AUDIO DIGEST FOUNDATION

INTERNAL MEDICINE

Volume 62, Issue 42 **November 14, 2015**

THE GUT AND LUNG MICROBIOMES

Manipulating the Gut Microbiota

Nasia Safdar, MD, PhD, *Assistant Professor, Department of Medicine, Division of Infectious Disease, University of Wisconsin School of Medicine and Public Health, Madison*

Gut Microbiome

Introduction: Bacteroidetes and Firmicutes 2 most important phyla, and ratio between them largely determines health of microbiome; diverse microbiome healthier

Reasons for changes in microbiome with aging: changes in dentition, salivary function, intestinal transit time, and diet; medications, particularly antibiotics

Consortium study: composition of fecal microbiota of older men and women analyzed and compared to young and healthy controls; found that even though gut microbiome fairly stable within one individual over time, dominant microbiota changed with age; different microbiota seen in elder group, compared to younger group; normal aging associated with "inflamm-aging" (increased background level of inflammation that affects immunity and gut microbiome)

Role of diet: *study* — obtained extensive dietary information on subjects not treated with antibiotics; found that diet had significant impact on composition of gut microbiome; microbiota most diverse in dietary group (DG) 1 (most diverse diet, with complex carbohydrates, little red meat or high-sugar/low-nutrient dense foods) and least diverse in DG3 and DG4 groups (fewer complex carbohydrates, more meat, more unhealthy foods); preclinical data for *Clostridium difficile* suggest that cruciferous vegetables (particularly broccoli and kale) beneficial in restoring diversity

C Difficile Infection (CDI)

Recurrent CDI: occurs in 15% to 20% of patients; past recurrence increases likelihood of subsequent recurrences; can be difficult to distinguish between recurrence and irritable bowel syndrome (IBS) following CDI; relapses can last for months to years

Community-associated CDI: *study* — determined percentage of people with CDI who did not have traditional health care exposures; found that ≈35% of people did not receive anti-infective medication, 18% had no outpatient health care exposure, and 40% had only low-level outpatient exposure; 31% of patients without antibiotic exposure received proton pump inhibitors (PPIs); other studies have shown that PPIs seem to increase risk for CDI; *other risk factors* — exposure to infants <1 yr of age and to household members with CDI

Pathogenesis: *reservoirs* — community; infants; hospital; contaminated foods; dogs (usually different strains); once exposed, healthy gut microbiome prevents CDI; CDI toxin mediated, resulting in profuse watery diarrhea until toxins passed; for most patients, exposure to health care system required, resulting in infection (diarrhea) or asymptomatic *C Difficile* colonization (no diarrhea); outcome depends primarily on host characteristics

Recurrent CDI: related to impaired host response and altered intestinal microbiome; study looking at levels of immunoglobulin (Ig)G antibody in blood against toxin A of *C Difficile* found that lower levels meant greater likelihood that diarrhea present; age, renal illness, transplantation status, and immunosuppression lower ability to produce IgG response; study found relative bacterial composition of gut microbiome in recurrent CDI significantly different from that of normal gut microbiome

Management: efficacy of metronidazole equivalent to that of vancomycin for treating mild or first episode; otherwise, vancomycin superior; *Infectious Diseases Society of America guidelines (2010)* — for mild to moderate disease, metronidazole for ≈2 wk; for severe disease (high white blood cell count or low albumin), vancomycin; for severe and complicated disease, vancomycin plus metronidazole; for recurrent cases, repeat same treatment for first episode; metronidazole not recommended beyond first recurrence; guidelines do not mention fecal microbiota transplantation (FMT); *antimotility agents* — study found higher likelihood of prolonged illness, compared to those not on drug; not recommended, except for IBS following CDI

Replenishment of Gut Microbiota

Probiotics: replace only 1 or 2 bacterial species; must be viable and contain adequate quantities; studies looking at efficacy for primary prevention of CDI suggest benefit, but each study used different type of probiotic, and patient populations different; study looking at *Lactobacillus* preparations to prevent antibiotic-associated diarrhea (AAD; CDI not primary outcome) found marked decline in rates of CDI in those who received probiotic combination (DanActive); study using *Lactobacillus acidophilus* and *Bifidobacterium* found no difference in rates of CDI between probiotic and placebo groups of older inpatients; unknown whether probiotics effective for prevention of diarrhea from CDI, but beneficial for AAD

Fecal microbiota transplantation: *definition* — instillation of stool from healthy person into sick person to cure CDI

Donor: if living in same household with presumably same diet, possibly colonized with CD; blood testing limited;

Educational Objectives

The goals of this program are to improve the management of *Clostridium difficile* infection (CDI) and the recognition of the importance of the respiratory microbiome in exacerbations of chronic lung diseases. After hearing and assimilating this program, the clinician will be better able to:

1. Recognize the effects of diet on the components of the gut microbiome.
2. Recommend probiotics for the replenishment of gut microbiota.
3. Explain the role of fecal microbiota transplantation in the treatment of CDI.
4. Describe the respiratory ecosystem and the changes that occur in chronic lung disease.
5. Discuss the role of the lung microbiome in exacerbations of chronic lung disease.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing to disclose. In her lecture, Dr. Safdar presents information that is related to the off-label or investigational use of a therapy, product, or device.

preferred donor related to patient, but not from household; *exclusions* — antibiotic use within past 3 mo; gastrointestinal condition that would lead to malabsorption or IBS; high-risk behaviors

Protocol: discontinue antibiotics 2 to 3 days before procedure; administration by enema preferred (risk lower compared to colonoscopy or esophagogastroduodenoscopy); use freshly passed stool if possible; stool need not be refrigerated; majority of patients have no objection to procedure (large survey found that most patients willing to receive FMT [hypothetical cases]); difference in opinion among providers about when to recommend; most providers recommend after 3 episodes of CDI, or after 2 if severe enough; transmission of undiscovered pathogens main concern

Studies: *randomized trial* — FMT by duodenal infusion; terminated early due to dramatic results compared to oral vancomycin; success rate 81% after first infusion and 93% if patient received second infusion; vancomycin success rate 30%; efficacy against CDI confirmed in multiple nonrandomized trials; diversity of microbiota after FMT resembled that of donor; dramatic results seen within 1 wk; multiple studies show benefit regardless of mode of administration; *study* — looked at whether any differences seen between enema, endoscopy, or nasojejunal tube and how stool prepared (normal saline *vs* water); found no difference; 92% experienced resolution; no deaths due to procedure

Outcomes: some recent studies suggest that enema has higher resolution rate, but studies nonrandomized; related donor has higher resolution rate *vs* unrelated donor; administration in water more effective than in normal saline; larger volume of suspension had higher rate of resolution; primary cure rate 91% 3 mo after FMT; receiving antibiotics after FMT can erase benefit

Disadvantages: esthetically unpleasant; issues with reimbursement; potential transmission of pathogens

Indications: for recurrent refractory disease; possibly for severe disease; arguably first-line therapy; unclear for treating IBS after CDI (not listed as indication by Food and Drug Administration)

Stool substitutes: Robogut device used to develop 30 of most common species; *FMT in pill form* — 20 to 30 capsules of freeze-dried stool required; success rates similar to that of enema; not yet commercially available

Suggested Reading

Alasmari F et al: Prevalence and risk factors for asymptomatic Clostridium difficile carriage. *Clin Infect Dis*, 2014Jul 15;59(2):216-22; **Butel MJ:** Probiotics, gut microbiota and health. *Med Mal Infect*, 2014Jan;44(1):1-8; **Jeffery IB, O'Toole PW:** Diet-microbiota interactions and their implications for healthy living. *Nutrients*, 2013 Jan 17;5(1):234-52; **Lofland D et al:** Fecal transplant for recurrent Clostridium difficile infection. *Clin Lab Sci*, 2013 Summer;26(3):131-5; **Seekatz AM et al:** Recovery of the gut microbiome following fecal microbiota transplantation. *MBio*, 2014 Jun 17;5(3):e00893-14; **Seekatz AM, Young VB:** Clostridium difficile and the microbiota. *J Clin Invest*, 2014 Oct;124(10):4182-9; **Song Y et al:** Microbiota dynamics in patients treated with fecal microbiota transplantation for recurrent Clostridium difficile infection. *PLoS One*, 2013 Nov 26;8(11):e81330; **Youngster I et al:** Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. *JAMA*, 2014 Nov 5;312(17):1772-8; **Zapata HJ, Quagliarello VJ:** The microbiota and microbiome in aging: potential implications in health and age-related diseases. *J Am Geriatr Soc*, 2015 Apr;63(4):776-81.

The Lung Microbiome

Robert P. Dickson, MD, *Clinical Lecturer, Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan Health System, Ann Arbor*

Respiratory ecosystem: *terrain* — respiratory tract topologically outside body; enormous internal surface area (≈70 m^2) because of branching of airways; lungs have largest exposed surface area in body; population of any community determined by immigration, elimination, and reproduction rates; *microbial immigration* — main mode via upper respiratory tract, specifically via microaspiration; 1997 study concluded that aspiration occurs commonly in healthy young men during sleep, aspiration variable within subjects studied on >1 occasion, and quantity aspirated is of order of magnitude likely to contain bacterial organisms in physiologically significant quantities; *microbial elimination* — cough; mucociliary clearance; host defenses; *regional growth conditions* — nutrient availability (lungs typically nutrient-poor); O_2 tension (not uniform throughout lungs; higher at apex and base); temperature (gradient); concentration and activation of inflammatory cells

Changes in ecosystem with lung disease: *topology* — decreased internal surface area seen in advanced chronic obstructive pulmonary disease (COPD) or advanced pulmonary fibrosis; *immigration* — esophageal dysfunction and reflux common; *elimination* — increased cough; impaired mucociliary clearance; increased number and activation of inflammatory cells; *regional growth conditions* — increased mucus production (increased nutrient supply, increased temperature, and anoxic zones); increased vascular permeability, leading to increased nutrient supply; host-microbe interactions (catecholamines recognized as stress signals and used as growth and virulence factors)

Feedback loop: inflammation and injury create intra-alveolar catecholamines, which promote growth of certain bacteria; in turn, this perpetuates inflammation and injury (not specific to catecholamines; shown in vitro with tumor necrosis factor-α, interleukin-1, and opiates); acute and chronic illnesses change environment and growth conditions for bacteria; fever state protective against some bacteria but advantageous to others; effects of stress on body change growth conditions in lung microbiome; in healthy state, microbiome largely determined by balance of immigration and elimination, with relatively little reproduction in lower respiratory tract; in any advanced chronic lung disease, same bacteria cultured from respiratory tract at each sample (bacteria uniquely adapted to specific set of environmental conditions)

Lung microbiome and disease

Asthma: the more hyperresponsive the airway (more sensitive to methacholine challenge), the more distinct the microbiome from normal, and the more likely to respond to macrolides; *study by Huang* — asthmatic patients classified according to response to methacholine (provocative concentration of methacholine causing 20% drop in forced expiratory volume in 1 sec [FEV_1], or PC_{20}); with lower PC_{20} (indicating hyperreactive, more bronchoconstrictive airway), greater diversity of microbiome; increased number of species seen in highly bronchospastic patients; increased diversity in those who had improvement in lung function with clarithromycin; in other study, associated with response to corticosteroids; patients with noneosinophilic asthma tend to have neutrophils (instead of eosinophils) in lungs, have more frequent and severe exacerbations, and not respond to steroids; may be responding to microbiome effect

COPD: changes associated with severity of disease; no significant difference between microbiomes of healthy patients and those with mild COPD; once patient reaches threshold of FEV_1 50% of predicted (moderate severity), bacteria detected, including those that potentially cause exacerbations; changes also associated with inhaled steroids

Cystic fibrosis (CF): microbiome changes with severity of disease (drop in diversity and narrowing of community around few potential pathogens in highly advanced disease); driven largely by cumulative antibiotic exposure

Non-CF bronchiectasis: microbiome predictive of frequency of subsequent exacerbations; influenced by macrolide treatment

Lung transplantation: association between finding *Pseudomonas* in airways and subsequent rejection

Idiopathic pulmonary fibrosis (IPF): most common reason for lung transplantation; association seen between microbiome and progression of disease; study by Han found that higher amounts of *Streptococcus* or *Staphylococcus* at baseline associated with greater likelihood of rapid decline; another study found that the larger the amount of bacterial DNA found, the greater the mortality rate; amount of bacterial DNA detected also associated with genetic mutation (*MUC5B*); 10% increase in mortality seen with immunosuppressants; IPF likely represents cycle of disordered microbial community and secondary immune dysregulation, so necessary to treat both

Role of microbiome in exacerbations: *exacerbation* — period of acute worsening of respiratory symptoms; usually followed by return to clinical baseline, though baseline often compromised; typically associated with accelerated progression of disease; in asthma, CF, and COPD, "frequent exacerbator" phenotype exists; *key lesson* — exacerbations not bacterial infections of airways

Hallmarks of acute infection: high microbial biomass, low microbial diversity, host inflammation, and tissue injury

Characteristics of chronic lung disease: inflammation in airways at baseline higher than normal; usually slight increase in diversity (not uniformly); only slight increase in bacterial burden; studies show no increase in bacterial burden during exacerbations

Respiratory exacerbations: inflammation increased, but not coupled with increase in biomass or drop in diversity; high level of airway inflammation disproportionate to bacterial burden; CF exacerbation is localized inflammation; antibiotics ineffective for exacerbations of asthma and controversial in COPD; benefit unclear for CF; in CF, no relationship between in vitro susceptibilities of bacteria and patient's response; associated with changes in community membership because of changes in regional growth conditions (Bacteroidetes overtaken by Proteobacteria); exacerbations represent occasions of respiratory dysbiosis coupled with dysregulated airway inflammation

New model of respiratory exacerbations: often start with trigger, setting off cascade of inflammation; macrophages activated and more neutrophils and eosinophils recruited; leads to increased mucus production, vascular permeability, and catecholamines; all have predictable effects on regional growth conditions, which translate into dysbiosis; atypical bacteria result in more inflammation; exacerbations last longer than trigger because of persistent airway inflammation (positive feedback loop perpetuates dysbiosis and inflammation); *CF* — antibiotics have effect by shifting communities, not eradicating pathogen; *macrolides* — effective in preventing exacerbations of CF, COPD, and non-CF bronchiectasis; both antibiotic and immunomodulatory

Suggested Reading

Carmody LA et al: Changes in cystic fibrosis airway microbiota at pulmonary exacerbation. *Ann Am Thorac Soc*, 2013 Jun;10(3):179-87; **Huang YJ et al:** National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma. *J Allergy Clin Immunol*, 2011 Feb;127(2):372-381.e1-3; **McGuigan L, Callaghan M:** The evolving dynamics of the microbial community in the cystic fibrosis lung. *Environ Microbiol*, 2015 Jan;17(1):16-28; **Zakharkina T et al:** Analysis of the airway microbiota of healthy individuals and patients with chronic obstructive pulmonary disease by T-RFLP and clone sequencing. *PLoS One*, 2013 Jul 9;8(7):e68302.

Acknowledgements

Dr. Safdar was recorded at *Hot Topics in Internal Medicine 2015: The Latest Knowledge to Impact Your Practice*, held April 29 to May 1, 2015, in Middleton, WI, and sponsored by the University of Wisconsin School of Medicine and Public Health and the University of Wisconsin Madison School of Nursing. For information about upcoming CME activities presented by the University of Wisconsin School of Medicine and Public Health, visit their website at www.ocpd.wisc.edu. Dr. Dickson was recorded at the *Third Annual Internal Medicine Spring Review*, held May 29-30, 2015, in Plymouth, MI, and sponsored by the University of Michigan Health System. For information about upcoming CME activities presented by the University of Michigan Health System, visit their website at www.med.umich.edu/intmed/cme. The Audio Digest Foundation thanks the speakers and the sponsors for their cooperation in the production of this program.

Accreditation: The Audio Digest Foundation is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Designation: The Audio Digest Foundation designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Academy of Physician Assistants (AAPA) accepts certificates of participation for educational activities designated for *AMA PRA Category 1 Credits™*. from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 2 AAPA Category 1 CME credits for each Audio Digest activity completed successfully.

Audio Digest Foundation is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's (ANCC's) Commission on Accreditation. Audio Digest designates each activity for 2.0 CE contact hours.

Audio Digest Foundation is approved as a provider of nurse practitioner continuing education by the American Academy of Nurse Practitioners (AANP Approved Provider number 030904). Audio Digest designates each activity for 2.0 CE contact hours, including 0.5 pharmacology CE contact hours.

The California State Board of Registered Nursing (CA BRN) accepts courses provided for *AMA PRA Category 1 Credit™* as meeting the continuing education requirements for license renewal.

Expiration: This CME activity qualifies for *AMA PRA Category 1 Credit™* for 3 years from the date of publication.

Cultural and linguistic resources: In compliance with California Assembly Bill 1195, Audio Digest Foundation offers selected cultural and linguistic resources on its website. Please visit this site: www.audiodigest.org/CLCresources.

Estimated time to complete the educational process:

Review Educational Objectives on page 1	5 minutes
Take pretest	10 minutes
Listen to audio program	60 minutes
Review written summary and suggested readings	35 minutes
Take posttest	10 minutes

THE GUT AND LUNG MICROBIOMES

*To test online, go to **www.audiodigest.org** and sign in to online services.*
*To submit a test form by mail or fax, complete Pretest section **before** listening and Posttest section **after** listening.*

1. Which of the following bacterial phyla are the 2 most important in the gut microbiome?
   1. Bacteroidetes
   2. Proteobacteria
   3. Firmicutes
   4. Actinobacteria

   (A) 1,3 (B) 2,4 (C) 1,4 (D) 2,3

2. All the following statements about recurrent *Clostridium difficile* infection (CDI) are true, EXCEPT:
   (A) Past recurrence increases likelihood of subsequent recurrences
   (B) Relapses can last for months to years
   (C) May be difficult to distinguish between recurrence of CDI and irritable bowel syndrome
   (D) Recurrence occurs in <5% of patients who have had CDI

3. Diarrhea associated with CDI is:
   (A) Attributable to mucosal invasion (B) Toxin mediated

4. It is unknown whether probiotics are effective for preventing _____, but they have been shown to be beneficial for preventing _____.
   (A) *C difficile* diarrhea; antibiotic-associated diarrhea (AAD)
   (B) AAD; *C difficile* diarrhea

5. Studies suggest that which of the following result in higher rates of resolution with fecal microbiota transplantation?
   1. Enema/colonoscopy (*vs* nasojejunal tube/gastroscopy)
   2. Related donor (*vs* unrelated donor)
   3. Large volume of suspension (*vs* small volume)
   4. Administration in water (*vs* in normal saline)

   (A) 1,3 (B) 2,4 (C) 1,2,3 (D) 1,2,3,4

6. There is no significant difference in the lung microbiome in mild chronic obstructive pulmonary disease (COPD), compared to that of healthy patients, but once the threshold of forced expiratory volume in 1 sec _____ of predicted is reached, bacteria are detected, including those that can cause potential exacerbations.
   (A) 30% (B) 40% (C) 50% (D) 60%

7. Which of the following conditions is now the most common reason for lung transplantation?
   (A) Cystic fibrosis (CF)
   (B) Non-CF bronchiectasis
   (C) COPD
   (D) Idiopathic pulmonary fibrosis

8. Exacerbations of chronic lung disease are typically caused by bacterial infections of the airways.
   (A) True (B) False

9. All the following are hallmarks of acute infection, EXCEPT:
   (A) High microbial biomass
   (B) High microbial diversity
   (C) Host inflammation
   (D) Tissue injury

10. In exacerbations of chronic lung disease, the level of airway inflammation is high and is _____ to the microbial burden.
    (A) Proportionate (B) Disproportionate

Answers to Audio Digest Internal Medicine Volume 62, Issue 40: 1-C, 2-A, 3-D, 4-D, 5-B, 6-C, 7-C, 8-B, 9-D, 10-C

Attention, CME/CE Participants

The cutoff date for logging 2015 credits is December 31, 2015. Test forms received after that date will be accrued to 2016.