Microbiological etiologies of pneumonia complicating stroke: A systematic review

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**Itemized list of Tables and Figures**

Table 1: Study characteristics

Table 2: Frequency of isolated organisms in pneumonia complicating stroke in comparison to other forms of pneumonia

Figure 1: Flow diagram of systematic search methodology

Figure 2: Forest plot of pneumonia frequency according to stroke subtype

Fig 3: Proportion of studies identifying the eight most commonly isolated organisms

Online only Table I: Search Terms

Online only Table II: Eligibility criteria

Online only Table III: Patient characteristics

Online only table IV: The eight most commonly isolated organisms in positive cultures (%) in the included studies

Online Only Table V: Definition of pneumonia terminologies

Online only Figure I: Funnel plot

Key words: stroke, pneumonia, infection, bacteria, systematic review
Abstract

Background and Purpose
Identifying the causal pathogens of pneumonia complicating stroke is challenging and antibiotics used are often broad spectrum, without recourse to the microbiological etiology. We aimed to review existing literature to identify organisms responsible for pneumonia complicating stroke, prior to developing a consensus based approach to antibiotic treatment.

Methods
A systematic literature review of multiple electronic databases using pre-defined search criteria was undertaken, in accordance with Cochrane and PRISMA guidance. Published studies of hospitalized adults with ischemic stroke (IS), intracerebral hemorrhage (ICH), or both, which identified microbiological etiologies for pneumonia complicating stroke up to 1st January 2017, were considered. Analysis included summary statistics and random-effects meta-analysis where appropriate.

Results
15 studies (40% IS, 60% IS and ICH) involving 7968 patients were included. Reported occurrence of pneumonia varied considerably between studies (2% to 63%) with a pooled frequency of 23% (95% Confidence Interval, 14%-34%; \( I^2 = 99\% \)). Where reported (60%), the majority of pneumonia occurred within 1 week of stroke (78%). Reported frequency of positive culture data (15% to 88%) varied widely. When isolated, aerobic Gram negative bacilli (AGNB, 38%) and Gram positive cocci (GPC, 16%) were most frequently cultured; commonly isolated organisms included Enterobacteriaceae (21.8%: Klebsiella pneumoniae, 12.8% and Escherichia coli, 9%), Staphylococcus aureus (10.1%), Pseudomonas aeruginosa (6%), Acinetobater baumanii (4.6%) and Streptococcus pneumoniae (3.5%). Sputum was most commonly used to identify pathogens, in isolation (40%) or in conjunction with tracheal aspirate (15%) or blood culture (20%).
Conclusions

Whilst analysis was limited by small and heterogeneous study populations, limiting determination of microbiological causality, this review suggests AGNB and GPC are frequently associated with pneumonia complicating stroke. This supports the need for appropriately designed studies to determine microbial etiology and a consensus based approach in antibiotic usage and further targeted antibiotic treatment trials for enhanced antibiotic stewardship.
Introduction

Pneumonia complicating stroke occurs frequently, independently increasing mortality 3-fold and increasing hospitalisation costs, length of stay and likelihood of poor outcome in survivors.\textsuperscript{1,2} While diagnosis remains challenging, the Pneumonia In Stroke ConsEnSus (PISCES) group recommended that “Stroke-Associated Pneumonia” (SAP) was the preferred diagnostic terminology covering the spectrum of lower respiratory tract infections complicating stroke within the first week and hospital acquired pneumonia (HAP) after 1 week.\textsuperscript{3} Further, acknowledging the limitations of current biomarkers and accessibility of microbiological samples, modified Centers for Disease Control and Prevention (CDC) criteria were proposed to aid clinicians and researchers in diagnosing SAP in non-ventilated patients.\textsuperscript{3}

Once SAP is suspected or diagnosed, however, use of antimicrobials vary and are either clinician dependant or guided by local policy for community acquired pneumonia (CAP) or HAP.\textsuperscript{4} Antibiotics used are often broad spectrum, without recourse to the microbiological etiology. The ability to better inform choice of antibiotic therapy in SAP, based on defined or likely microbial etiology, might lead to improved outcomes and enhanced antibiotic stewardship. Identifying microbiological etiology in non-ventilated stroke patients is challenging, due to the difficulties in obtaining direct samples from the lower respiratory tract (impaired cough and limited expectoration) and lack of applicable invasive procedures such as bronchoscopy in conscious stroke patients, in addition to reliance on sputum samples with the inherent risk of contamination from oropharyngeal commensal organisms.\textsuperscript{5} While bacterial colonisation of the oropharynx could potentially limit interpretation of positive sputum samples, poor diagnostic sensitivity of microbiological culture methods such as blood culture specimens (positive in <10%)\textsuperscript{6} and pleural fluid aspirate limit their use. Most importantly, prior use of antibiotics hampers the sensitivity of microbiological techniques and
current stroke guidelines do not recommend early nonselective preventive antibiotic treatment. As part of the ongoing PISCES collaboration, we sought to identify microbiological etiologies for pneumonia complicating stroke through a systematic review of available literature to help inform a planned consensus based approach for antibiotic treatment.
Methods
A systematic literature review was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Cochrane guidance. The authors declare that all supporting data are available within the article [and its online supplementary files].

Data sources and searches
Searches were undertaken in MEDLINE (NIHL interface, 1946-1st January 2017), EMBASE (NIHL interface, 1947-1st January 2017) and Cochrane Central Register of Controlled Trials (Wiley interface, current issue) using pre-defined search criteria and terms (Online only Table I). Hand searching of reference lists for additional eligible articles was also carried out, and the members of PISCES group were invited to provide any other potentially eligible articles. Non-English full-text articles were translated and considered for inclusion if eligibility criteria were met.

Study selection
Published studies of hospitalized adults with ischemic stroke, intracerebral hemorrhage (ICH), or both, which identified any potential pathogen responsible for pneumonia complicating stroke, or which had used objective criteria for diagnosing pneumonia complicating stroke (but not reported causative organisms) were independently screened for eligibility by two reviewers (AKK and CJS), using the study title and abstract (Online Only Table II). For those studies which used objective criteria for pneumonia but which hadn’t reported causative pathogens, corresponding authors were contacted by e-mail for unpublished information on pathogens responsible for pneumonia if available. Lead or corresponding authors of studies under consideration were also contacted by e-mail to resolve any issues relating to assessment of eligibility or data extraction. Discrepancies relating to
eligibility or data extraction were resolved by a consensus discussion between the same two study investigators.
Data Extraction

Data were independently extracted by two reviewers (AKK and AV) and included study design, sample size, publication status and demographical data (year of study, country of study, clinical environment), stroke type (ischemic, ICH or both), interval from admission to diagnosis of pneumonia, frequency of pneumonia, criteria used for pneumonia diagnosis, mean age, mean National Institutes of Health Stroke Scale (NIHSS) score, cardiovascular risk profile, swallow screening, proportion of nil oral/tube-fed, type of culture specimen (sputum, blood culture, pleural or tracheal aspirate, serology), organisms identified and antibiotic usage (prophylactic and/or treatment). Reported data in the identified eligible publications were supplemented by contacting corresponding or lead authors where necessary.

Study Outcomes

The primary outcomes were the frequencies of the most commonly isolated microbial species among the included studies and the proportion of these organisms responsible for pneumonia. Secondary outcomes included: (1) The frequency of positive microbiological cultures and proportions of isolated organisms in positive cultures; (2) Relationships between microbial species and time interval from stroke onset to pneumonia; (3) Frequency of identified pathogens across different geographical regions.

Risk of Bias and Quality Assessment

We anticipated inclusion of both randomized controlled trials (RCTs) and non-randomized studies that had pneumonia as an outcome but were not primarily designed to identify microbiological etiologies. Hence, a formal statistical tool for assessing bias or the individual quality of the studies was not used as we were less concerned about the design or the effects
of interventions used in the individual studies for this review. However, as cultures for organisms would only be undertaken when pneumonia is suspected or diagnosed, heterogeneity among studies reporting pneumonia was assessed using random-effects model. Heterogeneity was quantified with the $I^2$ statistic as reported in a previous study\textsuperscript{1}. This measures the proportion of variation ascribed to excess heterogeneity beyond that anticipated by chance. Because of anticipated heterogeneity between studies reporting pneumonia, further quantitative meta-analysis on bacterial etiology was not undertaken. Summary statistics were instead undertaken to describe primary and secondary outcomes. A post-hoc, descriptive comparison of the frequency of pathogen species detected in pneumonia complicating stroke with other forms of pneumonia (e.g. CAP, HAP) was also undertaken.
Results

Search Results

A total of 6231 unique publications were identified by electronic searches and through the PISCES collaborators (Figure 1). Fifteen fully published studies were finally considered eligible for inclusion.\textsuperscript{11-25}

Study and patient characteristics (Table 1, Online only Table III)

The studies included retrospective (40\%) or prospective (33\%) observational studies and randomised trials (27\%). 54\% were European or North American studies; 46\% were performed in South East Asia or Asia Pacific region. The majority of the studies were conducted on the acute stroke unit (72\%). Other clinical environments included rehabilitation wards (7.5\%) and intensive care units (15\%). The mean age of the patients in individual studies ranged from 58 to 83 years. Baseline stroke severity (NIHSS) was reported in only 73\% of studies, with a mean ranging from 5 to 19. Three studies were RCTs of prophylactic antibiotics.\textsuperscript{11,15,25} Two studies were exclusively in nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tube fed participants.\textsuperscript{21,23} 33\% of the studies included mechanically ventilated patients. Entry criteria to the studies varied widely, with only 1 study having the identification of microbiological etiology for pneumonia complicating stroke as a primary objective \textsuperscript{12}; 2 studies excluded patients on immunosuppressive medication, with prior malignancy, or other forms of immunosuppression prior to stroke.\textsuperscript{11,22} Other co-morbidities and cardiovascular risk factor profiles were reported varyingly (Online only Table III).

Diagnosis and frequency of pneumonia
Reported occurrence of pneumonia varied between studies (2% to 63%). Pooled frequency of reported pneumonia was 23% (95% CI 14%-34%; $I^2=99\%$; Figure 2). Substantial heterogeneity was noted even when adjusted to stroke subtype (ischemic stroke, $I^2=96\%$; mixed ischemic stroke and ICH, $I^2=99\%$) or geographical location (Asian studies, $I^2=97.4\%$ and European or North American studies, $I^2=97.8\%$). When reported (60%), the majority of pneumonia occurred within 1 week of stroke (78%). The Centers for Disease Control and Prevention (CDC) criteria (45%) and ad hoc objective criteria (40%) were the most commonly used objective criteria to diagnose pneumonia.

**Microbiological etiology**

Sputum culture was most commonly used to identify pathogens either in isolation (40%), or in conjunction with tracheal aspirate (15%), and blood culture (20%). Reported frequency of positive culture data (15% to 88%) varied considerably. Only 3 studies described the culture methods used to identify organisms. 4,13,25 No bacterial growths were reported in 2 studies (15% and 67%).12,25 Identification of bacterial species in positive cultures varied between studies (Online only table IV). No pathogen was identified in every study, although *Staphylococcus aureus* was identified in positive cultures in 14 of 15 (93%) studies whilst *Acinetobacter baumanii* was identified in positive cultures in only 6 of 15 (40%) studies (Online only Table IV and Figure 3). Antibiotic susceptibility was not reported in the majority of studies; no studies reported any viral or other atypical organisms, although it was unclear if these were tested for.

The proportions of microbial species associated with pneumonia also varied between studies. Overall, aerobic gram negative bacilli (AGNB, 38%) and gram positive coci (GPC, 16%) were most frequently responsible for pneumonia; commonly isolated phenotypes (Table 2) included *Enterobacteriaceae* (21.8%: *Klebsiella pneumoniae*, 12.8% and *Escherichia coli*,...
9%), S. aureus (10.1%), Pseudomonas aeruginosa (6%), Acinetobacter baumanii (4.6%) and Streptococcus pneumoniae (3.5%). Studies that included patients at relatively higher-risk of pneumonia i.e. exclusively dysphagic patients or intensive care studies \(^{15,17,19,21}\) were found to have a high proportion of AGNB and S. aureus, in comparison to lower risk studies (unselected stroke patients with \(\leq 15\) % ICH and/or mean NIHSS\(\leq 5\), Table 1). It was not possible to explore relationships between timing of pneumonia or it’s severity with individual organisms because of insufficient data.

We compared the frequencies of the 8 most commonly identified organisms in pneumonia complicating stroke with those of hospitalised CAP, VAP and HAP (Table 2) from recent reviews of literature (terminologies defined in Online only Table V). \(^{26,27,28,29}\) Geographical variations in bacterial etiology were observed in our study as seen as in the other reviews. In particular, gram-negative opportunistic pathogens such as P. aeruginosa and A. baumanii were more commonly isolated in South Asia or Asia Pacific regions (75% &100%) as opposed to Western Europe or the USA (28% & 0%). Several organisms were reported with comparable frequency (range) to VAP or HAP (e.g. K. pneumoniae, E. coli). S. pneumoniae, the organism most frequently identified in CAP, was detected less often in pneumonia complicating stroke. The organisms most often reported in HAP and VAP (S. aureus and P. aeruginosa) were also identified less frequently in pneumonia complicating stroke.

**Antibiotic usage**

Only 4 studies (24%) identified antibiotics used to treat pneumonia complicating stroke. \(^{13,15,20,25}\) The antibiotic of choice was determined by local hospital policy and commonly included \(\beta\)-lactam (including ureidopenicillin and 2\(^{nd}/3^{rd}\) generation cephalosporins) antibiotics +/- \(\beta\) lactamase inhibitors and 2\(^{nd}/3^{rd}\) generation fluoroquinolones and was always initiated prior to obtaining antibiotic sensitivities. Only 1 study reported the
proportion of patients with pneumonia receiving antibiotics, the number of pneumonia episodes and functional outcomes following treatment with antibiotics.\textsuperscript{25}

**Discussion**

Pneumonia occurs most frequently during the first week after stroke (SAP) \textsuperscript{1,3} and may therefore include microbiological etiologies associated with hospitalized CAP or HAP. Our study suggests that AGNB (e.g. *K. pneumoniae*, *E. coli* and *P. aeruginosa*) and GPC (e.g. *S. aureus* and *S. pneumoniae*) were associated with the majority of pneumonia complicating stroke when cultures were sent. A recent review suggested that close to 80% of hospitalized CAP were caused by *S. pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *H. influenzae*.\textsuperscript{26} The same review found that approximately 50% of HAP was caused by *S. aureus* and 35% by *Pseudomonas* species, *Klebsiella* species, *Escherichia* species, *Acinetobacter* species and *Enterobacter* species.\textsuperscript{26} The spectrum of identified organisms in our study appear to be more closely related to HAP than ventilator-associated pneumonia (VAP) or hospitalised CAP, although antibiotic susceptibilities were not reported in most of the included studies. Further, none of the included studies reported the results of investigations for viral or atypical pathogens, or even if they were done. Whilst our study is a comprehensive systematic literature research and collaboration within the PISCES group, our findings need to be interpreted with caution due to several inherent limitations.

First, there was marked heterogeneity between the included studies, which likely contributed to the variation in identified organisms and their relative contributions to pneumonia. For example, studies undertaken in the critical care environment might yield a higher proportion of organisms overall because of access to more direct sampling (e.g. bronchoscopy or tracheal aspirate) and also more frequent etiologies due to organisms typical of HAP or VAP.
We could not identify any single factor that fully explained the high heterogeneity \((I^2=99\%)\). Although both stroke type and our prospective risk categorisation (Table 2) showed anticipated differences in pneumonia frequency, even within our ‘very high risk’ category frequency ranged from 14% to 63% (Figure 2), and heterogeneity remained extremely high \((I^2>90\%)\) within each risk category. The asymmetry of the scatterplots seen in the funnel plot also reflects the high heterogeneity among studies which was not corrected even when subgroup analysis was undertaken with pneumonia risk stratification (Online only Figure I). 66% of the included studies in our review were deemed high or very high risk (Table I) for developing pneumonia reflecting the higher frequency of pneumonia seen in this review as opposed to a previous systematic review.\(^1\) Apart from patient selection, the overall high heterogeneity also reflects varying geographical location, different study designs, inclusion criteria, timing from stroke onset to sampling, and differences in standardised outcome definition for SAP. We were unable to differentiate pneumonia and causative pathogens for patients admitted from institutional environments such as nursing homes, which may have also contributed to heterogeneity. Stroke registries, not routinely expected to collect and maintain data on microbiological etiology, were also excluded unless specific mention was made regarding determining bacterial etiology, which could have contributed to selection bias and heterogeneity. The variation in approach to diagnosis of pneumonia complicating stroke is well-recognised,\(^1\) and may therefore influence the threshold for sending microbiological samples, contributing to verification bias. Second, only one of the studies was primarily designed to identify the microbial etiology of pneumonia complicating stroke,\(^12\) whilst the remaining studies collected microbiological data when available within the context of their individual study objectives. It is reasonable to assume that the proportion of positive cultures could be higher if culture samples were sent systematically in all suspected cases of pneumonia. However, compared to other clinical settings (e.g. CAP or
VAP), consistently obtaining sputum samples in non-ventilated stroke patients is challenging and alternative strategies (e.g. bronchoscopy for VAP) are limited. Third, it was unclear amongst most studies as to when culture samples were sent in relation to onset of stroke and suspicion or diagnosis of pneumonia. Although the majority of pneumonia in our review occurred within a week of stroke symptom onset, it was not possible to further explore microbiological etiologies in relation to timing of pneumonia relative to stroke symptom onset. Whilst one could hypothesise that organisms commonly associated with CAP are most likely causal in early SAP (≤72 hours), and those associated with HAP causal in SAP beyond 72h, we were unable to confirm or refute this finding because of limited data in the individual studies. Our observations of an apparent low yield of CAP organisms, and higher yield of HAP organisms could be at least in part due to sampling bias beyond 48-72h after stroke onset. Fourth, microbiological methods used to collect sputum samples, number of specimens sent when pneumonia was diagnosed, delays in analysing samples if any, and laboratory techniques used were inadequately reported. None of the studies used modern molecular based polymerase chain reaction (PCR) methods or urinary antigen testing (for organisms such as *S. pneumoniae* and *Legionella pneumophila*). This may also contribute to differences in the observed frequencies of positive culture data and the apparent lack of atypical or viral etiologies. Interestingly, a recent study reviewing hospitalised patients identified close to 22% of CAP inpatients had viral pathogens (most commonly rhinovirus, 9% and influenza, 6%) implying that a viral etiology of SAP in at least some individuals may be possible. Finally, antibiotics preceding index stroke (especially for patients with chronic lung disease) may have influenced microbiological cultures. For example, in the PANTHERIS study, when sputum samples were analysed, 36% of samples were positive for organisms in the placebo group as opposed to 9% in the prophylactic antibiotic group. While the numbers are too
small to form further conclusions, prophylactic antibiotics administered to the participating stroke patients in the 3 RCTs may have affected frequency of identified organisms.

It is important to emphasise the differences in frequency of pathogens identified in Asian compared to European or North American studies. For example, in a study of hospitalized CAP patients, \textit{S. pneumoniae} appeared to have a lower frequency (13\% v 26\%) and \textit{Enterobacteriaceae} appeared to have a higher frequency (9\% v 2.7\%) in in Asian studies as compared to European studies.\textsuperscript{5} Similarly, while limited comparison was possible in our study, the frequency of certain nosocomial pathogens appeared to be higher in Asia or Asia-Pacific regions (\textbf{Online only Table IV}) in keeping with higher prevalence of hospital-acquired infection (15.5\%) in comparison to Europe (7.1\%) or the USA (4\%).\textsuperscript{31} However this incongruity may be as a result of selection pressure on clinically relevant bacteria from differing prior antibiotic exposure of patients across continents, as well as possible implementation of pneumococcal vaccination programmes.
The scarce amount of available data on microbiological etiologies of pneumonia complicating stroke might also reflect the clinical routine, as suggested by a recent survey on German stroke units. Treatment guidelines for pneumonia complicating stroke, nevertheless, should take into account these commonly isolated organisms and also consider local surveillance data, community pathogens and demographical variations, together with guidance from the WHO global strategy for containment of antimicrobial resistance when recommendations are being made for prescribing empirical antibiotic regimens. Anaerobes, while not identified in our study, are commonly seen in the upper airway mixed with oral flora and in the stomach, are often thought to be responsible for aspiration pneumonia. However anaerobes are difficult to culture, and if aspiration is suspected, then broader spectrum antibiotics may be required.

The risk of contamination with oral flora, low diagnostic yield (30-40% sensitivity) with current diagnostic methods and delay in producing a positive result (at least 24hrs-48hrs) often predisposes to initial broad spectrum antibiotic prescriptions. An ideal diagnostic method would be more timely and sensitive to identifying pathogens. PCR assays involving comprehensive molecular testing platforms significantly improve pathogen detection (87% v 39%) in comparison to sputum culture (including viral pathogens) and provide results within 24hrs, which may help in initiation of pathogen directed microbial therapy or a rapid de-escalation of broad spectrum antibiotic therapy. However, validating such technology still depends on a reliable microbiological reference standard (sputum analysis) which may limit its potential utility in non-ventilated stroke patients.
Conclusion

Our study demonstrates an evidence gap in appropriately designed studies that robustly identify microbiological etiologies in pneumonia complicating stroke. Although limited by small and heterogeneous study samples, this review suggests AGNB and GPC species are frequently associated with pneumonia complicating stroke. Difficulties in obtaining suitable sputum samples among non-ventilated stroke patients and poor sensitivity of current diagnostic methods often results in broad spectrum antibiotic prescriptions for pneumonia. Our study however supports the need for a consensus based approach to antibiotic initiation and further targeted antibiotic treatment trials for enhanced antibiotic stewardship.

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Disclosures/Conflicts of Interest:

Dr Meisel received project funding by Thermo Fisher Scientific BRAHMS GmbH, Germany for a stroke trial.
Figure legends

Figure 1: Flow diagram of systematic search methodology

Figure 2: Forest plot of pneumonia frequency according to stroke subtype

Fig 3: Proportion of studies identifying the eight most commonly isolated organisms
References


**Table 1: Study characteristics**

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<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Warusewitaine</td>
<td>2008-2011</td>
<td>2014</td>
<td>UK</td>
<td>1</td>
<td>60</td>
<td>2</td>
<td>1</td>
<td>77.5</td>
<td>57</td>
<td>19</td>
<td>94% &lt;7d</td>
<td>sputum</td>
<td>41</td>
<td>4</td>
<td>3*</td>
</tr>
<tr>
<td>Li</td>
<td>2009-2011</td>
<td>2014</td>
<td>China</td>
<td>3</td>
<td>1279</td>
<td>1</td>
<td>1</td>
<td>63</td>
<td>NR</td>
<td>NR</td>
<td>sputum</td>
<td>NR</td>
<td>22</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Westendorp</td>
<td>2010-2014</td>
<td>2015</td>
<td>Netherlands</td>
<td>1</td>
<td>2538</td>
<td>2</td>
<td>1</td>
<td>73.5</td>
<td>57</td>
<td>5</td>
<td>NR</td>
<td>sputum/blood</td>
<td>17</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Design-1 = randomized controlled study, 2 = prospective observational study, 3 = retrospective study; Stroke type - 1 = ischemic stroke, 2 = ischemic stroke and intracerebral hemorrhage; Setting - 1 = Acute Stroke Unit (ASU); 2 = Stroke Intensive Care; 3 = ASU and rehabilitation unit; 4 = Unclear; Criteria-1 = Centers for Disease Control and Prevention Criteria, 2 = Ad hoc Objective criteria, 3 = Mann Criteria, 4 = British Thoracic Society Criteria; NIHSS = National Institutes of Health Stroke Scale; NR = not reported; Pneumonia risk stratification criteria-1 = low risk (unselected stroke patients with ≤15% intracerebral haemorrhage, mean NIHSS ≤5); 2 = high risk (≥15% intracerebral haemorrhage, NIHSS ≥5), 3 = very high risk (exclusively dysphagia studies and/or tube-fed patients); *studies involving stroke patients in intensive care*
Table 2: Frequency of isolated organisms in pneumonia complicating stroke in comparison to other forms of pneumonia

<table>
<thead>
<tr>
<th>Identified organisms</th>
<th>HAP (range, %)</th>
<th>VAP (range, %)</th>
<th>CAP (range, %)</th>
<th>Pneumonia complicating stroke (Weighted average with range, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram Positive Cocci</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>26.6-36.5</td>
<td>19.5-31.9</td>
<td>3-14.1</td>
<td>10.1 (0-36.3)</td>
</tr>
<tr>
<td>Streptococcal pneumoniae</td>
<td>1.8-3.2</td>
<td>&lt;3</td>
<td>35-80</td>
<td>3.5 (0-10.7)</td>
</tr>
<tr>
<td><strong>Gram Negative Bacilli</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>8-10.5</td>
<td>6.6-10.2</td>
<td>3-6</td>
<td>12.8 (0-51)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>4.6-10.1</td>
<td>3-5</td>
<td>6-12</td>
<td>9 (0-21.7)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>19-22.4</td>
<td>21.4-26.6</td>
<td>2.8-9</td>
<td>6 (0-11.7)</td>
</tr>
<tr>
<td>Acinetobacter baumanii</td>
<td>4.4-13.3</td>
<td>14.3</td>
<td>3-14.3</td>
<td>4.6 (0-22.9)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>1.3-3.7</td>
<td>NR</td>
<td>5-40</td>
<td>1.9 (0-11.5)</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>6.3-8.5</td>
<td>6-8.8</td>
<td>NR</td>
<td>1.7 (0-10)</td>
</tr>
</tbody>
</table>

HAP=hospital acquired pneumonia, VAP =ventilator associated pneumonia, CAP=community acquired pneumonia, NR=not recorded
Fig. 1

Records identified through database searching (N)
- Medline: 2945
- Embase: 7480
- CINAHL: 5083
- Cochrane Library: 281

Records after duplicates removed (N=6231)

Screening criteria
- a) English or non-English published studies/abstracts
- b) Ischemic stroke or intracerebral hemorrhage
- c) Pneumonia complicating stroke identified

Records screened N=983

Records excluded N=936

Screening criteria
- a) English or non-English published studies/abstracts
- b) Ischemic stroke or intracerebral hemorrhage
- c) Pneumonia complicating stroke identified

Eligibility criteria
- a) Age ≥ 18 years
- b) Inpatients with ischemic stroke, intracerebral hemorrhage or both
- c) Fully published/completed prospective or retrospective observational studies, quasi-experimental or randomised trials
- d) Frequency of pneumonia complicating acute stroke identified
- e) Objective criteria used to diagnose pneumonia complicating stroke and/or Microbiological etiologies identified for pneumonia complicating stroke

Full-text articles/abstracts assessed for eligibility N=47

Full-text articles/abstracts excluded with reasons N=32

Studies included for qualitative analysis N=15

References; Citations; PISCES collaboration N=13

Animal studies=10
Non-stroke studies=163
Frequency of pneumonia not identified=763

Microbiological etiology not collected=25
Oral microbiology (colonisation) only=2
Infection preceding stroke included=1
Predominantly intubated/ventilated and/or post-operative stroke patients =4

Microbiological etiology not collected=25
Oral microbiology (colonisation) only=2
Infection preceding stroke included=1
Predominantly intubated/ventilated and/or post-operative stroke patients =4
**Fig. 2**

<table>
<thead>
<tr>
<th>Author</th>
<th>Participant (n)</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satou</td>
<td>16</td>
<td>63</td>
</tr>
<tr>
<td>Harms</td>
<td>79</td>
<td>14</td>
</tr>
<tr>
<td>Becker</td>
<td>113</td>
<td>8</td>
</tr>
<tr>
<td>Fluri</td>
<td>383</td>
<td>5</td>
</tr>
<tr>
<td>Chen</td>
<td>495</td>
<td>10</td>
</tr>
<tr>
<td>Li</td>
<td>1279</td>
<td>24</td>
</tr>
<tr>
<td><strong>Pooled (Ischemic)</strong></td>
<td><strong>16</strong></td>
<td></td>
</tr>
<tr>
<td>Warusevitane</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td>Chamorro</td>
<td>136</td>
<td>20</td>
</tr>
<tr>
<td>Yeh</td>
<td>163</td>
<td>51</td>
</tr>
<tr>
<td>Vargas</td>
<td>229</td>
<td>18</td>
</tr>
<tr>
<td>Ros</td>
<td>258</td>
<td>23</td>
</tr>
<tr>
<td>Chen</td>
<td>341</td>
<td>30</td>
</tr>
<tr>
<td>Hassan</td>
<td>443</td>
<td>23</td>
</tr>
<tr>
<td>Sui</td>
<td>1435</td>
<td>38</td>
</tr>
<tr>
<td>Westendorp</td>
<td>2538</td>
<td>2</td>
</tr>
<tr>
<td><strong>Pooled (Mixed stroke)</strong></td>
<td><strong>27</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total (I²=99%)</strong></td>
<td><strong>23</strong></td>
<td></td>
</tr>
</tbody>
</table>

$I^2=96%$

$I^2=99%$
Fig. 3
SUPPLEMENTAL MATERIAL

Microbiological etiologies of pneumonia complicating stroke: A systematic review

Amit K Kishore1,2 FRCP, Andy Vail3 MSc, Adam Jeans4 MD, Angel Chamorro5 PhD, Mario Di Napoli6 MD, Lalit Kalra7 PhD, Peter Langhorne8 PhD, Christine Roffe9 MD, Willeke Westendorp10 MD, Paul J Nederkoorn10 PhD, Javier Garau11 PhD, Diederik van de Beek10 PhD, Joan Montaner12,13 PhD, Mark Woodhead14 DM, Andreas Meisel15 MD, Craig J Smith1 MD, on behalf of Pneumonia In Stroke Consensus (PISCES) Group.

1Greater Manchester Comprehensive Stroke Centre, Manchester Academic Health Science Centre, Salford Royal Foundation Trust, UK; 2Division of Cardiovascular Sciences, University of Manchester, Manchester, UK; 3Centre for Biostatistics, University of Manchester, Salford Royal Foundation Trust, UK; 4Department of Microbiology, Salford Royal NHS Foundation Trust; 5Comprehensive Stroke Center, Department of Neuroscience, Hospital Clinic, University of Barcelona, Barcelona, Spain; 6Neurological Service, San Camillo de’ Lellis General Hospital, Rieti, Italy; 7Clinical Neurosciences, King’s College Hospital NHS Foundation Trust London, UK; 8Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow Royal Infirmary, Glasgow, UK; 9Keele University Institute for Science and Technology in Medicine, Guy Hilton Research Centre, Stoke-on-Trent, UK; 10Department of Neurology, Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; 11Department of Medicine, Hospital Universitari Mutua de Terrassa, Barcelona, Spain; 12Neurovascular Research Lab, Vall d’Hebron Research Institute, Barcelona, Spain; 13Institute de Biomedicine of Seville, IBiS/Hospital Universitario Virgen del Rocío, University of Seville, Seville, Spain; 14Faculty of Medical and Human Sciences, University of Manchester & Department of Respiratory Medicine, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; 15NeuroCure Clinical Research Center, Center for Stroke Research Berlin Department of Neurology Charité Universitätsmedizin Berlin, Germany

Cover title: Bacterial etiology of pneumonia complicating stroke

Corresponding author: Dr Amit K Kishore

Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Stott lane, Salford, M6 8HD, UK;

Tel: +44 161 206 4044 Fax: +44 161 707 6534 Amit.Kishore@manchester.ac.uk
## Online only Table I: Search Terms

<table>
<thead>
<tr>
<th>Search Areas</th>
<th>Thesaurus terms</th>
<th>Free Text Terms</th>
</tr>
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<tbody>
<tr>
<td><strong>MEDLINE</strong></td>
<td>Subject Search in MESH: exp *Cerebrovascular disorders/; exp *Pneumonia/;</td>
<td>Stroke*, Pneumonia*, “respiratory tract infection*”, “chest infection*”</td>
</tr>
<tr>
<td></td>
<td>[Limit to: Publication Year 1946-2016]</td>
<td>[Limit to: Publication Year 1946-2016]</td>
</tr>
<tr>
<td><strong>EMBASE</strong></td>
<td>Subject Search on EMTREE: exp *Cerebrovascular disease/ exp *Pneumonia/;</td>
<td>Stroke*, Pneumonia*, “respiratory tract infection*”, “chest infection*”</td>
</tr>
<tr>
<td></td>
<td>[Limit to: Publication Year 1901-2016]</td>
<td>[Limit to: Publication Year 1901-2016]</td>
</tr>
<tr>
<td><strong>CINAHL</strong></td>
<td>Subject Search: exp *Cerebrovascular disorders/; exp *Pneumonia/;</td>
<td>Stroke*, Pneumonia*, “respiratory tract infection*”, “chest infection*”</td>
</tr>
<tr>
<td></td>
<td>[Limit to: Publication Year 1946-2016]</td>
<td>[Limit to: Publication Year 1901 to 2016]</td>
</tr>
<tr>
<td><strong>Cochrane Central Register of Controlled Trials</strong></td>
<td>[Limit to: Publication Year 1980-2016]</td>
<td>All text: “stroke” “pneumonia”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Publication Year from 1980 to 2016, in Cochrane Reviews (Protocols only), Trials and Methods Studies (Word variations have been searched)</td>
</tr>
</tbody>
</table>
Online only Table II: Eligibility criteria

**Inclusion criteria:**

Age ≥ 18 years

Fully published studies or abstracts

English or non-English language

Inpatients with ischemic stroke, intracerebral haemorrhage, or both

Randomized (RCT’s) and other controlled trials, including cluster RCTs, controlled (non-randomized) clinical trials (CCTs) or cluster trials, prospective comparative cohort studies, retrospective observational studies, case-control or nested case-control studies.

Inclusion or prevalence of pneumonia following admission with stroke reported

Possible microbiological etiologies identified as responsible for pneumonia complicating stroke OR objective criteria used for diagnosing pneumonia

**Exclusion criteria:**

Age < 18 years

Exclusively intubated and mechanically ventilated patients

Exclusively pneumonia preceding index stroke

Case reports
### Online only Table III: Patient characteristics

<table>
<thead>
<tr>
<th>Author</th>
<th>NG or PEG feeding (%)</th>
<th>Prophylactic antibiotics</th>
<th>COPD/other lung pathology</th>
<th>Immunosuppression</th>
<th>Co-morbidities (%)</th>
<th>MV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamorro</td>
<td>48</td>
<td>Yes</td>
<td>9.5</td>
<td>Excluded</td>
<td>17.6</td>
<td>16.9</td>
</tr>
<tr>
<td>Hassann</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Vargas</td>
<td>42</td>
<td>NR</td>
<td>10</td>
<td>4.3</td>
<td>16.1</td>
<td>16.6</td>
</tr>
<tr>
<td>Ros</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Harms</td>
<td>66</td>
<td>Yes</td>
<td>7.5</td>
<td>8.8</td>
<td>11.4</td>
<td>11.4</td>
</tr>
<tr>
<td>Sul</td>
<td>47</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>49</td>
</tr>
<tr>
<td>Yeh</td>
<td>73</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fluri</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chen</td>
<td>58</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chen</td>
<td>NR</td>
<td>NR</td>
<td>25.5*</td>
<td>14*</td>
<td>31.4*</td>
<td>43*</td>
</tr>
<tr>
<td>Satou</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Becker</td>
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<td>No</td>
<td>Excluded</td>
<td>35.3</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>Warusevitane</td>
<td>100</td>
<td>No</td>
<td>16</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Li</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Westendorp</td>
<td>NR</td>
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<td>8.2</td>
<td>17.3</td>
<td>32.5</td>
<td>24.4</td>
</tr>
</tbody>
</table>

NR=Not Reported, COPD=Chronic Obstructive Pulmonary Disease, AF=Atrial fibrillation, HTN=hypertension, DM=diabetes mellitus, MV=mechanical ventilation, *with pneumonia
### Online only Table IV: The eight most commonly isolated organisms in positive cultures (%) in the included studies

<table>
<thead>
<tr>
<th>GRAM POSITIVE COCCI</th>
<th>European or North American Studies</th>
<th>Asian Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chamorro</td>
<td>Vargas</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>11</td>
<td>×</td>
</tr>
<tr>
<td><strong>Streptococcal pneumoniae</strong></td>
<td>3.7</td>
<td>2.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GRAM NEGATIVE BACILLI</th>
<th>European or North American Studies</th>
<th>Asian Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
<td>×</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Enterobacter cloacae</strong></td>
<td>×</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td>×</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae</strong></td>
<td>3.7</td>
<td>21.9</td>
</tr>
<tr>
<td><strong>Acinetobacter baumanii</strong></td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>

For each study, data represent % of positive cultures due to the microbial species listed. X indicates not identified.
### Online only Table V: Definition of pneumonia terminologies

<table>
<thead>
<tr>
<th>Types of pneumonia</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized community acquired pneumonia (CAP)</td>
<td>Pneumonia i.e. symptoms and signs consistent with an acute lower respiratory tract infection in the community, associated with new radiographic shadowing for which there is no other explanation and needing hospital admission</td>
</tr>
<tr>
<td>Hospital acquired pneumonia (HAP)</td>
<td>Pneumonia in a hospitalised patient &gt; 48-72 hours after admission, without any incubation period</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia (VAP)</td>
<td>Pneumonia in a patient occurring &gt; 48-72 hours after intubation</td>
</tr>
<tr>
<td>Stroke associated pneumonia (SAP)</td>
<td>Pneumonia in a patient ≤7 days from stroke symptom onset (HAP after this period); Early SAP&lt; 72hrs, late SAP&gt;72hrs</td>
</tr>
</tbody>
</table>
Online only Figure I: Funnel Plot

Scatterplots representing individual studies

Proportion of pneumonia

Standard error

-0.2  0.0  0.2  0.4  0.6  0.8
0.15  0.2  0.3  0.4  0.5  0.6  0.7  0.8

Online only Figure I: Funnel Plot
References


**References for excluded studies with reasons (32 studies)**

**Infection preceding stroke included**


**Oral microbiology (colonisation only)**


**Predominantly intubated/ventilated and/or post-operative stroke patients**


**Microbiological etiology not collected**


