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Microbiological etiologies of pneumonia complicating stroke: A systematic review

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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%), *Acinetobacter baumannii* (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.^{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.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.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.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.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%)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.^{7,8} 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.^{9, 10} 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 study¹. 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.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.^{11,15,25} Two studies were exclusively in nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tube fed participants.^{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 objective¹²; 2 studies excluded patients on immunosuppressive medication, with prior malignancy, or other forms of immunosuppression prior to stroke.^{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 baumannii* 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 cocci (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 baumannii* (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 ≤ 5 , Table 1). It was not possible to explore relationships between timing of pneumonia or its 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. baumannii* 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 β -lactam (including ureidopenicillin and 2nd/3rd generation cephalosporins) antibiotics +/- β lactamase inhibitors and 2nd/3rd 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.²⁵

Discussion

Pneumonia occurs most frequently during the first week after stroke (SAP)^{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*.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.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.³⁰ 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.¹⁵ 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, *S. pneumoniae* appeared to have a lower frequency (13% v 26%) and *Enterobacteriaceae* appeared to have a higher frequency (9% v 2.7%) in Asian studies as compared to European studies.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 (**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%).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.³² 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 resistance³³ 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.²⁸

The risk of contamination with oral flora, low diagnostic yield (30-40% sensitivity) with current diagnostic methods³¹ 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.²⁹ 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

1. Kishore AK, Vail A, Chamorro A, Garau J, Hopkins SJ, Di Napoli M, et al. How is pneumonia diagnosed in clinical stroke research? A systematic review and meta-analysis. *Stroke*. 2015; 46:1202-1209.
2. Westendorp WF, Nederkoorn PJ, Vermeij JD, Dijkgraaf MG, van de Beek D. Post-stroke infection: a systematic review and meta-analysis. *BMC Neurology*.2011; 11:110.
3. Smith CJ, Kishore AK, Vail A, Chamorro A, Garau J, Hopkins SJ, et al. Diagnosis of stroke-associated pneumonia: recommendations from the Pneumonia In Stroke ConsEnsuS Group. *Stroke*. 2015; 46:2335-2340.
4. Harms H, Hoffmann S, Malzahn U, Ohlraun S, Heuschmann P, Meisel A. Decision-making in the diagnosis and treatment of stroke-associated pneumonia. *J Neurol Neurosurg Psychiatry*. 2012; 83:1225-30.
5. Peto L, Nadjm B, Horby P, Dieu Ngan TT, van Doorn Ra, Kinh NV, et al. The bacterial aetiology of adult community-acquired pneumonia in Asia: a systematic review. *Trans R Soc Trop Med Hyg*. 2014; 108: 326–337.
6. Campbell SG, Marrie TJ, Anstey R, Dickinson G, Ackroyd-Stolarz S. The contribution of blood cultures to the clinical management of adult patients admitted to the hospital with community-acquired pneumonia: a prospective study. *Chest*.2003; 123:1142–50.
7. Adams HP, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary

Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*.2007; 38:1655–711.

8. Guidelines for management of ischaemic stroke and transient ischaemic attack.

Cerebrovasc Dis. 2008; 25:457–507.

9. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols

(PRISMA-P): elaboration and explanation. *BMJ*. 2015; 349:g7647.

10. Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009. Available from

www.cochrane-handbook.org (accessed 22nd February 2017).

11. Chamorro A, Horcajada JP, Obach V, Vargas M, Revilla M, Torres F, et al. The Early Systemic Prophylaxis of Infection After Stroke study: a randomised clinical trial. *Stroke*

2005; 36: 1495–500.

12. Hassan A, Khealani BA, Shafqat S, Aslam M, Salahuddin N, Syed N A, et al. Stroke-associated pneumonia: microbiological data and outcome. *Singapore Med J*. 2006; 47: 204-

207.

13. Vargas M, Horcajada JP, Obach V, Revilla M, Cervera A, Torres F, et al. Clinical consequences of infection in patients with acute stroke: is it prime time for further antibiotic

trials? *Stroke*. 2006; 37: 461–65.

14. Ros L, García M, Prat J, González C, Gimeno C Albert A , et al. Factores predisponentes a la infección nosocomial en el ictus agudo y su influencia en la morbimortalidad. *Med Clin (Barc)*. 2007; 128:441-7.

15. Harms H, Prass K, Meisel C, Klehmet J, Rogge W, Drenckhahn C, et al. Preventive

antibacterial therapy in acute ischemic stroke: a randomised controlled trial. *PLoS One*. 2008;

3: e2158.

16. Sui R, Zhang L. Risk factors of stroke-associated pneumonia in Chinese patients. *Neurological Research*.2011; 33:508:514.
17. Yeh S, Huang K, Wang T, Chen Y, Chen C, Tang S, et al. Dysphagia screening decreases pneumonia in acute stroke patients admitted to the stroke intensive care unit. *Journal of the Neurological Sciences*. 2011; 306:38–41.
18. Fluri F, Morgenthaler NG, Mueller B, Christ-Crain M, Katan M. Copeptin, Procalcitonin and Routine Inflammatory Markers–Predictors of Infection after Stroke. *PLoS ONE*. 2012; 7: e48309.
19. Chen L, Chang C, Hsu L, Tsai P, Chang S, Chang S, et al. Bacterial pneumonia following acute ischemic stroke. *Journal of the Chinese Medical Association*. 2013; 76:78-82
20. Chen CM, Hsu HC, TsaiWS, Chang CH, Chen KH, Hong CZ. Infections in acute older stroke inpatients undergoing rehabilitation. *Am J Phys Med Rehabil*.2012; 91:211-219.
21. Satou Y, Oguro H, Murakami Y, Onoda K, Mitaki S, Hamada C, et al. Gastroesophageal Reflux during Enteral Feeding in Stroke Patients: A 24-hour Esophageal pH-monitoring Study. *Journal of Stroke and Cerebrovascular Diseases*. 2013; 22:185-189.
22. Becker KJ, Dankwa D, Lee R, Schulze J, Zierath D, Tanzi P, et al. Stroke, IL-1ra, IL1RN, Infection and Outcome. *Neurocrit Care*. 2014; 21:140–146.
23. Warusevitane A, Karunatilake D, Sim J Lally F, Roffe C. Safety and Effect of Metoclopramide to Prevent Pneumonia in Patients With Stroke Fed via Nasogastric Tubes Trial. *Stroke*. 2015; 46:454-460.
24. Li Y, Song B, Fang H, Gao Y, Zhao L, Xu Y. External validation of the A2DS2 score to predict stroke-associated pneumonia in a Chinese Population: a prospective cohort study. *PLoS ONE*. 2014; 9: e109665.

25. Westendorp WF, Vermeij JD, Zock E, Hooijenga IJ, Kruyt ND, Bosboom HJ, et al for the PASS investigators. The Preventive Antibiotics in Stroke Study (PASS): a pragmatic randomised open-label masked endpoint clinical trial. *Lancet*.2015; 385: 1519–26.
26. Jones RN. Microbial Etiologies of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia. *Clinical Infectious Diseases*. 2010; 51:S81–S87.
27. Garau J, Calbo E. Community acquired pneumonia. *Lancet*.2008; 371:455-458
28. Armstrong JR, Mosher BD. Aspiration Pneumonia After Stroke. *Neurohospitalist*. 2011;1:85–93.
29. Gadsby NJ, Russell CD, McHugh MP, Mark H, Morris AC, Laurenson IF, et al. Comprehensive Molecular Testing for Respiratory Pathogens in Community-Acquired Pneumonia. *Clinical Infectious Diseases*.2016; 62:817–23.
30. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med*. 2015;373:415-27.
31. Allegranzi B, Nejad SB, Combescure C, Graafmans W, Attar H, Donaldson L. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet*. 2011; 377:228–41.
32. Harms H, Hoffmann S, Malzahn U, Ohlraun S, Heuschmann P, Meisel A, et al. Decision-making in the diagnosis and treatment of stroke-associated pneumonia. *J Neurol Neurosurg Psychiatry*.2012; 83: 1225-1230.
33. WHO (World Health Organization). 2015. Global Action Plan on Antimicrobial Resistance. Available on: <http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/> [accessed 10 November 2017].

Table 1: Study characteristics

First Author	Year of recruitment	Year Published	Country	Design	Participants (n)	Stroke Type	Setting	Mean Age (y)	Male (%)	Mean NIHSS	Time to pneumonia diagnosis (d)	Culture specimen	Positive culture (%)	Diagnostic criteria	Pneumonia risk stratification
Chamorro	2002-2004	2005	Spain	1	136	2	1	72.9	50	12	66% <7d	sputum/tracheal aspirate	45	2	2
Hassan	1998-2001	2006	Pakistan	3	443	2	1	64	68	NR	67% <2d	sputum/tracheal aspirate	38	1	2
Vargas	2001-2002	2006	Spain	2	229	2	1	72.3	51	9	≤7d	tracheal aspirate	41	2	2
Ros	1998-1999	2007	Spain	2	258	2	1	74.9	48.8	NR	NR	blood	22	2	1
Harms	2003-2006	2008	Germany	1	79	1	1	72.5	NR	16	≤11d	tracheal aspirate	45	1	3
Sui	2000-2009	2011	China	3	1435	2	2	67.2	55.4	7	63% <3d	sputum	38	1	2
Yeh	2006-2007	2011	Taiwan	3	163	2	2	67.4	54	14	NR	sputum	39	1	3
Fluri	2006-2007	2012	Switzerland	2	383	1	1	71.4	57.7	5	≤5d	sputum/blood	15	1	1
Chen	2002-2010	2012	Taiwan	3	341	2	3	73.4	48.6	NR	NR	sputum	NR	3	2
Chen	2006-2011	2013	Taiwan	3	495	1	4	80.3	72.5	15	53% <3d	sputum/blood	75	1	2
Satou	NR	2013	Japan	2	16	1	1	83.2	NR	NR	NR	NR	30	2	3*
Becker	2005-2009	2014	USA	2	113	1	1	58	66	10	<15d	sputum	88	2	1
Warusevitane	2008-2011	2014	UK	1	60	2	1	77.5	37	19	94% <7d	sputum	41	4	3*
Li	2009-2011	2014	China	3	1279	1	1	63	NR	NR	NR	sputum	NR	2	1
Westendorp	2010-2014	2015	Netherlands	1	2538	2	1	73.5	57	5	NR	sputum/blood	17	1	1

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

Identified organisms	HAP (range, %) ²⁶	VAP (range, %) ²⁶	CAP (range, %) ^{26,27,28}	Pneumonia complicating stroke (Weighted average with range, %)
Gram Positive Cocci				
<i>Staphylococcus aureus</i>	26.6-36.5	19.5-31.9	3-14.1	10.1 (0-36.3)
<i>Streptococcal pneumoniae</i>	1.8-3.2	<3	35-80	3.5 (0-10.7)
Gram Negative Bacilli				
<i>Klebsiella pneumoniae</i>	8-10.5	6.6-10.2	3-6	12.8 (0-51)
<i>Escherichia coli</i>	4.6-10.1	3-5	6-12	9 (0-21.7)
<i>Pseudomonas aeruginosa</i>	19-22.4	21.4-26.6	2.8-9	6 (0-11.7)
<i>Acinetobacter baumannii</i>	4.4-13.3	14.3	3-14.3	4.6 (0-22.9)
<i>Haemophilus influenzae</i>	1.3-3.7	NR	5-40	1.9 (0-11.5)
<i>Enterobacter cloacae</i>	6.3-8.5	6-8.8	NR	1.7 (0-10)

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

Fig. 1

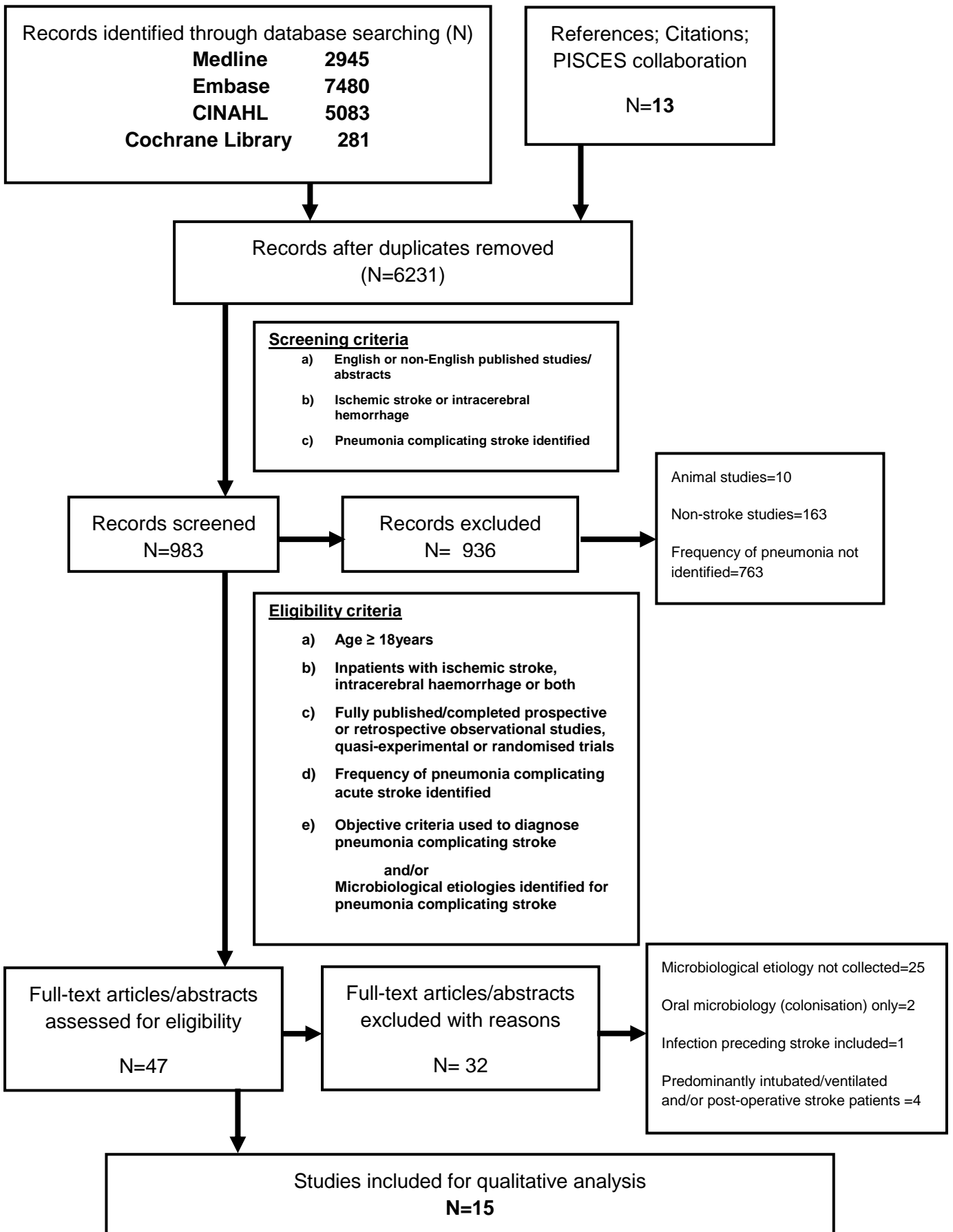
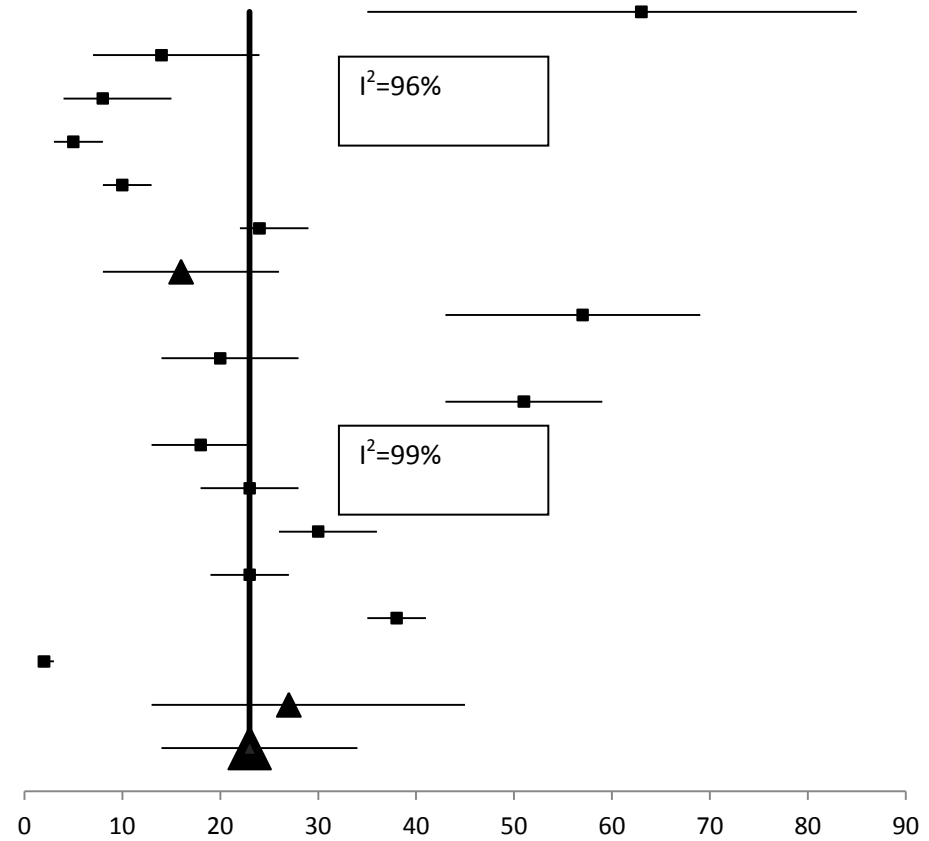


Fig. 2

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



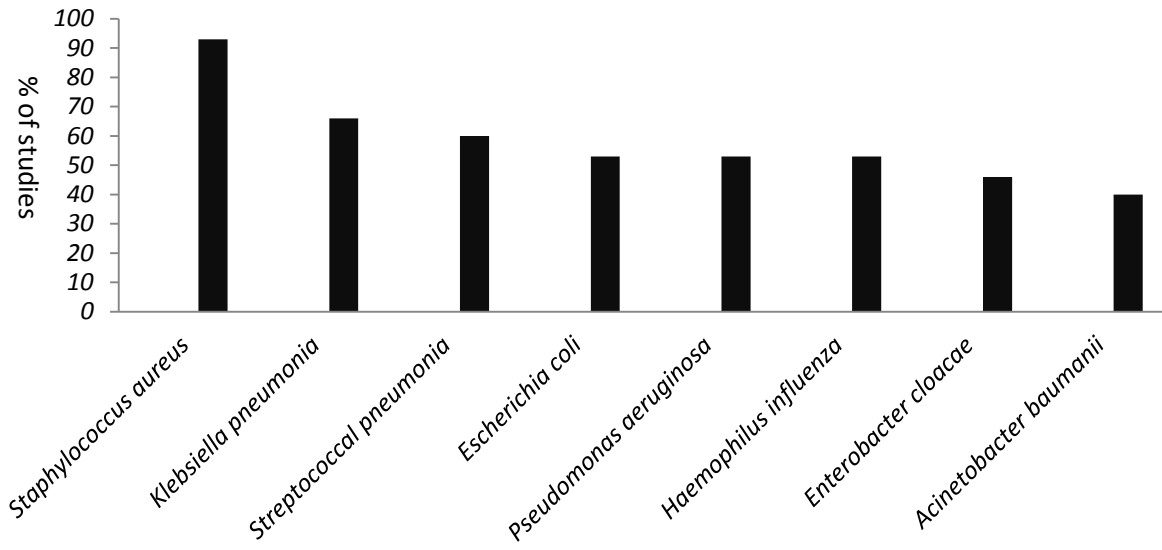


Fig. 3

SUPPLEMENTAL MATERIAL

Microbiological etiologies of pneumonia complicating stroke: A systematic review

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Online only Table I: Search Terms

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

Online only Table II: Eligibility criteria

Inclusion criteria:

Age \geq 18years

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.

Incidence 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 < 18years

Exclusively intubated and mechanically ventilated patients

Exclusively pneumonia preceding index stroke

Case reports

Online only Table III: Patient characteristics

Author	NG or PEG feeding (%)	Prophylactic antibiotics	Co-morbidities (%)								MV (%)
			COPD/other lung pathology	Immunosuppression	Previous Stroke	Smoking history	Heart disease	AF	HTN	DM	
Chamorro¹	48	Yes	9.5	Excluded	17.6	16.9	12.5	NR	63.2	22.8	0
Hassan²	NR	No	NR	NR	NR	NR	NR	NR	NR	NR	NR
Vargas³	42	NR	10	4.3	16.1	16	NR	NR	60	19	0
Ros⁴	NR	NR	NR	NR	12.4	NR	13.2	12.8	63.2	35.3	0
Harms⁵	66	Yes	7.5	8.8	11.4	11.4	37.2	34.1	64.5	31.6	8.8
Sui⁶	47	NR	NR	NR	NR	49	32	NR	NR	44	2.2
Yeh⁷	73	No	NR	NR	NR	NR	NR	NR	NR	NR	12.2
Fluri⁸	NR	NR	NR	NR	NR	NR	34	19.4	80	19.3	0
Chen⁹	58	NR	NR	NR	NR	NR	NR	NR	82	39	0.3
Chen¹⁰	NR	NR	25.5*	14*	31.4*	43*	27.5*	NR	70.6*	29.4*	23.5*
Satou¹¹	100	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Becker¹²	NR	No	NR	Excluded	35.3	37	24	NR	53.1	24	NR
Warusevitane¹³	100	No	16	NR	NR	NR	NR	60	66	28	0
Li¹⁴	NR	NR	NR	NR	NR	40	NR	NR	74	20	NR
Westendorp¹⁵	NR	Yes	8.2	17.3	32.5	24.4	13	15.4	55.2	19.7	0

NR=Not Reported, COPD=Chronic Obstructive Pulmonary Disease, AF=Atrial fibrillation, HTN=hypertension, DM=diabetes mellitus, MV=mechanical ventilation, * with pneumonia

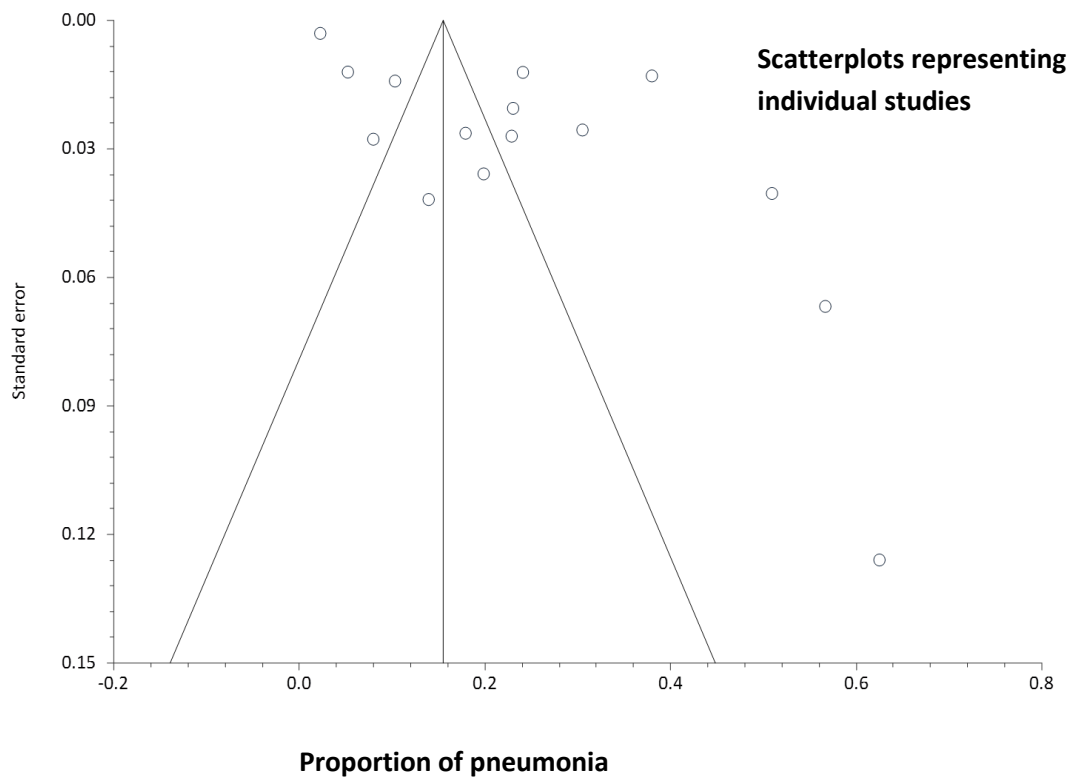
Online only Table IV: The eight most commonly isolated organisms in positive cultures (%) in the included studies

	European or North American Studies								Asian Studies						
	Chamorro	Vargas	Ros	Harms	Fluri	Becker	Warusevitane	Westendorp	Sui	Yeh	Li	Satou	Hassan	Chen	Chen
GRAM POSITIVE COCCI															
<i>Staphylococcus aureus</i>	11	×	5	36.3	5	22.2	11.7	1.7	9.3	19.2	6.8	20	11.7	24.1	1.9
<i>Streptococcal pneumoniae</i>	3.7	2.4	×	9	×	×	×	1.7	0.5	1.2	10.7	×	3.9	2.8	1
GRAM NEGATIVE BACILLI															
<i>Klebsiella pneumoniae</i>	×	×	5	×	×	11.1	11.7	×	8.8	51	18.2	10	3.9	15.4	23.5
<i>Escherichia coli</i>	×	7.3	×	×	×	×	5.8	×	7.7	9	21.7	×	1.9	2.8	10
<i>Enterobacter cloacae</i>	×	7.3	1.7	×	×	×	5.8	×	×	9.6	×	×	1.9	3.8	10
<i>Pseudomonas aeruginosa</i>	×	2.4	×	×	×	11.1	×	×	6.6	4.8	8.2	×	11.7	6.7	3.9
<i>Haemophilus influenzae</i>	3.7	21.9	×	×	5	11.1	×	×	6.6	×	×	×	3.9	11.5	7.8
<i>Acinetobacter baumannii</i>	×	×	×	×	×	×	×	×	1.4	22.9	8.4	×	3.9	6.7	7.8

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

Types of pneumonia	Definition
Hospitalized community acquired pneumonia (CAP)¹⁶	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
Hospital acquired pneumonia (HAP)¹⁷	Pneumonia in a hospitalised patient > 48-72 hours after admission, without any incubation period
Ventilator-associated pneumonia (VAP)¹⁷	Pneumonia in a patient occurring > 48-72 hours after intubation
Stroke associated pneumonia (SAP)¹⁸	Pneumonia in a patient ≤ 7 days from stroke symptom onset (HAP after this period); Early SAP < 72hrs, late SAP > 72hrs



Online only Figure I: Funnel Plot

References

1. Chamorro A, Horcajada JP, Obach V, Vargas M, Revilla M, Torres F, et al. The Early Systemic Prophylaxis of Infection After Stroke study: a randomised clinical trial. *Stroke* 2005; 36: 1495–500.
2. Hassan A, Khealani BA, Shafqat S, Aslam M, Salahuddin N, Syed N A, et al. Stroke-associated pneumonia: microbiological data and outcome. *Singapore Med J.* 2006; 47: 204-207.
3. Vargas M, Horcajada JP, Obach V, Revilla M, Cervera A, Torres F, et al. Clinical consequences of infection in patients with acute stroke: is it prime time for further antibiotic trials? *Stroke.* 2006; 37: 461–65.
4. Ros L, García M, Prat J, González C, Gimeno C Albert A , et al. Factores predisponentes a la infección nosocomial en el ictus agudo y su influencia en la morbimortalidad. *Med Clin (Barc).* 2007; 128:441-7.
5. Harms H, Prass K, Meisel C, Klehmet J, Rogge W, Drenckhahn C, et al. Preventive antibacterial therapy in acute ischemic stroke: a randomised controlled trial. *PLoS One.* 2008; 3: e2158.
6. Sui R, Zhang L. Risk factors of stroke-associated pneumonia in Chinese patients. *Neurological Research.*2011; 33:508:514.
7. Yeh S, Huang K, Wang T, Chen Y, Chen C, Tang S, et al. Dysphagia screening decreases pneumonia in acute stroke patients admitted to the stroke intensive care unit. *Journal of the Neurological Sciences.* 2011; 306:38–41.
8. Fluri F, Morgenthaler NG, Mueller B, Christ-Crain M, Katan M. Copeptin, Procalcitonin and Routine Inflammatory Markers—Predictors of Infection after Stroke. *PLoS ONE.* 2012; 7: e48309.
9. Chen L, Chang C, Hsu L , Tsai P, Chang S, Chang S, et al. Bacterial pneumonia following acute ischemic stroke. *Journal of the Chinese Medical Association.* 2013; 76:78-82
10. Chen CM, Hsu HC, Tsai WS, Chang CH, Chen KH, Hong CZ. Infections in acute older stroke inpatients undergoing rehabilitation. *Am J Phys Med Rehabil.*2012; 91:211-219.
11. Satou Y, Oguro H, Murakami Y, Onoda K, Mitaki S, Hamada C, et al. Gastroesophageal Reflux during Enteral Feeding in Stroke Patients: A 24-hour Esophageal pH-monitoring Study. *Journal of Stroke and Cerebrovascular Diseases.* 2013; 22:185-189.
12. Becker KJ, Dankwa D, Lee R, Schulze J, Zierath D, Tanzi P, et al. Stroke, IL-1ra, IL1RN, Infection and Outcome. *Neurocrit Care.* 2014; 21:140–146.
13. Warusevitane A, Karunatilake D, Sim J Lally F, Roffe C. Safety and Effect of Metoclopramide to Prevent Pneumonia in Patients With Stroke Fed via Nasogastric Tubes Trial. *Stroke.* 2015; 46:454-460.
14. Li Y, Song B, Fang H, Gao Y, Zhao L, Xu Y. External validation of the A2DS2 score to predict stroke-associated pneumonia in a Chinese Population: a prospective cohort study. *PLoS ONE.* 2014; 9: e109665.
15. Westendorp WF, Vermeij JD, Zock E, Hooijenga IJ, Kruyt ND, Bosboom HJ, et al for the PASS investigators. The Preventive Antibiotics in Stroke Study (PASS): a pragmatic randomised open-label masked endpoint clinical trial. *Lancet.*2015; 385: 1519–26.
16. Guidelines for the management of community acquired pneumonia in adults: A quick reference guide (2009 update). *British Thoracic Society Reports.* 2009; 1
17. Armstrong JR, Mosher BD. Aspiration Pneumonia After Stroke. *Neurohospitalist.* 2011; 1: 85–93.

18. Kishore AK, Vail A, Chamorro A, Garau J, Hopkins SJ, Di Napoli M, et al. How is pneumonia diagnosed in clinical stroke research? A systematic review and meta-analysis. *Stroke*. 2015; 46:1202-1209.

References for excluded studies with reasons (32 studies)

Infection preceding stroke included

1. Grau AJ, Bugglea F, Schnitzlerb P, Spiela M, Lichya C, Hacke W. Fever and infection early after ischemic stroke. *Journal of the Neurological Sciences*. 1999; 115 –120.

Oral microbiology (colonisation only)

1. Gosney M, Martin MV, Wright AE. The role of selective decontamination of the digestive tract in acute stroke. *Age and Ageing* .2006; 35: 42–47.

2. Millns B ,Gosney M, Jack CIA, Martin MV, Wright AE . Acute Stroke Predisposes to Ora Gram-Negative Bacilli – a Cause of Aspiration Pneumonia. *Gerontology* 2003;49:173–176.

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

1. Gumbinger C, Hug A, Mürle B, Berger B, Zorn M, Becker K, et al. Early blood-based microbiological testing is ineffective in severe stroke patients. *Journal of the Neurological Sciences*. 2013; 325: 46–50.

2. Alsumrain M, Melillo N, Debari VA, Kirmani J, Moussavi M, Doraiswamy V, et al. Predictors and outcomes of pneumonia in patients with spontaneous intracerebral haemorrhage. *Journal of Intensive Care Medicine*.2013; 28:118-123.

3. Naidech AM, Liebling SM, Duran IM, Moore MJ, Wunderink RG, Zembower TR. Reliability of the validated clinical diagnosis of pneumonia on validated outcomes after intracranial hemorrhage. *Journal of Critical Care*.2012; 27:527.e7-11.

4. Divani AA, Hevesi M, Pulivarthi S, Luo X, Souslian F , Suarez JI, et al. Predictors of Nosocomial Pneumonia in Intracerebral Hemorrhage Patients: A Multi-center Observational Study. *Neurocrit Care*. 2015; 22:234–242.

Microbiological etiology not collected

1. WarneckeT, Ritter MA, Kröger B, Oelenberg, Teismann I, Heuschmann PU, et al. Fiberoptic endoscopic dysphagia severity scale predicts outcome after acute stroke. *Cerebrovascular Diseases*. 2009; 28:283–289.

2. Zhang X, Wang F, Zhang G, Ge Z. Risk Factors for Developing Pneumonia in Patients with Diabetes Mellitus Following Acute Ischaemic Stroke. *The Journal of International Medical Research*.2012; 40: 1860–1865.

3. Steinhagen, Grossman A, Benecke R, Walter U. Swallowing disturbance pattern relates to brain lesion location in acute stroke patients. *Stroke*.2009; 40:1903-1906.

4. Miles A, Zengc ISL, McLauchland H, Huckabee M. Cough reflex testing in dysphagia following Stroke: A randomized controlled trial. *Journal of Clinical Medicine Research*. 2013;5:222-233.

5. Ji R, Shen H, Pan Y, Wang P, Liu G, Wang Y, et al: China National Stroke Registry Investigators. Novel risk score to predict pneumonia after acute ischemic stroke. *Stroke*.2013; 44:1303-1309.

6. Minnerup J, Wersching H, Brokinkel B, Dziewas R, Heuschmann PU, Nabavi DG, et al. The impact of lesion location and lesion size on post stroke infection frequency. *Journal of Neurology, Neurosurgery and Psychiatry*. 2010; 81:198-202.
7. Vermeij FH, Reimer WJMS, Man P, Oostenbrugge RJV, Franke CL, Jong GD, et al. Stroke-associated infection is an independent risk factor for poor outcome after acute ischemic stroke: data from the Netherlands stroke survey. *Cerebrovascular Diseases*. 2009; 27:465–471.
8. Busti C, Agnelli G, Duranti M, Orlandi C, Marcucci M, Paciaroni M. Lung ultrasound in the diagnosis of stroke-associated pneumonia. *Internal and Emergency Medicine*. 2014; 9:173-178.
9. Popovic N, Stefanovic-Budimkic M, Mitrovic N, Urosevic A, Milosevic B, Pelemis M, et al. The frequency of poststroke infections and their impact on early stroke outcome. *Journal of Stroke and Cerebrovascular Diseases*. 2013; 22:424-9.
10. Chumbler NR, Williams LS, Wells CK, Lo AC, Nadeau S, Peixoto AJ, et al. Derivation and validation of a clinical system for predicting pneumonia in acute stroke. *Neuroepidemiology*. 2010; 34:193–199.
11. Suntrup S, Warnecke T, Kemmling A, Teismann IK, Hamacher C, Oelenberg S. Dysphagia in patients with acute striatocapsular haemorrhage. *Journal of Neurology*. 2012; 259:93–99.
12. Titsworth WL, Abram J, Fullerton A, Hester J, Guin P, Waters MF, et al. Prospective quality initiative to maximize dysphagia screening reduces hospital-acquired pneumonia prevalence in patients with stroke. *Stroke*. 2013; 44:3154-3160.
13. Arnold M, Liesirova K, Broeg-Morvay A, Meisterernst J, Schlager M, Mono M et al. Dysphagia in Acute Stroke: Incidence, Burden and Impact on Clinical Outcome. *PLoS ONE* . 2015; 11: e0148424.
14. Bruening T, Al-Khaled M. Stroke-Associated Pneumonia in Thrombolysed Patients: Incidence and Outcome. *Journal of Stroke and Cerebrovascular Diseases*. 2014; 24: 1724-1729.
15. Dziedzic T, Pera J, Klimkowicz A, Turaj W, Slowik A, Rog TM, et al. Serum albumin level and nosocomial pneumonia in stroke patients. *European Journal of Neurology* . 2006; 13: 299–301.
16. Walter U, Kolbaskea S, Patejdl R, Steinhagen V, Abu-Mugheisiba M, Grossmann A, et al. Insular stroke is associated with acute sympathetic hyperactivation and immunodepression. *European Journal of Neurology*. 2013; 20:153–159.
17. Fromm A, Waje-Andreassen U, Thomassen L, Naess H. Comparison between ischemic stroke patients <50 years and ≥50 years admitted to a single centre: The Bergen Stroke Study. *Stroke Research and Treatment*. 2011:183256.
18. Masrur S, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Zhao X, et al. Dysphagia screening and hospital-acquired pneumonia in patients with acute ischemic stroke: findings from get with the guidelines–stroke. *Journal of Stroke and Cerebrovascular Diseases*. 2013; 22:e301-e309.
19. Schwarz S, Al-Shajlawi F, Sick C, Meairs S, Hennerici MG. Effects of Prophylactic Antibiotic Therapy With Mezlocillin Plus Sulbactam on the Incidence and Height of Fever After Severe Acute Ischemic Stroke. *Stroke*. 2008; 39:1220-1227.
20. Kalra L, Irshad S, Hodson J, Simpson M, Gulliford G, Smithard D, et al, on behalf of the STROKE-INF Investigators. Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): a prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial. *Lancet*. 2015; 386: 1835–44.
21. Ran L, Khatibi NH, Qin X, Zhang JH. Proton Pump Inhibitor Prophylaxis Increases the Risk of Nosocomial Pneumonia in Patients with an Intracerebral Hemorrhagic Stroke.

Intracerebral Hemorrhage Research, *Acta Neurochirurgica Supplementum*, 2011;111:435-439.

22. Sreeraj K, Iype T, Madhavan N, Balan CS. Prevalence of Post stroke complications in south India-a descriptive study. *International Journal of Pharmacy and Technology*. 2012; 4:3859-3868.

23. Lam OL, McMillan AS, Samaranayake LP, Li LS, McGrath C. Randomized clinical trial of oral health promotion interventions among patients following stroke. *Archives of Physical Medicine and Rehabilitation*. 2013; 94:435-43.

24. Ingeman A, Andersen G, Hundborg HH, Svendsen ML and Johnsen SP. Processes of care and medical complications in patients with stroke. *Stroke*.2011; 42:167-172.

25. Marciniak C, Korutz AW, Lin E, Roth E, Welty L, Lovell L. Examination of selected clinical factors and medication use as risk factors for pneumonia during stroke rehabilitation: a case-control study. *American Journal of Physical Medicine & Rehabilitation*.2009; 88:30–38.