Stroke-associated pneumonia: aetiology and diagnostic challenges

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Scope of the problem

Stroke-associated pneumonia (SAP):

• **Common:** around 10% but >30% in those at greatest risk

• **Adversely impacts on outcome:** mortality increase 2-6 fold

• **Expensive:** almost doubles length of stay

• **Does everyone with suspected SAP need antibiotics?**

• **Urgent need for improved diagnosis and antibiotic stewardship**

Pathophysiology of SAP

INFECTIOUS SUBSTRATE

ORO-PHARYNGEAL ASPIRATION

PULMONARY CLEARANCE

TRANSIENT IMMUNE-SUPPRESSION
- Innate
- Adaptive
Stroke severity and SAP......

Bray B, unpublished data

SSNAP cohort
n=33,935
148 hospitals
Risk factors for SAP: dysphagia & aspiration

- Dysphagia is a consistent risk factor (RR 3.17; 95% CI 2.07-4.87)
- Confirmed aspiration RR 11.56; 95% CI 3.36-39.77)
- “Modern-day” stroke unit care:

<table>
<thead>
<tr>
<th>Registry</th>
<th>n</th>
<th>Dysphagia (%)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>German</td>
<td>15 335</td>
<td>24</td>
<td>2.64 (2.21-3.15)</td>
</tr>
<tr>
<td>Chinese</td>
<td>8 820</td>
<td>10</td>
<td>1.9 (1.62-2.24)</td>
</tr>
</tbody>
</table>

Cellular immune suppression

**MONOCYTE FUNCTION**

- LPS-stimulated TNF-α production (ng/million monocytes)
- **p<0.01**

**B-CELL FUNCTION**

- IgM concentration (log mg/ml)
- **p<0.01**

*Emsley, Smith et al, 2007; McCulloch, Smith et al, 2017*
A common scenario

- 78 year-old man, LMCA territory infarction, NIHSS=16; NBM
- Day 2: temperature 37.6°C; “chesty”
- Examination: GCS 12/15; transmitted sounds throughout; RR 18/min
- CRP 11mg/L (from 8mg/L)
- Total WBC count 12 from 9

ANTIBIOTICS?
The spectrum of acute respiratory illness in stroke

- BACTERIAL INFECTIVE SYNDROME
  +/− infiltrates/ consolidation

- VIRAL SYNDROME

- ASPARATION PNEUMONITIS

- MUCOUS PLUGGING/ COLLAPSE

- OTHER
  e.g. PULMONARY EMBOLISM
  e.g. PULMONARY OEDEMA

*****??NEED FOR ANTIBIOTICS??*****

PROGNOSIS

OTHER SPECIFIC MANAGEMENT
(e.g. anticoagulation)
Which organisms cause SAP?

<table>
<thead>
<tr>
<th></th>
<th>WMA (%)</th>
<th></th>
<th>Range (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAP</td>
<td>VAP</td>
<td>HAP</td>
<td>CAP</td>
</tr>
<tr>
<td>Gram (+) cocci</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>10 (0-36)</td>
<td>20-32</td>
<td>27-37</td>
<td>3-14</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>4 (0-11)</td>
<td>&lt;3</td>
<td>2-3</td>
<td>35-80</td>
</tr>
<tr>
<td>Gram (-) bacilli</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>13 (0-51)</td>
<td>7-10</td>
<td>8-11</td>
<td>3-6</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>9 (0-22)</td>
<td>3-5</td>
<td>5-10</td>
<td>6-12</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>6 (0-12)</td>
<td>21-27</td>
<td>19-22</td>
<td>4-9</td>
</tr>
<tr>
<td><em>H. influenza</em></td>
<td>2 (0-12)</td>
<td>NR</td>
<td>1-4</td>
<td>5-6</td>
</tr>
<tr>
<td><em>E. cloacae</em></td>
<td>2 (0-10)</td>
<td>6-9</td>
<td>6-9</td>
<td>NR</td>
</tr>
</tbody>
</table>

Kishore et al, 2017 (submitted)
How is SAP diagnosed?

64 studies (around 640,000 patients)
• 9% - no record of criteria
• 19% - unspecified clinician diagnosis
• 41% - objective criteria (ad hoc)
• 31% - published respiratory/societal criteria

Kishore et al, 2015
Does variation in diagnostic approach influence frequency of pneumonia?

- Pneumonia occurred in 14.3% (95% CI 13.2%–15.4%)
- Substantial level of observed heterogeneity ($I^2=98.9\%$)
- This was not explained by stratifying for other potential confounders

<table>
<thead>
<tr>
<th>Author</th>
<th>Criteria</th>
<th>Proportion (%)</th>
<th>Mean age (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeh, 2011</td>
<td>CDC</td>
<td>56.8</td>
<td>67.6</td>
</tr>
<tr>
<td>Warnecke, 2009</td>
<td>Mann</td>
<td>16.3</td>
<td>67.7</td>
</tr>
<tr>
<td>Harms, 2013</td>
<td>CDC</td>
<td>31.3</td>
<td>69.9</td>
</tr>
<tr>
<td>Zhang, 2012</td>
<td>Mann</td>
<td>30.1</td>
<td>70.2</td>
</tr>
<tr>
<td>Steinhagen, 2009</td>
<td>CDC</td>
<td>65</td>
<td>72.3</td>
</tr>
<tr>
<td>Miles, 2013</td>
<td>Mann</td>
<td>26.6</td>
<td>77.6</td>
</tr>
<tr>
<td>Suntrup, 2012</td>
<td>Mann</td>
<td>30</td>
<td>71.1</td>
</tr>
<tr>
<td><strong>Pooled (Selected)</strong></td>
<td></td>
<td><strong>35.9</strong></td>
<td></td>
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Kishore et al, 2015
Observed SAP prevalence is highly variable in SSNAP

- $n=230,838$; 186 hospitals in SSNAP (2013-16)
- **Predicted prevalence** estimated using multifactorial model and compared with **observed prevalence**

  - Lowest 20 units, obs 2.3% (95% CI 1.7-2.9),
  - Highest 20 units, obs 18.8% (95% CI 17.2-20.4%)

*Bray B, et al (unpublished data)*
Towards standardised diagnostic criteria?

At least 1 of the following:

1. Fever (>38°C) with no other recognized cause
2. Leukopenia (<4000 WBC/mm³) or leukocytosis (>12 000 WBC/mm³)
3. For adults ≥70 y old, altered mental status with no other recognized cause

And at least 2 of the following:

1. New onset of purulent sputum, or change in character of sputum over a 24 h period, or increased respiratory secretions, or increased suctioning requirements
2. New onset or worsening cough, or dyspnea, or tachypnea (respiratory rate >25/min)
3. Rales, crackles, or bronchial breath sounds
4. Worsening gas exchange (eg, O₂ desaturation [eg, \( \text{Pa}_2/\text{FiO}_2 \leq 240 \)], increased oxygen requirements*)

And ≥2 serial chest radiographs† with at least 1 of the following:

New or progressive and persistent infiltrate, consolidation, or cavitation

Note: In patients without underlying pulmonary or cardiac disease, 1 definitive chest radiograph is acceptable

Smith et al, 2015
Algorithm-based diagnosis improves diagnostic performance..........

- Expert blinded adjudication panel (STROKE-INF)
- Fever in 75%; infiltrates on CXR in 37%
- A structured algorithm improves diagnostic performance compared to “physician-diagnosis”

<table>
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<tr>
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<th>Algorithm diagnosis</th>
<th>“Physician-diagnosis”</th>
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<td>Sensitivity</td>
<td>72 (64-80)%</td>
<td>65 (56-73)%</td>
</tr>
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<td>Specificity</td>
<td>97 (96-98)%</td>
<td>90 (88-92)</td>
</tr>
<tr>
<td>False positive rate</td>
<td>24%</td>
<td>52%</td>
</tr>
<tr>
<td>False negative rate</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Diagnostic OR</td>
<td>80 (42-136)</td>
<td>18 (12-27)</td>
</tr>
</tbody>
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Kalra et al, 2016
Can blood biomarkers detect early SAP?

Plasma CRP; AUC 0.87 (95% CI 0.80-0.95)  
Plasma CRP; AUC 0.83 (95% CI 0.72-0.93)

ANY INFECTION

STROKE-ASSOCIATED PNEUMONIA

Warusevitane et al, 2016; Bustamante et al, 2016
Elevated CRP increases diagnostic accuracy of algorithm

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<th>Algorithm + (Fever or CRP)*</th>
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<tr>
<td>False negative rate</td>
<td>4%</td>
<td>1%</td>
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*Algorithm + (Fever or CRP):*

1. Temp $\geq 38.0^\circ C$ or $\geq 37.5^\circ C$ on two consecutive measurements OR CRP $>30$ mg/dL AND
2. Respiratory rate $\geq 20 / \text{min}$ OR cough and breathlessness OR purulent sputum AND
3. White cell count $>11.0 \times 10^9/\text{L}$ OR new chest infiltrates on X-ray OR positive sputum culture/microbiology OR positive blood culture

Kalra et al, submitted
Exhaled breath biomarkers for discriminating SAP?
Is pulmonary CT a useful diagnostic reference standard for SAP?

51 yo male, NIHSS=25
NBM
Day 3:
• Peak RR 22/min
• Peak Temp 37.8°C
• Lowest sats 95%
• Transmitted chest signs
• WBC 11.3X10⁹/L
• Peak CRP 19mg/L

CXR (13h later)

Chest CT (13h later)

73 yo male, NIHSS=19
NBM
Within hours of admission:
• Peak RR 19/min
• Peak Temp 37.6°C
• Lowest sats 94%
• WBC 8.3X10⁹/L
• CRP<4mg/L

CXR admission

Chest CT (41h later)
Summary

• Pathophysiology of acute lower respiratory tract syndrome
• Clinical, laboratory and prognostic correlates
• Validation of diagnostic algorithms for SAP

_BUT a move toward “personalised medicine”_

• Defining ANTIBIOTIC-requiring (and responsive) syndromes
• Emphasis on improved antibiotic stewardship
Acknowledgements

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