Respiratory microbiota and in-ICU pneumonia

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HAP slightly increase the risk of death in ICU

- Rello et al. Chest 2002
- Bekaert et al. AJRCCM 2011
- Van Vught et al. JAMA 2016
Respiratory microbiota

Fashion or revolution?

Results by year

Selected 2016 - 7,238 items

MESH “Microbiome“

Results by year

Selected 2017 - 277 items

MESH “respiratory Microbiome“
Revised Estimates for the Number of Human and Bacteria Cells in the Body

Ron Sender¹, Shai Fuchs²*, Ron Milo¹*
Respiratory microbiota

What can we know? – taxonomia / metabolomic

Lankelma et al. ICM 2017

Risk of Mechanical ventilation in children with bronchiolitis

Stewart et al. AJRCCM 2017
Pneumonia

Do we need new tools to improve patient outcomes?

• For the Prevention?
• For the Treatment?
Causes of hospital-acquired pneumonia: classical physiopathology

Cross-contamination

Colonization from digestive tract

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Number of Randomized Clinical Trial (RCT), Number of patients (N), ( I^2 )</th>
<th>Relative Risk (CI95%)</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidified enteral feeding</td>
<td>1 RCT, N=120, ( I^2 )=NA</td>
<td>2.07 (0.90-4.49)</td>
<td>P=0.09</td>
</tr>
<tr>
<td>Tracheal cuff monitoring</td>
<td>2 RCT, N=264, ( I^2 )=0%</td>
<td>1.22 (0.70-2.11)</td>
<td>P=0.49</td>
</tr>
<tr>
<td>PEEP</td>
<td>1 RCT, N=127, ( I^2 )=NA</td>
<td>1.17 (0.66-2.06)</td>
<td>P=0.59</td>
</tr>
<tr>
<td>Silver-coated ET</td>
<td>1 RCT, N=1509, ( I^2 )=NA</td>
<td>1.14 (0.97-1.34)</td>
<td>P=0.11</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>2 RCT, N=204, ( I^2 )=81%</td>
<td>1.14 (0.20-6.59)</td>
<td>P=0.88</td>
</tr>
<tr>
<td>Patient position</td>
<td>5 RCT, N=785, ( I^2 )=0%</td>
<td>1.06 (0.82-1.38)</td>
<td>P=0.65</td>
</tr>
<tr>
<td>Decreased gastric content</td>
<td>3 RCT, N=810, ( I^2 )=0%</td>
<td>1.06 (0.83-1.35)</td>
<td>P=0.65</td>
</tr>
<tr>
<td>Tracheal saline instillation</td>
<td>1 RCT, N=262, ( I^2 )=NA</td>
<td>1.05 (0.82-1.33)</td>
<td>P=0.71</td>
</tr>
<tr>
<td>Ulcer prophylaxis</td>
<td>16 RCT, N=3365, ( I^2 )=0%</td>
<td>1.00 (0.89-1.13)</td>
<td>P=0.97</td>
</tr>
<tr>
<td>SOD</td>
<td>23 RCT, N=9666, ( I^2 )=0%</td>
<td>0.99 (0.92-1.08)</td>
<td>P=0.89</td>
</tr>
<tr>
<td>Subglottic secretion drainage</td>
<td>9 RCT, N=2241, ( I^2 )=0%</td>
<td>0.98 (0.84-1.15)</td>
<td>P=0.85</td>
</tr>
<tr>
<td>Heat Moisture Exchanger</td>
<td>13 RCT, N=2431, ( I^2 )=0%</td>
<td>0.98 (0.86-1.12)</td>
<td>P=0.78</td>
</tr>
<tr>
<td>Closed suctioning system</td>
<td>5 RCT, N=909, ( I^2 )=0%</td>
<td>0.98 (0.83-1.17)</td>
<td>P=0.85</td>
</tr>
<tr>
<td>Aerosolised antibiotic</td>
<td>5 RCT, N=450, ( I^2 )=23%</td>
<td>0.95 (0.66-1.38)</td>
<td>P=0.80</td>
</tr>
<tr>
<td>Post-pyloric feeding</td>
<td>6 RCT, N=582, ( I^2 )=0%</td>
<td>0.93 (0.67-1.28)</td>
<td>P=0.64</td>
</tr>
<tr>
<td>Probiotic / Symbiotic</td>
<td>13 RCT, N=1569, ( I^2 )=23%</td>
<td>0.89 (0.66-1.18)</td>
<td>P=0.41</td>
</tr>
<tr>
<td>Early tracheal feeding</td>
<td>6 RCT, N=1000, ( I^2 )=43%</td>
<td>0.85 (0.64-1.12)</td>
<td>P=0.24</td>
</tr>
<tr>
<td>SDD</td>
<td>30 RCT, N=10227, ( I^2 )=16%</td>
<td>0.84 (0.76-0.92)</td>
<td>P=0.0003</td>
</tr>
<tr>
<td>Early enteral feeding</td>
<td>1 RCT, N=150, ( I^2 )=16%</td>
<td>0.75 (0.42-1.35)</td>
<td>P=0.34</td>
</tr>
<tr>
<td>Phytotherapy</td>
<td>1 RCT, N=36, ( I^2 )=NA</td>
<td>0.67 (0.13-3.53)</td>
<td>P=0.65</td>
</tr>
<tr>
<td>Overall</td>
<td>145 RCT, N=37156, ( I^2 )=4%</td>
<td>0.95 (0.92-0.99)</td>
<td>P=0.02</td>
</tr>
</tbody>
</table>

Prevention of pneumonia
30 years of failed fight against bacteria

Pneumocare study
n=1800 patients, 35 hospitals (2018)

Roquilly et al. (unpublished)
Treatment of pneumonia

Clinical / bacterial failure

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Pneumocare study
n=1800 patients, 35 hospitals (2018)

<table>
<thead>
<tr>
<th></th>
<th>Before reco. (N=600)</th>
<th>After reco. (N=669)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>99 (66%)</td>
<td>117 (75%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Death at day 28</td>
<td>104 (17%)</td>
<td>113 (17%)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

*Figure 2: Clinical cure rates at test-of-cure visit*

Data are number of patients with clinical cure (%). Dashed line indicates non-inferiority margin of -12.5%.
Knowledge on respiratory microbiota

any potential to improve our understanding?
Respiratory microbiota

What can we learn? – healthy lungs

NP: nasopharynx
OP: oropharynx
HAP result from a reduction of the microbiome diversity 
*rather than exogeneous input?*

*Kelly et al. microbiome 2016*

*Dickson et al. Lancet Respir med 2016*
Treatment of pneumonia considering of the “hidden bacteria”

Exemple of a viral pneumonia (Respiratory Syncitial Virus Infection)

de Steenhuijsen Piters et al. AJRCCM 2016
The respiratory microbiota challenges the concept of the “dominant bacteria”

Exemple of a non tuberculous mycobacteria

Sulaiman et al. Eur Respir J 2018

Kudzu
(From Dickson et al. Eur Respir J 2018)
Treatment of pneumonia targeting the “ecological niche”

Faecium + Thyphimurium infection

Rangan et al. Science 2016
The respiratory microbiota should be interpreted with host-status data.

Man et al. Lancet Respir Med 2019

Langelier PNAS 2018
Physiopathology of HAP

time to change the hard-drive?

In couples quarrels, no party is innocent!

Restauration of the symbiosis
Hospital acquired pneumonia
... historical view

Roquilly et al. Lancet respir Med 2019
Respiratory microbiome and treatment of pneumonia

... «historical» treatment

Roquilly et al. Lancet Respir Med 2019
But we need to do better and respiratory microbiome has blown our comprehension.
Knowledge on respiratory microbiota

Is it possible to shape the microbiome as a therapy?
Modulation of the microbiome in patients

microbiota transplantation

Table 2. Outcome Measures Comparing Fecal Microbial Transplantation With Placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>FMT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission, n (%)</td>
<td>2 (5)</td>
<td>9 (24)</td>
<td>.03</td>
</tr>
<tr>
<td>Clinical response, n (%)</td>
<td>9 (24)</td>
<td>15 (39)</td>
<td>.16</td>
</tr>
<tr>
<td>Full Mayo score</td>
<td>6.34</td>
<td>6.09</td>
<td>.42</td>
</tr>
<tr>
<td>IBDOQ score</td>
<td>149.38</td>
<td>152.13</td>
<td>.44</td>
</tr>
<tr>
<td>EQ-5D score</td>
<td>70.07</td>
<td>68.52</td>
<td>.99</td>
</tr>
<tr>
<td>CRP, mg/L (n = 17 placebo, n = 15 FMT)</td>
<td>3.3 ± 3.4</td>
<td>4.9 ± 5.9</td>
<td>.38</td>
</tr>
<tr>
<td>ESR, mm/h (n = 17 placebo, n = 15 FMT)</td>
<td>13.1 ± 11.2</td>
<td>15.9 ± 17.0</td>
<td>.59</td>
</tr>
<tr>
<td>Proportion with high ESR, n (%)</td>
<td>4 (24)</td>
<td>3 (20)</td>
<td>1.0</td>
</tr>
<tr>
<td>Proportion with high CRP, n (%)</td>
<td>5 (29)</td>
<td>2 (13)</td>
<td>.40</td>
</tr>
<tr>
<td>Patients with serious adverse events n (%)</td>
<td>2* (5)</td>
<td>3* (8)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Modulation of the microbiome

specific drug intervention? Tungstate treatment

Zhu et al. Nature 2018
Modulation of the microbiome shaping the microbiome through immune modulation?
IL12+ Dendritic cells, bacterial control and HAP
Long lasting reprogramming independent from the pathogen

Roquilly et al. Immunity 2017
Treatment of pneumonia

What can microbiome analysis currently afford to the clinicians?
Respiratory microbiome and treatment of pneumonia

... a rational for limitation of Abttt?

Figure 2: Effect on mortality of prescribing empirical antimicrobial therapy according to guidelines

Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis

Emelie C Schuts, Marlies E J L Hulscher, Johan W Mouton, Cees M Verduin, James W T Cohen Stuart, Hans W P M Overdiek, Paul D van der Linden, Stephanie Natsch, Cees M P M Hertogh, Tom F W Wolfs, Jeroen A Schouten, Bart Jan Kullberg, Jan M Prins
Treatment of pneumonia

What can microbiome analysis **currently** afford to the clinicians?

- « low-cost microbiome » PCR multiplex for gene of resistance?
- Rational to limit antimicrobial therapy
- New theories...

**Promises of the microbiote?**

Symbiosis approaches and the end of antimicrobial resistance?
Respiratory microbiome and treatment of pneumonia

... a therapeutical revolution

Roquilly et al. Lancet Respir Med 2019