerobes, most gut species are difficult to culture
- Non-Culture Techniques: Use high-throughput, parallel, multiplex sequencing to define the microbial community
- 16s rRNA Surveys: By sequencing bacterial hypervariable regions specific to prokaryotes, we can identify and monitor phyllogenetic relationships

*Clostridium difficile* Infection (CDI)
- Infection: *C. diff* is a gram-positive, spore-forming bacteria that leads to 30,000 deaths annually. The infection is manageable with abx; though in severe cases, with abx-resistance, infection may lead to sepsis, UC, D, and death
  - Non-Modifiable Risk Factors: Age, Hospitalization
  - Modifiable Risk Factors: Usage of PPIs, Broad spectrum abx (cleocin, cephalo-, aminopenicillins, fq)
  - Decreased microbial diversity is associated with severe and recurrent CDI
- Recurrent CDI: The high rate of recurrence of most likely due to persisting low-grade microbial diversity. Recurrence most frequently occurs within 1-2 weeks of finishing tx, and has the following risk factors:
  - Age, Abx in follow-up period, PPIs, Renal insufficiency
  - *Nood et al* – ‘Duodenal Infusion of Donor Feces for Recurrent *C. diff*’
    - Open-label, RCT, treating CDI patients with Fecal Microbiota Transplantation vs Vancomycin. The fecal transplants are significantly more efficacious! Role of the microbial community
  - *Drekonja et al* – Follow-up systematic review of FMT for *C. diff*
    - Showed an overall cure rate of 85% for CDI
Fecal Microbiota Transplantation (FMT)
- The introduction of a fecal suspension derived from a healthy donor into the GI tract of a diseased individual. The rationale is that the re-introduction of a complete and stable community of gut microbiota will repair and replace disrupted native microbiota. –Exogenously replenishing the microbiome of patients
- Methods: Naso-duodenal tube, Colonoscopy, Rectal Enema
- Mechanism: Combats the Resistome (the dramatically strengthened incidence of abx-resistance bacteria)
  - Abx tx depletes the abx-susceptible bacteria, allowing for the overgrowth of abx-resistance bacteria. Following FMT tx, there is less resistance and a replenishment of eubacteria.

Probiotic vs Prebiotic - The seed and the fertilizer -
- Probiotics: *Live* microorganisms that have health benefits when consumed
  o Source: Yogurt (non-pasteurized), supplements
  o Main Contributors: *Lactobacillus, Bifidobacterium, Saccharomyces*
  o *Hempel et al:* Large meta-analysis consisting of 63 RCT and >11k participants, found that:
    ▪ Using probiotics as adjunct therapy to abx reduced the risk of Abx-Associated-Diarrhea by **58%**
- Prebiotics: *Non-living*, non-digestible carbohydrates that stimulate the healthy gut microbiota metabolism
  o 3 Requirements: (1) Must resist mammalian metabolism/absorption in the upper GI, (2) must be fermented by intestinal bacteria, and (3) selectively stimulate the growth/activity of intestinal bacteria associated with health
  o Main Contributors: Inulin, Resistant Starch, Gum