The Pulmonary Microbiome in Pneumonia

Changes in Gut and Lung Microbiome in Critically Ill Patients
Disclosures

• none
Agenda

• reconsider the interaction between host and bacteria
  • microbiome in critically ill patients
  • gut and lung
  • evidence for benefit of manipulation of the microbiome
Traditional Hypothesis
These Lungs are \textit{NOT} Sterile
Culture–independent Microbiological Techniques

• immigration
• elimination
• relative growth rates
• adapted island model

Dickson R *Lancet RM* 2014; 384:691
Agenda

• reconsider the interaction between host and bacteria
• microbiome in critically ill patients
• gut and lung
• evidence for benefit of manipulation of the microbiome
‘Everything is Everywhere, but the Environment Selects’

- exposure to ‘hospital setting’
- change depends on severity of the illness

Johanson W New Eng J Med 1969; 281:1137
Balance of Three Ecologic Factors

- immigration into the community
- elimination from the community
- reproduction rates of community members

Dickson R *Lancet RM* 2016; 4:59
Agenda

• reconsider the interaction between host and bacteria
• microbiome in critically ill patients
• gut and lung
• evidence for benefit of manipulation of the microbiome
Increased Immigration of Potential Pathogens into the Oral Cavity

- prospective study
- USA
- Gram–bacilli
- dependency of antibiotic exposure, duration of stay, etc.

Johanson W *New Eng J Med* 1969; 281:1137
Decreased Gastric Emptying Due to Supine Positioning

- healthy males
- normal meal in 5 minutes
- radiolabeling
- dependence on body position

Decreased Passage of Stools Due to Intestinal Dysmotility

- mixed medical – surgical ICU
- 44 critically ill patients
- first defecation at mean 6 days

van der Spoel J Intensive Care Med 2006; 32:875
Enhanced Growth Induced by Inflammatory Mediators

- *in vitro* study
- clinically relevant strains
- various concentrations of cytokines

Manipulation of the Gut Microbiome Prevents Critical Illness

- germ–free mice are protected from ALI
- protection against infections, MOF and death in humans

Dickson R, Lancet RM 2016; 4:59
Agenda

• reconsider the interaction between host and bacteria
• microbiome in critically ill patients
• gut and lung
• evidence for benefit of manipulation of the microbiome
Colonization of the Islands

- immigration
- elimination
- relative growth rates
- ‘adapted island model’

Dickson R *Lancet RM* 2016; 4:59
The Endotracheal Tube is the Gateway to VAP

- defect mucociliary clearance
- impaired and insufficient cough reflex

Zolfaghari P *Crit Care* 2011; 15:310
Increased Immigration of Potential Pathogens into the Lungs

- trauma patients
- overlap between pathogens in mouth and in lungs
- 88% of VAP patients

Bahrani–Mougeot F J Clin Micr 2007; 45:1588
Decreased Elimination Due to Impaired Mucociliary Clearance

- medical non-intubated ICU patients
- healthy controls
- transit on admission and after 90 days

Nakagawa N *Chest* 2005; 128:2772
Increased Nutrition Substrates Due to Increased Mucus Production

- Lung corridors start to look more as the gut
- \(O_2\) and temperature gradients

Dickson R *Lancet* RM 2016; 4:59
Selective Promotion of Growth and Virulence of Potential Pathogens

- *in vitro* growth and virulence assays
- inotropes are potent stimulators of *P. aeruginosa* growth

Freestone P *Chest* 2012; 142:1200
Agenda

• two small–sized studies of the lung microbiome in critically ill patients
• diversity
Agenda

- two small–sized studies of the lung microbiome in critically ill patients
- diversity
Diversity

• alpha–diversity – number of species and their proportion within one sampling site (‘Shannon index’)

• beta–diversity – dissimilarity between communities of two sites (or two samples) (‘Bray Curtis dissimilarity’)

Diversity

• decreased alpha–diversity – colonization or overgrowth by a restricted set of bacteria

• increased beta–diversity – sites have changed over time
Dynamics of the Lung Microbiome during Mechanical Ventilation

- prospective cohort
- 35 patients in 4 Iberian ICUs
- 4 groups

Zakharkina T, Thorax 2017; 72;803
Dynamics of the Lung Microbiome during Mechanical Ventilation

• prospective cohort
• 35 patients in 4 Iberian ICUs
• alpha–diversity

Zakharkina T *Thorax* 2017; 72;803
Dynamics of the Lung Microbiome during Mechanical Ventilation

- prospective cohort
- 35 patients in 4 Iberian ICUs
- beta–diversity

Zakharkina T *Thorax* 2017; 72;803
Dynamics of the Lung Microbiome during Mechanical Ventilation

- one or more micro-organisms are becoming more dominant during MV
- more profound in patients who develop VAP
- independent of antibiotic exposure (!)
- Pseudomonas and Bacillales

Zakharkina T *Thorax* 2017; 72:803
Dynamics of the Lung Microbiome during Mechanical Ventilation

- patients with respiratory failure
- oropharynx and lungs
- alpha–diversity

Kelly B Microbiome 2016; 4:7
Agenda

- reconsider the interaction between host and bacteria
- microbiome in critically ill patients
- gut and lung
- evidence for benefit of manipulation of the microbiome
Evidence for Benefit of Selective Decontamination Strategies

- single–center RCT
- the Netherlands
- 934 mixed medical–surgical patients
- SDD vs. control

de Jonge E *Lancet* 2003; 362:1011
Evidence for Benefit of Selective Decontamination Strategies

- multi-center RCT
- the Netherlands
- 5,939 medical–surgical patients
- SDD vs. SOD vs. control

Table 2. Primary End Points.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Adjusted Odds Ratio or Hazard Ratio (95% CI)†</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Standard Care</td>
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<tr>
<td>Death — no. (%)</td>
<td></td>
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<tr>
<td>During the first 28 days</td>
<td>1.00</td>
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<tr>
<td>In the ICU</td>
<td>1.00</td>
</tr>
<tr>
<td>In the hospital</td>
<td>1.00</td>
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</tbody>
</table>

Evidence for no Benefit in ICUs with Resistant Microorganisms

- multi-center RCT
- Europe
- 8,665 medical–surgical patients
- SDD vs. SOD vs. CHX

Wittekamp B *JAMA* 2018; in press
Evidence for Benefit of Probiotic Strategies

- multi-site RCT
- 4,556 Indian neonates
- probiotics vs. placebo
- death and sepsis

Probiotics as a Preventive Measure against VAP

- metaanalysis
- 30 trials
- 2,972 patients
- outcome – all infections; VAP

Manzanares W Critical Care 2016; 20:262
Evidence Pending for Benefit of Probiotic Strategies

• running RCT in Canada – PROSPECT
• planned RCT in India and Bangladesh – PROBINBA

Cook D *TRIALS* 2016; 17:377
Conclusions

- critical illness causes acute perturbations of gut and lung microbiome
- changes in the microbiome are associated with outcomes
- microbiome is therapeutic (or preventive) target