Probiotics and Allergic Rhinitis

G.A. Richards

MBBCh PhD FCP(SA) FRCP
Academic Head Critical Care
University of the Witwatersrand
Director Critical Care CMJAH
The Microbiome

- Microbial species & their associated genomes living on & in humans
- Multiple distinct microbiomes at different sites; Individual variation; composition at any site broadly similar in health
- Microbiome interacts extensively with host & outnumbers human gene content by 100 fold
- Contributes to metabolic capacity, drives immune development & mucosal protection

Cope Curr Allergy Asthma Rep 2015
The Microbiome in Health

► The RT has an area of 75m$^2$ & direct exposure to inhaled pollutants, allergens, microbes
► Cleared from sinonasal cavity, naso-pharynx, trachea & lungs by mucociliary clearance
► Nares lined by keratinized, stratified squamous epithelia with sebaceous & sweat glands & hair each with discrete ecosystems colonized by compositionally distinct microbiomes

Cope Curr Allergy Asthma Rep 2015
Airway Microbiome

- Niche specificity: nares & oropharynx exhibit distinct bacterial taxa
- Nares: enriched with skin-associated Actinobacteria & oropharynx enriched more commonly with members of the Firmicutes & Proteobacteria

Lemon MBio 2010
Airway epithelia express PRRs such as toll-like receptors

Recognize & respond to microbes (PAMPS) - recruiting PMNL, eosinophils &/or macrophages & epithelial secretion of antimicrobial peptides, chemokines & cytokines
Intracellular signaling

TLR

LPS

LPB

Soluble CD 14

Membrane CD 14

Intracellular signaling

TLR

Neutrophils, monocytes macrophages

Noursadeghi; JRCP, 2000
The Burden of Microbes & Diversity of Airway Microbiome

- Greatest in the URT diminishes in LRT
- 3 studies examined microbiota of healthy subjects - diverse & included potentially pathogenic bacteria, PsA, Staph, Strep

CRS: Pathology

- Associated with substantial microbiome dysbiosis
- Microbiome community-collapse occurs in maxillary sinuses with overgrowth of organisms such as Corynebacterium tuberculostearicum & with Staphylococcus enrichment

Abreu Science Translational Medicine 2012
Choi Allergy 2014
CRS: Pathology

Healthy Stable Community
- Species-Rich
- Even Species Distribution

Perturbation(s)
- Acute Infection
- Antibiotics
- Chronic Environmental Stressors

Disease Stable Community
- Species-Poor
- Uneven Species Distribution

Immune Homeostasis.
Resistant to colonization by or outgrowth of harmful sinus microbiota.

Immune Activation.
Colonized or outgrowth of inflammation-tolerant community.
Resistant to colonization by healthy sinus microbiota.

Cope Curr Allergy Asthma Rep 2015
CRS

- As such current therapy- INCS ± antibiotics are only variably successful
- Culture-directed antibiotics have some success but recurrence is common
- Some patients rebuild native microbiome & epithelium with FESS, but many require revision

Cincik Laryngoscope 2006
Drilling Int Forum Allergy Rhinol 2014
Fokkens Rhinol Suppl 2012
Microbiome in Asthma

- Asthmatics have significantly increased LRT bacteria
- Composition related to extent of disease: severe bronchial hypereactivity has greatest burden & diversity
- Contrary to gut microbiome - where chronic inflammatory disorders have diversity depletion

Dickson Ann Am Thorac Soc 2015
Bassis Mbio 2015
Charlsonal Am J Respir Crit Care Med 2011
56 adults, 26 with severe asthma: recent onset asthma, rhinosinusitis & sputum eosinophilia associated with enrichment of specific Streptococcus taxa

Bronchial bacterial composition in severe asthma (n = 40) correlated with BMI, sputum PMNL count & bronchial biopsy eosinophils

Each phenotype was associated with distinct airway bacterial community compositions

Huang J Allergy Clin Immunol 2015
Microbiome in Asthma

- Strong association between bacterial communities & asthma
- Modulated by diet, antibiotics, early-life microbial exposures
- Gut & lung microbiota influence inception & progress of asthma
- In infants pathogenic lung & gut bacteria associated with subsequent allergy & asthma

Chung J Allergy Clin Immunol 2017
Asthma and the microbiome

Unclear if different microbiota are caused by asthma-associated airway inflammation with increased mucus secretion or are causative driving disease pathology.

Given these findings- Can modification of the microbiome influence pathology
Intranasal administration of L rhamnosus GG

- After 3 days of intranasal exposure mice were infected with influenza A/PR/8/34(H1N1)
- Mice treated with LGG showed a lower frequency of accumulated symptoms & higher survival P<0.05

Harata Letters in Applied Microbiology 2010
Intragastric & Intranasal L. paracasei in a mouse model

- Intranasal L. paracasei NCC2461 efficiently protected sensitized mice in a dose-dependent manner vs controls.
- Inflammatory cell number, eotaxin and IL-5 were significantly reduced in BALF.
- Intranasal L. paracasei NCC2461 was more potent than intragastric administration.

Pellaton International Journal of Inflammation 2012
Probiotics in Airway Disease: GI-Respiratory Axis

- Risks for airway diseases e.g., childhood allergic asthma, include antibiotics, C-section, formula feeding – all affect neonatal gut microbiome.
- Asthma & AR in adults have altered microbiota.
- Positive results with oral probiotic administration would provide evidence for a relationship between gut microbiome & airway health.

Cope Curr Allergy Asthma Rep 2015
Kuitunen J Allergy Clin Immunol 2009
Kalliomaki Lancet 2001
Probiotics in Airway Disease: GI-Respiratory Axis

- In mice, early-life exposure to microbiota was protective against induced IBD & asthma by preventing NK T cell accumulation in colon & lungs

- Migration of CD3+, CD4+, IFNγ+T cells from GIT to lung was induced by oral L rhamnosus

Olszak Science 2012; VillenaVillena BMC Immunol 2012
Probiotics in Airway Disease: GI-Respiratory Axis

- By 1-3yrs gut microbiome has reached stability & immune system is mostly developed
- Oral probiotics later in life is more complex-
  limited clinical trials, mostly small cohorts (<100), show a range from zero to modest effects on AR or asthma
Probiotics in Airway Disease: GI-Respiratory Axis

- Gut microbiome changes composition based on site, ethnicity & age

- These are not considered when designing probiotic therapies & will likely have more effect if they are taken into account

Mukerji Otolaryngol Head Neck Surg 2009
Clinical efficacy in CRS

- Systematic search of published literature included 7 RPCTs
- Predefined outcomes were assessed
- All had to be off all conventional therapy
- Different probiotics (L paracasei, L bulgaricus, Bifidobacterium longum 536, L Acidophilus), different administration methods; Different doses, different combinations
Assessment of Study Quality

1. Was the study described as randomized?
2. Was the study described as double-blind?
3. Were withdrawals & drop-outs described?
4. Was randomization & double blinding well described & appropriate?
5. 1 point for each & 1 deducted if randomization or blinding inappropriate.
6. Studies with scores ≥3 considered good quality

Das World Allergy Organization 2010
Results

- 2 studies (n=170) evaluated QOL (frequency of symptoms, level of bother): Probiotics improved QOL; SMD -1.17 (-1.47 to -0.86) P=0.00001

- Decreased episodes of rhinitis/year, adjusted OR 0.39 (0.19 to 0.82) P=0.01

- No change in blood/ immunologic parameters

- No effect on time free from rhinitis episodes, or mean duration of episodes
Quality of Life

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>1.1.1 Change in frequency</td>
<td>Peng et al (7)</td>
<td>23.9</td>
<td>2.28</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Wang et al (8)</td>
<td>22.48</td>
<td>1.88</td>
<td>60</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>90</td>
<td></td>
<td>50</td>
<td>46.4%</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 66.43, df = 1 (P &lt; 0.00001); I² = 98%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.91 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.2 Change in level of bother</td>
<td>Peng et al (7)</td>
<td>19.86</td>
<td>2.14</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Wang et al (8)</td>
<td>17.03</td>
<td>1.83</td>
<td>60</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>90</td>
<td></td>
<td>50</td>
<td>53.6%</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 18.57, df = 1 (P &lt; 0.0001); I² = 95%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 6.58 (P &lt; 0.000001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>180</td>
<td>100</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 87.59, df = 3 (P &lt; 0.000001); I² = 97%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 7.47 (P &lt; 0.000001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 2.60, df = 1 (P = 0.11), I² = 61.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Das World Allergy Organization 2010
Peng Pediatr Allergy Immunol 2005
Wang Pediatr Allergy Immunol 2004
Clinical Effects

- RDBPCT: out-of-season nasal allergen challenge following a daily dairy drink ± L casei Shirota

- No clinical differences but differences in percentages of CD86⁺ epithelial cells, CD86⁺ CD252⁺ non-epithelial cells, sIL-1RII release & IL-1b in the nasal mucosa

- Decreased sCD23, TGF-β & increased IFN-γ in supernatants of cultured peripheral blood
Clinical Effects

- Systematic review & meta-analysis: Medline, EMBASE & Cochrane Library databases
- 21 DBRCTs, 2 randomised X-over studies n=1919
- Multiple probiotics, populations & outcomes
- 17 showed significant clinical benefit in ≥ 1 outcome measure, 6 trials- no benefit.
- Among trials eligible for meta-analysis, rhinitis QOL score significantly improved: SMD -2.23; p=0.02); no effect on total symptom score or IgE

Zajac Int Forum Allergy Rhinol 2015
Asthma and Probiotics

- RDBPCT of Lactobacillus rhamnosus GG (LGG)
- 92 infants received 10 billion CFU of LGG & 225 mg inulin x 6mnths vs 325mg inulin alone (n=92)
- 2yrs: eczema incidence in controls was 30.9% (21.4–40.4%) vs 28.7% (19.4–38.0%) P = .83
- 5yrs asthma incidence was 17.4% (7.6–27.1%) in controls vs 9.7% (2.7%–16.6%) P = .25

Cabana PEDIATRICS Volume 140, number 3, September 2017
Clinical trials are inconsistent: partly explained by crosstalk among probiotic bacteria, host microbiota & immune cells.

Screening of probiotic supernatants for agents decreasing CCL17 secretion from a lymphoma cell line & preventing upregulation of costimulatory molecules of LPS-stimulated human dendritic cells yielded D-tryptophan.

In mice this increased lung & gut regulatory T cells, decreased TH2 responses, inflammation & hyperreactivity.

Allergic airway inflammation reduced gut microbial diversity, reversed by D-tryptophan.

Kepert J Allergy Clin Immunol 2016
Conclusion

- Probiotics for the treatment of allergic rhinitis and asthma have produced inconsistent results.
- Currently insufficient evidence to suggest a role for probiotics in the treatment of allergic rhinitis and asthma.