Nasal and Sinus Microbiome: the potential for microbiota-targeted therapeutics

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Microbes live throughout the human nasal passages
We think about these bacteria in terms of how they affect humans

- **Commensal (benign)** → no harm, no benefit
- **Mutualist (beneficial)** → benefit to us
- **Pathobiont*** → can cause severe disease

*Mazmanian, Round & Kasper Nature 2008*
Two key pathobionts that colonize the human nose

*Staphylococcus aureus* colonizes the nostrils of ~25% of the U.S. population

*Streptococcus pneumoniae* colonizes the nose of ≥40% of children ages 6 months to 7 years
These pathobionts invade & reside in a microbiota with commensal bacteria
Can other members of the microbiota keep these pathobionts out, or under control?

Benign or beneficial

Pathobionts
Twin studies indicate genetics has little influence on *S. aureus* colonization.

Andersen et al JID 2012; Liu et al mBio 2015
Twin study indicates nasal microbiota is environmentally, not genetically, determined

Liu et al mBio 2015
The bacterial nasal microbiome in children

• Prepubertal
  – Proteobacteria
    • *Haemophilus*
    • *Moraxella*
  – Firmicutes
    • *Streptococcus*
    • *Dolosigranulum*
  – Bacteroides
  – Actinobacteria
    • *Corynebacterium*
  – Fusobacteria

• Laufer et al. mBio 2011
• Bogaert et al. PONE 2011
• Pettigrew et al. AEM 2012
• Oh et al. Gen Med 2012
• Biesbroek et al. AJRCCM 2014
The bacterial nasal microbiome in adults

- Costello et al. Science 2009
- Grice et al. Science 2009
- Frank et al. PONE 2009
- Lemon et al. mBio 2010
- Wos-Oxley et al. ISME 2010
- Charlson et al. PONE 2010
- HMP Nature 2012
- Yan et al. CHM 2013

- Post-pubertal
  - Actinobacteria
    - Propionibacterium
    - Corynebacterium
  - Firmicutes
    - Staphylococcus
A developmental shift in the composition of the nasal microbiota

- **Prepubertal**
  - Proteobacteria
    - *Haemophilus*
    - *Moraxella*
  - Firmicutes
    - *Streptococcus*
    - *Dolosigranulum*
  - Bacteroides
  - Actinobacteria
    - *Corynebacterium*
  - Fusobacteria

- **Post-pubertal**
  - Actinobacteria
    - *Propionibacterium*
    - *Corynebacterium*
  - Firmicutes
    - *Staphylococcus*
Properties of nasal microbiota make it amenable to microbiota-targeted therapy
Properties of nasal microbiota that make it amenable to microbiota-targeted therapy

- Environmental factors much stronger than host genetics in determining composition
  - Liu et al. mBio 2015

- Environmental factors associated with differences in early childhood microbiota
  - Bogaert et al. PONE 2011

- Less stable over time than fecal microbiota
  - Franzosa et al. PNAS 2015
Potential areas for future microbiota-targeted therapeutics

- Chronic rhinosinusitis
- Recurrent otitis media
- Asthma
- Recurrent S. aureus infection
Potential areas for future microbiota-targeted therapeutics

Chronic rhinosinusitis

Recurrent otitis media

Asthma

Recurrent S. aureus infection
Human paranasal sinuses
Chronic rhinosinusitis (CRS)

- Sinus inflammation ≥3 months even with medical intervention – CRS in clinically heterogeneous.
- Estimated to affect >5% of people in the U.S. – Hamilos JACI 2011
- Emerging data indicating that bacterial microbiota differs in health and CRS
- A possible role for host genetics in predisposition to CRS (e.g., heterozygous for mutations in CFTR)
- Recommended recent reviews
  - Cope & Lynch Curr Allergy Asthma Rep 2015
  - Ramakrishnan et al. Curr Opin ORL 2016
# Healthy Sinuses vs CRS

<table>
<thead>
<tr>
<th>Healthy Sinuses</th>
<th>CRS</th>
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<tbody>
<tr>
<td>Diverse microbiome</td>
<td>Reduced diversity</td>
</tr>
<tr>
<td><em>Propionibacterium,</em> <em>Corynebacterium</em> and <em>Staphylococcus</em></td>
<td>Sinonasal microbiome dysbiosis and microbiome community collapse</td>
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</tbody>
</table>

Includes genera with pathogenic members (*Staphylococcus, Streptococcus* and *Pseudomonas*)

Outgrowth of *Corynebacterium tuberculostearicum* (Abreu et al) or *Staphylococcus* (Choi et al)
Current treatments for CRS

• Antibiotics
  – Initial course of 3 weeks with possible extension for ongoing symptoms up to 10 weeks

• Immunomodulation via corticosteroids

• If likely allergy-related, may include antihistamine

• Endoscopic sinus surgery
Research needs

• Do microbiome changes instigate/perpetuate disease?

• Properly designed studies to assess if microbiota-targeted therapies impact sinus/nasal microbiome composition and alter disease course?

• Function significances of different species and strain within common genera, e.g., are some Corynebacterium species preferable?

• Studies to determine if differences in composition correspond to differences in community function

• Include viruses (of both eukaryotes and bacteria) and fungi in microbiome analyses.
Risks of microbiota transplantation

• Introducing common pathobionts, e.g., *S. aureus*
  – Careful and repeated donor screening

• Introduction of eukaryotic viruses

• Unknown consequences of introducing bacteriophage

• Potential to swap one problem, e.g., recurrent *S. aureus* infection, for another, e.g., CRS
Getting there from here?

Lemon et al. Sci Trans Med 2012
Potential areas for future microbiota-targeted therapeutics

Chronic rhinosinusitis

Recurrent otitis media

Asthma

Recurrent S. aureus infection
Recurrent middle ear infections in early childhood (otitis media)

- Current treatment is sequential 7-14 day courses of antibiotics targeting *S. pneumoniae*, and then *H. influenzae* and *M. catarrhalis*

- There is interest in prebiotics to reduce *S. pneumoniae*, e.g., research on xylitol
Potential areas for future microbiota-targeted therapeutics

- Chronic rhinosinusitis
- Recurrent otitis media
- Asthma
- Recurrent S. aureus infection
Asthma

- Evidence for a role of early childhood viral respiratory tract infections in risk for asthma
- Evidence for potential effect of early childhood exposure to environmental microbes
- Evidence for a gut-respiratory tract interaction impacting the propensity for asthma
- A possible role for host genetics
- Current treatment via immunomodulation primarily with inhaled corticosteroids
Research underway to explore potential small molecule, prebiotic and probiotic therapeutics.

Chronic rhinosinusitis

Recurrent otitis media

Asthma

Recurrent S. aureus infection
Eradication of *S. aureus* colonization in cases of recurrent *S. aureus* infection

- Current protocols involve repeated rounds of 5 days of intranasal mupirocin and chlorhexidine body washes  
  – e.g., Fritz et al. CID 2012

- This results in repeated perturbations without any active guidance of secondary succession

- Potential role for pre- or probiotics, or introduction of a healthy nasal consortium
The better we understand the biology from the molecular-level to the ecosystem-level, the better we will manage our microbiota.
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Boston Children’s Hospital
Microbial factors that drive of human microbiome structure and dynamics
Defining the molecular mechanisms of commensal-pathobiont interactions

Growth inhibition

Behavior modification*

Habitat modification

*Wollenberg et al. mBio 2014
Propionibacterium-Produced Coproporphyrin III Induces S. aureus Aggregation & Biofilm

Propionibacterium spp.

S. aureus

Wollenberg et al. mBio 2014
Corynebacterium spp. modify their habitat to make it inhospitable for S. pneumoniae

Lindsey Bomar
Model: *C. accolens* modifies its habitat in a manner that inhibits pneumococcus

*pneumo*  

*Coryne*  

*Coryne* secreted lipase  

anti-bacterial FFAs  

Host surface triacylglycerols  

Bomar et al. mBio in press