Complications after stroke: ‘Thus bad begins and worse remains behind’*

* Shakespeare; Hamlet, Act 3, Scene 4. The Queen's closet
Beyond the stroke unit: Targeting of complications after stroke will be the next big thing....

- Therapeutic reperfusion strategies are highly successful but only a minority of patients benefit
- Pharmacological brain protection is elusive
- Complications after stroke are frequent, highly relevant for outcome, and only partially understood
Immune system
Infection

Metabolism
Waisting / Sarcopenia

Gut and Brain
Brain immune system interactions after stroke

1a. CNS injury → 2. Release of immune modulators →

Blood vessel → Adrenal gland → Nerve terminal →

Noradrenaline, glucocorticoids, acetylcholine

Neutrophil → Natural killer cell → T-helper cell 1 → T-helper cell 2 → Macrophage →

Apoptosis → Phagocytic activity, NO → Cytotoxic activity → IFNγ → IL-4 → IL-10

Phagocytic activity, MHC II, Pro-inflammatory cytokines

3. Immunodepression →

1b. Dysphagia, aspiration, bladder dysfunction + 4. Breakdown of immunological barriers → 5. Infection

6. Worsening of outcome
Immunodepression after stroke

**Lymphocytes**

<table>
<thead>
<tr>
<th>Time after MCAO</th>
<th>Sham</th>
<th>14h</th>
<th>2d</th>
<th>5d</th>
<th>14d</th>
<th>42d</th>
</tr>
</thead>
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<td></td>
<td>0</td>
<td>2.5</td>
<td>5.0</td>
<td>7.5</td>
<td>***</td>
<td>***</td>
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</tbody>
</table>

**Monocytes**

<table>
<thead>
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<th>Time after MCAO</th>
<th>Sham</th>
<th>14h</th>
<th>2d</th>
<th>5d</th>
<th>14d</th>
<th>42d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.4</td>
<td>0.8</td>
<td>1.2</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Vogelgesang et al. Stroke 2007
**Preventive Antibiotics for Infections in Acute Stroke**

*A Systematic Review and Meta-analysis*

_Diederik van de Beek, MD, PhD; Eelco F. M. Wijdicks, MD, PhD; Frederique H. Vermeij, MD; Rob J. de Haan, PhD; Jan M. Prins, MD, PhD; Lodewijk Spanjaard, MD, PhD; Diederik W. J. Dippel, MD, PhD; Paul J. Nederkoorn, MD, PhD_

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**infections**

- Chamorro et al\(^6\)
- Lampl et al\(^8\)
- Harms et al\(^9\)
- Schwarz et al\(^10\)
- Meta-analysis

**mortality**

- Chamorro et al\(^6\)
- Lampl et al\(^8\)
- Harms et al\(^9\)
- Schwarz et al\(^10\)
- Meta-analysis

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**Conclusions:** In adults with acute stroke, preventive antibiotics reduced the risk of infection, but did not reduce mortality. The observed effect warrants evaluation of preventive antibiotics in large stroke trials.

*Arch Neurol.* 2009;66(9):1076-1081
Catabolism after stroke

Tissue wasting after stroke - day 7

**Delta body weight [g]**

- Control
- Sham
- Stroke

**Delta fat mass [g]**

- Control
- Sham
- Stroke

**Delta lean mass [g]**

- Control
- Sham
- Stroke

* Doehner, Springer, Dirnagl
Muscle cell death after stroke

MCAO mouse model
Gastrocnemius muscle
Contralateral leg
day 7 post stroke

** vs control
#, vs sham

Caspase-3 activity

Caspase-6 activity

Doehner, Springer, Dirnagl
Brain gut interactions after stroke

- Immuno-depression
- ANS HPA
- Antibiotics
- Infection Sepsis
- Systemic metabolism
- Cardiovasc. system
- Motility Permeability Mucus
- Enteric micro biome
- GALT, ENS
- Metabolites
- Peptides, Monoamines
- Translocation
- Immunomodulation
- SCFAs
- VIP, Natriuretic peptide
- Th17, Tregs Cytokines
- Bacteria
- PAMPs
- CNS lesion
- Inflammation, Autoaggression, Depression
- CBF reduction, ....
- Brain gut interactions after stroke
- CNS lesion
- Enteric micro biome
- GALT, ENS
- Metabolites
- Peptides, Monoamines...
Gut microbiota change after experimental stroke
Gnotobiotic mice die after stroke

- Bacteria; Proteobacteria
- Bacteria; Firmicutes (Gram +)
- Bacteria; Bacteroidetes (Gram -)

Survival proportions over time:
- Gnotobiotic MCAO
- Gnotobiotic sham
- SPF AB MCAO
- SPF MCAO

PCR with bar-coded primers targeting V1-V3 and V6-V8 hypervariable regions of 16S rRNA
The Human Body

- pelvis
- brain
- kidneys
- bladder
- stomach
- liver
- muscles
- arteries
- bones
- joints

Immuno-depression, ANS, HPA, Motility, Permeability, Mucus...

Anti-biotics, GALT, ENS, Enteric microbiome

Infection, Sepsis, Inflammation, autoaggression, depression, mood/behavior, neurotransmission, CBF reduction, ...

Translocation, Immunomodulation

Metabolites, Peptides, Monoamines ...

Systemic metabolism, Cardiovascular system

Bacteria, PAMPs, VIP, Natriuretic peptide ...

SCFAs ...

CNS lesion, Th17, Tregs, Cytokines ...