Microbiological Etiologies of Pneumonia Complicating Stroke
A Systematic Review

Amit K. Kishore, MRCP; Andy Vail, MSc; Adam R. Jeans, MD; Angel Chamorro, PhD; Mario Di Napoli, MD; Lalit Kalra, PhD; Peter Langhorne, PhD; Christine Roffe, MD; Willeke Westendorp, MD; Paul J. Nederkoorn, PhD; Javier Garau, PhD; Diederik van de Beek, PhD; Joan Montaner, PhD; Mark Woodhead, DM; Andreas Meisel, MD; Craig J. Smith, MD; on behalf of Pneumonia in Stroke Consensus (PISCES) Group

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 cause. We aimed to review existing literature to identify organisms responsible for pneumonia complicating stroke, before developing a consensus-based approach to antibiotic treatment.

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

Results—Fifteen studies (40% ischemic stroke, 60% ischemic stroke and intracerebral hemorrhage) involving 7968 patients were included. Reported occurrence of pneumonia varied considerably between studies (2%–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%–88%) varied widely. When isolated, aerobic Gram-negative bacilli (38%) and Gram-positive cocci (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 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—Although the analysis was limited by small and heterogeneous study populations, limiting determination of microbiological causality, this review suggests aerobic Gram-negative bacilli and Gram-positive cocci are frequently associated with pneumonia complicating stroke. This supports the need for appropriately designed studies to determine microbial cause and a consensus-based approach in antibiotic usage and further targeted antibiotic treatment trials for enhanced antibiotic stewardship. **(*Stroke*. 2018;49:1602-1609. DOI: 10.1161/STROKEAHA.117.020250.)**

Key Words: bacteria ■ infection ■ pneumonia ■ stroke

Pneumonia complicating stroke occurs frequently, independently increasing mortality 3-fold and increasing hospitalization costs, length of stay, and likelihood of poor outcome in survivors.[1,2] Although diagnosis remains challenging, the PISCES (Pneumonia in Stroke Consensus) group recommended that Stroke-Associated Pneumonia (SAP) was the preferred

Received November 28, 2017; final revision received May 2, 2018; accepted May 14, 2018.

From the Greater Manchester Comprehensive Stroke Centre, Manchester Academic Health Science Centre, Salford Royal Foundation Trust, United Kingdom (A.K.K., C.J.S.); Division of Cardiovascular Sciences (A.K.K., C.J.S.) and Centre for Biostatistics, Salford Royal Foundation Trust (A.V.), University of Manchester, United Kingdom; Department of Microbiology, Salford Royal NHS Foundation Trust, United Kingdom (A.R.J.); Department of Neuroscience, Comprehensive Stroke Center, Hospital Clinic, University of Barcelona, Spain (A.C.); Neurological Service and Stroke Unit, San Camillo de' Lellis General Hospital, Rieti, Italy (M.D.N.); Clinical Neurosciences, King's College Hospital NHS Foundation Trust London, United Kingdom (L.K.); Institute of Cardiovascular and Medical Sciences, Glasgow Royal Infirmary, University of Glasgow, United Kingdom (P.L.); Keele University Institute for Science and Technology in Medicine, Guy Hilton Research Centre, Stoke-on-Trent, United Kingdom (C.R.); Department of Neurology, Academic Medical Center, Amsterdam Neuroscience, University of Amsterdam, Netherlands (W.W., P.J.N., D.v.d.B.); Department of Medicine, Hospital Universitari Mutua de Terrassa, Barcelona, Spain (J.G.); Neurovascular Research Lab, Vall d'Hebron Research Institute, Barcelona, Spain (J.M.); Institute de Biomedicine of Seville, IBiS/Hospital Universitario Virgen del Rocío, University of Seville, Spain (J.M.); Department of Respiratory Medicine, Faculty of Medical and Human Sciences, Manchester Academic Health Science Centre, University of Manchester, Manchester University NHS Foundation Trust, United Kingdom (M.W.); and Department of Neurology, NeuroCure Clinical Research Center, Center for Stroke Research Berlin, Charité Universitaetsmedizin Berlin, Germany (A.M.).

Guest Editor for this article was Harold P. Adams, MD.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.020250/-/DC1.

Correspondence to Amit K. Kishore, MRCP, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Stott Lane, Salford, M6 8HD, United Kingdom. E-mail Amit.Kishore@manchester.ac.uk

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] Furthermore, acknowledging the limitations of current biomarkers and accessibility of microbiological samples, modified Centers for Disease Control and Prevention criteria were proposed to aid clinicians and researchers in diagnosing SAP in nonventilated 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 cause. The ability to better inform choice of antibiotic therapy in SAP, based on defined or likely microbial cause, might lead to improved outcomes and enhanced antibiotic stewardship. Identifying microbiological cause in nonventilated stroke patients is challenging because of 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] Although bacterial colonization 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 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and Cochrane guidance.[9,10] The authors declare that all supporting data are available within the article (and its online-only Data Supplement).

Data Sources and Searches

Searches were undertaken in medical databases including Medical Literature Analysis and Retrieval System Online (MEDLINE, National Institute of Health Library Interface, 1946–January 1, 2017), Excerpta Medica database (EMBASE, National Institute of Health Library Interface, 1947–January 1, 2017), Cumulative Index of Nursing and Allied Health Literature (CINAHL, National Institute of Health Library interface, 1937–January 1, 2017) and Cochrane Central Register of Controlled Trials (Wiley interface, current issue) using predefined search criteria and terms (Table I in the online-only Data Supplement). Hand searching of reference lists for additional eligible articles was also performed, 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, 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 2 reviewers (A.K.K. and C.J.S.), using the study title and abstract (Table II in the online-only Data Supplement). For those studies that used objective criteria for pneumonia but which had not 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 2 study investigators.

Data Extraction

Data were independently extracted by 2 reviewers (A.K.K. and A.V.) and included study design, sample size, publication status and demographical data (year of study, country of study, clinical environment), stroke type (ischemic, intracerebral hemorrhage, 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 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 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; and (3) frequency of identified pathogens across different geographical regions.

Risk of Bias and Quality Assessment

We anticipated inclusion of both randomized controlled trials and nonrandomized 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.[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 cause 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 (eg, 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

The studies included retrospective (40%) or prospective (33%) observational studies and randomized trials (27%).

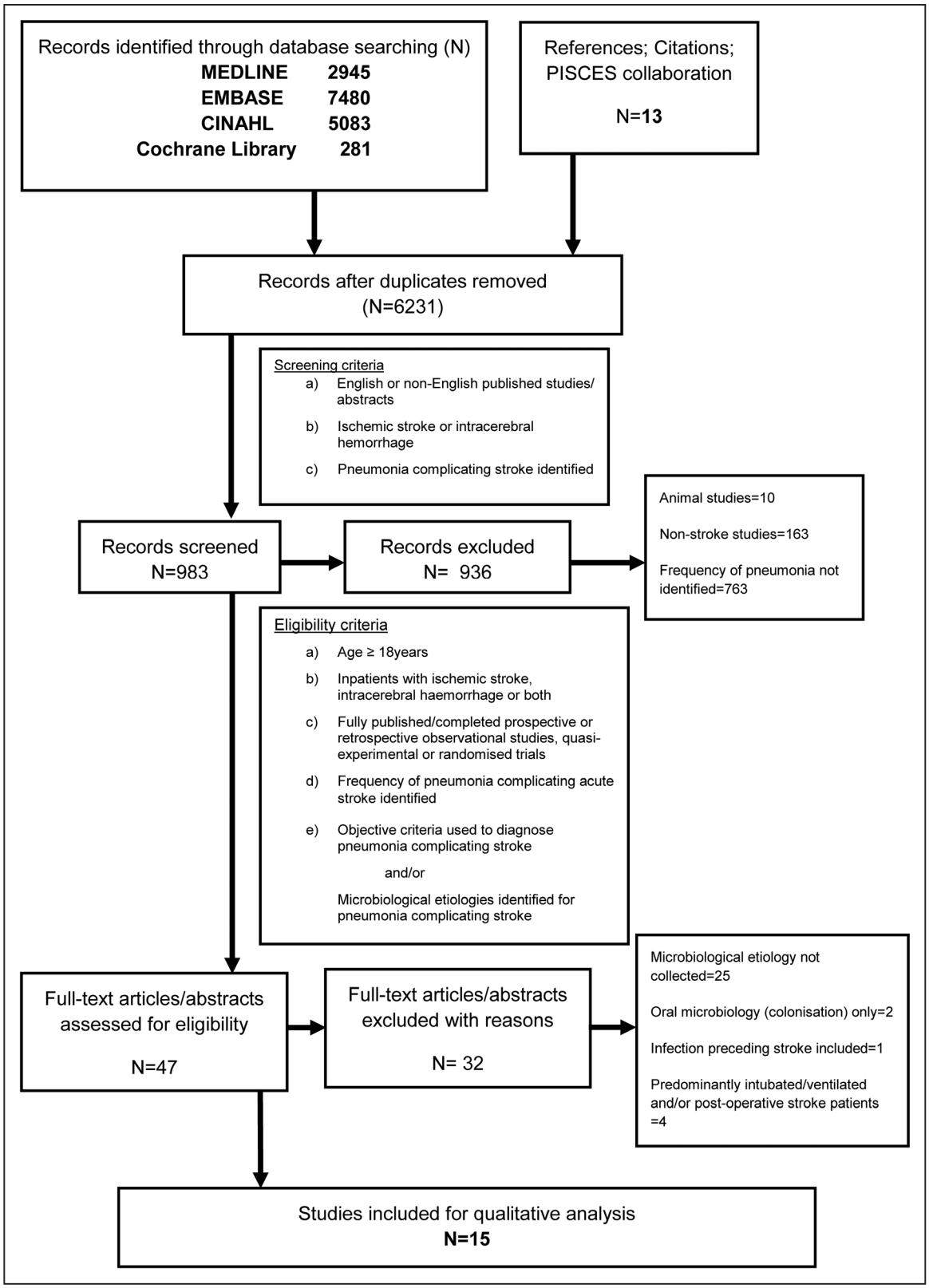


Figure 1. Flow diagram of systematic search methodology. CINAHL indicates Cumulative Index of Nursing and Allied Health Literature; and PISCES, Pneumonia in Stroke Consensus.

Fifty-four percent 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

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% <7 d	Sputum/ tracheal aspirate	45	2	2
Hassan	1998–2001	2006	Pakistan	3	443	2	1	64	68	NR	67% <2 d	Sputum/ tracheal aspirate	38	1	2
Vargas	2001–2002	2006	Spain	2	229	2	1	72.3	51	9	≤7 d	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	≤11 d	Ttracheal aspirate	45	1	3
Sui	2000–2009	2011	China	3	1435	2	2	67.2	55.4	7	63% <3 d	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% <3 d	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	United States	2	113	1	1	58	66	10	<15 d	Sputum	88	2	1
Warusevitane	2008–2011	2014	United Kingdom	1	60	2	1	77.5	37	19	94% <7 d	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	The Netherlands	1	2538	2	1	73.5	57	5	NR	Sputum/ blood	17	1	1

Design-1 denotes randomized controlled study; 2, prospective observational study; and 3, retrospective study. Stroke type-1 denotes ischemic stroke; 2, ischemic stroke and intracerebral hemorrhage. Setting-1 denotes ASU; 2, Stroke Intensive Care; 3, ASU and rehabilitation unit; and 4, unclear. Criteria-1 denotes Centers for Disease Control and Prevention Criteria; 2, Ad hoc objective criteria; 3, Mann Criteria; and 4, British Thoracic Society Criteria. Pneumonia risk stratification criteria-1 denotes low risk (unselected stroke patients with ≤15% intracerebral hemorrhage, mean NIHSS ≤5); 2, high risk (≥15% intracerebral hemorrhage, NIHSS ≥5); 3, very high risk (exclusively dysphagia studies, exclusively tube fed patients or studies involving patients in intensive care). ASU indicates acute stroke unit; NIHSS, National Institutes of Health Stroke Scale; and NR, not reported.

58 to 83 years. Baseline stroke severity (National Institutes of Health Stroke Scale) was reported in only 73% of studies, with a mean ranging from 5 to 19. Three studies were randomized controlled trials of prophylactic antibiotics.[11,15,25] Two studies were exclusively in nasogastric or percutaneous endoscopic gastrostomy tube-fed participants.[21,23] Thirty-three percent of the studies included mechanically ventilated patients. Entry criteria to the studies varied widely, with only 1 study having the identification of microbiological cause for pneumonia complicating stroke as a primary objective[12]; 2 studies excluded patients on immunosuppressive medication, with prior malignancy, or other forms of immunosuppression before stroke.[11,22] Other comorbidities and cardiovascular risk factor profiles were reported varyingly (Table III in the online-only Data Supplement; Table 1).

Diagnosis and Frequency of Pneumonia

Reported occurrence of pneumonia varied between studies (2%–63%). Pooled frequency of reported pneumonia was 23% (95% confidence interval, 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 intracerebral hemorrhage, 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 criteria (45%) and ad hoc objective criteria (40%) were the most commonly used objective criteria to diagnose pneumonia.

Microbiological Cause

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%–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 (Table IV in the online-only Data Supplement). No pathogen was identified in every study although *Staphylococcus aureus* was identified in positive cultures in 14 of 15 (93%) studies, whereas *Acinetobacter baumanii* was identified in positive cultures in only 6 of 15 (40%) studies (Table IV in the online-only

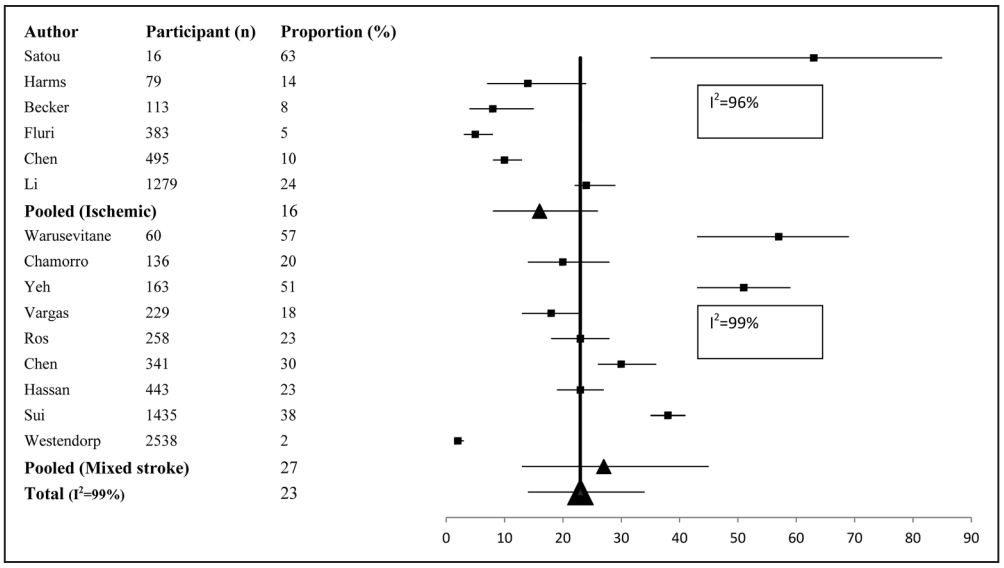


Figure 2. Forest plot of pneumonia frequency according to stroke subtype.

Data Supplement; 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 (38%) and Gram-positive cocci (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%), *A. baumanii* (4.6%), and *Streptococcus pneumoniae* (3.5%). Studies that included patients at relatively higher-risk of pneumonia, that is, exclusively dysphagic patients or intensive care studies,[15,17,19,21] were found to have a high proportion of aerobic Gram-negative bacilli and *S. aureus*, in comparison to lower risk studies (unselected stroke patients with ≤15% intracerebral hemorrhage and mean National Institutes of Health Stroke Scale score ≤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 hospitalized CAP, ventilator-associated pneumonia (VAP), and HAP (Table 2) from recent reviews of literature (terminologies defined in Table V in the online-only Data Supplement).[26–29] Geographical variations in bacterial cause 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% and 100%) as opposed to Western Europe or the United States (28% and 0%). Several organisms were reported with comparable frequency (range) to VAP or HAP (eg, *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 second/third generation cephalosporins) antibiotics±β-lactamase inhibitors and

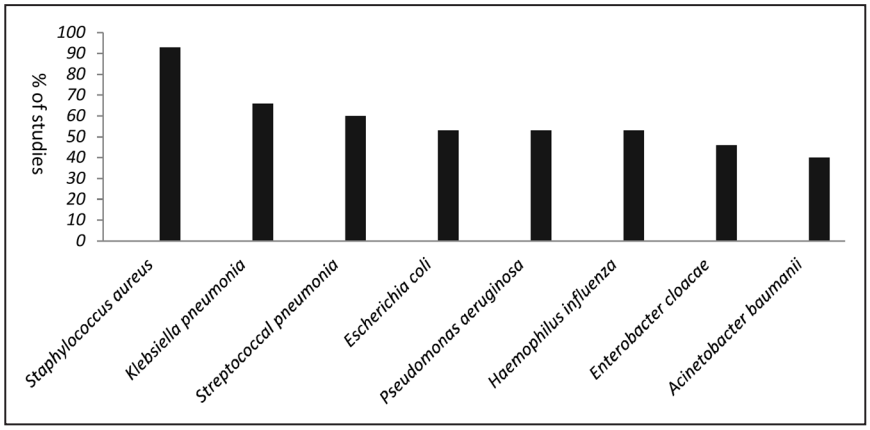


Figure 3. Proportion of studies identifying the 8 most commonly isolated organisms.

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, %)[26–28]	Pneumonia Complicating Stroke (Weighted Average With Range, %)
Gram-positive cocci				
Staphylococcus aureus	26.6–36.5	19.5–31.9	3–14.1	10.1 (0–36.3)
Streptococcal pneumoniae	1.8–3.2	<3	35–80	3.5 (0–10.7)
Gram-negative bacilli				
Klebsiella pneumoniae	8–10.5	6.6–10.2	3–6	12.8 (0–51)
Escherichia coli	4.6–10.1	3–5	6–12	9 (0–21.7)
Pseudomonas aeruginosa	19–22.4	21.4–26.6	2.8–9	6 (0–11.7)
Acinetobacter baumanii	4.4–13.3	14.3	3–14.3	4.6 (0–22.9)
Haemophilus influenzae	1.3–3.7	NR	5–40	1.9 (0–11.5)
Enterobacter cloacae	6.3–8.5	6–8.8	NR	1.7 (0–10)

CAP indicates community-acquired pneumonia; HAP, hospital-acquired pneumonia; NR, not recorded; and VAP, ventilator-associated pneumonia.

second/third generation fluoroquinolones and was always initiated before obtaining antibiotic sensitivities. Only 1 study reported the proportion of patients with pneumonia receiving antibiotics, the number of pneumonia episodes, and functional outcomes after 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 aerobic Gram-negative bacilli (eg, *K pneumoniae*, *E coli*, and *P aeruginosa*) and Gram-positive cocci (eg, *S aureus* and *S pneumoniae*) were associated with the majority of pneumonia complicating stroke when cultures were sent. A recent review suggested that ≈80% of hospitalized CAP were caused by *S pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Haemophilus influenza.*[26] The same review found that ≈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 seems to be more closely related to HAP than VAP or hospitalized CAP although antibiotic susceptibilities were not reported in most of the included studies. Furthermore, none of the included studies reported the results of investigations for viral or atypical pathogens, or even if they were done. Although our study is a comprehensive systematic literature research and collaboration within the PISCES group, our findings need to be interpreted with caution because of 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 (eg, bronchoscopy or tracheal aspirate) and also more frequent causes because of 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 categorization (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 (Figure I in the online-only Data Supplement). Sixty-six percent of the included studies in our review were deemed high or very high risk (Table I in the online-only Data Supplement) 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 standardized 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 cause, were also excluded unless specific mention was made about determining bacterial cause, which could have contributed to selection bias and heterogeneity. The variation in approach to diagnosis of pneumonia complicating stroke is well recognized,[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 cause of pneumonia complicating stroke,[12] whereas 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 with other clinical settings (eg, CAP or VAP), consistently obtaining sputum samples in nonventilated stroke patients is challenging and alternative strategies (eg, bronchoscopy for VAP) are limited. Third, it was unclear among 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. Although one could hypothesize that organisms commonly associated with CAP are most likely causal in early SAP (≤72 hours), and those associated with HAP causal in SAP beyond 72 hours, 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 because of sampling bias beyond 48 to 72 hours after stroke onset. Fourth, microbiological methods used to collect sputum samples, number of specimens sent when pneumonia was diagnosed, delays in analyzing samples if any, and laboratory techniques used were inadequately reported. None of the studies used modern molecular-based polymerase chain reaction methods or urinary antigen testing (for organisms, such as *S. pneumonia*e and *Legionella pneumophilia*). This may also contribute to differences in the observed frequencies of positive culture data and the apparent lack of atypical or viral causes. Interestingly, a recent study reviewing hospitalized patients identified ≈22% of CAP inpatients had viral pathogens (most commonly rhinovirus, 9% and influenza, 6%) implying that a viral cause 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 (Preventive Antibacterial Therapy in Acute Ischemic Stroke), when sputum samples were analyzed, 36% of samples were positive for organisms in the placebo group as opposed to 9% in the prophylactic antibiotic group.[15] Although the numbers are too small to form further conclusions, prophylactic antibiotics administered to the participating patients with stroke in the 3 randomized controlled trials may have affected frequency of identified organisms.

It is important to emphasize the differences in frequency of pathogens identified in Asian compared with European or North American studies. For example, in a study of hospitalized CAP patients, *S. pneumoniae* appeared to have a lower frequency (13% versus 26%) and *Enterobacteriaceae* appeared to have a higher frequency (9% versus 2.7%) in Asian studies as compared with European studies.[5] Similarly, although limited comparison was possible in our study, the frequency of certain nosocomial pathogens appeared to be higher in Asia or Asia Pacific regions (Table IV in the online-only Data Supplement) in keeping with higher prevalence of hospital-acquired infection (15.5%) in comparison to Europe (7.1%) or the United States (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.[4] 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 World Health Organization global strategy for containment of antimicrobial resistance[32] when recommendations are being made for prescribing empirical antibiotic regimens. Anaerobes, although not identified in our study, are commonly seen in the upper airway mixed with oral flora and in the stomach and 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 methods,[31] and delay in producing a positive result (at least 24–48 hours) often predisposes to initial broad-spectrum antibiotic prescriptions. An ideal diagnostic method would be more timely and sensitive to identifying pathogens. Polymerase chain reaction assays involving comprehensive molecular testing platforms significantly improve pathogen detection (87% versus 39%) in comparison to sputum culture (including viral pathogens) and provide results within 24 hours, 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 nonventilated stroke patients.

Conclusions

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 aerobic Gram-negative bacilli and Gram-positive cocci species are frequently associated with pneumonia complicating stroke. Difficulties in obtaining suitable sputum samples among nonventilated stroke patients and poor sensitivity of current diagnostic methods often result 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.

Acknowledgments

We acknowledge Dr Ryan Keh (Speciality Trainee in Neurology, Salford Royal NHS Foundation Trust) and Dr Luciana Miguel Alhambra (Clinical Fellow in Stroke Medicine, Salford Royal NHS Foundation Trust) for their assistance in translating non-English language studies for this review.

Sources of Funding

Dr Meisel is supported by the German Research Foundation (EXC257 and SFB-TR84).

Disclosures

Dr Meisel received project funding by Thermo Fisher Scientific BRAHMS GmbH, Germany for a stroke trial. The other authors report no conflicts.

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. doi: 10.1161/STROKEAHA.114.007843.
2. Westendorp WF, Nederkoorn PJ, Vermeij JD, Dijkgraaf MG, van de Beek D. Post-stroke infection: a systematic review and meta-analysis. *BMC Neurol*. 2011;11:110. doi: 10.1186/1471-2377-11-110.
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. doi: 10.1161/STROKEAHA.115.009617.
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;83:1225–1230. doi: 10.1136/jnnp-2012-302194.
5. Peto L, Nadjm B, Horby P, Ngan TT, van Doorn R, Van Kinh N, 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. doi: 10.1093/trstmh/tru058.
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 observational study. *Chest*. 2003;123:1142–1150.
7. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al; American Heart Association; American Stroke Association Stroke Council; Clinical Cardiology Council; Cardiovascular Radiology and Intervention Council; Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. 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;38:1655–1711. doi: 10.1161/STROKEAHA.107.181486.
8. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack. *Cerebrovasc Dis*. 2008; 25:457–507. doi: 10.1159/000131083.
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) 2015: elaboration and explanation. *BMJ*. 2015;350:g7647. doi: 10.1136/bmj.g7647.
10. Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration, 2011. http://handbook.cochrane.org. Accessed February 22, 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 randomized clinical trial. *Stroke*. 2005;36:1495–1500. doi: 10.1161/01.STR.0000170644.15504.49.
12. Hassan A, Khealani BA, Shafqat S, Aslam M, Salahuddin N, Syed NA, 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;37:461–465. doi: 10.1161/01.STR.0000199138.73365.b3.
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; 128:441–447.
15. Harms H, Prass K, Meisel C, Klehmet J, Rogge W, Drenckhahn C, et al. Preventive antibacterial therapy in acute ischemic stroke: a randomized controlled trial. *PLoS One*. 2008;3:e2158. doi: 10.1371/journal.pone.0002158.
16. Sui R, Zhang L. Risk factors of stroke-associated pneumonia in Chinese patients. *Neurol Res*. 2011;33:508–513. doi: 10.1179/016164111X13007856084205.
17. Yeh SJ, Huang KY, Wang TG, Chen YC, Chen CH, Tang SC, et al. Dysphagia screening decreases pneumonia in acute stroke patients admitted to the stroke intensive care unit. *J Neurol Sci*. 2011;306:38–41. doi: 10.1016/j.jns.2011.04.001.
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. doi: 10.1371/journal.pone.0048309.
19. Chen LF, Chang CY, Hsu LC, Tsai PH, Chang SJ, Chang SC, et al. Bacterial pneumonia following acute ischemic stroke. *J Chin Med Assoc*. 2013;76:78–82. doi: 10.1016/j.jcma.2012.10.005.
20. 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. doi: 10.1097/PHM.0b013e31824661a9.
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. *J Stroke Cerebrovasc Dis*. 2013;22:185–189. doi: 10.1016/j.jstrokecerebrovasdis.2011.07.008.
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. doi: 10.1007/s12028-013-9899-x.
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. doi: 10.1161/STROKEAHA.114.006639.
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. doi: 10.1371/journal.pone.0109665.
25. Westendorp WF, Vermeij JD, Zock E, Hooijenga IJ, Kruyt ND, Bosboom HJ, et al; PASS Investigators. The Preventive Antibiotics in Stroke Study (PASS): a pragmatic randomised open-label masked endpoint clinical trial. *Lancet*. 2015;385:1519–1526. doi: 10.1016/S0140-6736(14)62456-9.
26. Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis*. 2010;51(suppl 1):S81–S87. doi: 10.1086/653053.
27. Garau J, Calbo E. Community-acquired pneumonia. *Lancet*. 2008;371:455–458. doi: 10.1016/S0140-6736(08)60216-0.
28. Armstrong JR, Mosher BD. Aspiration pneumonia after stroke: intervention and prevention. *Neurohospitalist*. 2011;1:85–93. doi: 10.1177/1941875210395775.
29. Gadsby NJ, Russell CD, McHugh MP, Mark H, Conway Morris A, Laurenson IF, et al. Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. *Clin Infect Dis*. 2016;62:817–823. doi: 10.1093/cid/civ1214.
30. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among US adults. *N Engl J Med*. 2015;373:415–427. doi: 10.1056/NEJMoa1500245.
31. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet*. 2011;377:228–241. doi: 10.1016/S0140-6736(10)61458-4.
32. WHO (World Health Organization). Global Action Plan on Antimicrobial Resistance. http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/. Accessed November 10, 2017.

Stroke
Journal of the American Heart Association

Microbiological Etiologies of Pneumonia Complicating Stroke: A Systematic Review

Amit K. Kishore, Andy Vail, Adam R. Jeans, Angel Chamorro, Mario Di Napoli, Lalit Kalra, Peter Langhorne, Christine Roffe, Willeke Westendorp, Paul J. Nederkoorn, Javier Garau, Diederik van de Beek, Joan Montaner, Mark Woodhead, Andreas Meisel and Craig J. Smith on behalf of Pneumonia in Stroke Consensus (PISCES) Group

Stroke. 2018;49:1602-1609; originally published online June 18, 2018;
doi: 10.1161/STROKEAHA.117.020250
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENTAL MATERIAL

Microbiological etiologies of pneumonia complicating stroke: A systematic review

Amit K Kishore[1, 2] FRCP, Andy Vail[3] MSc, Adam Jeans[4] MD, Angel Chamorro[5] PhD, Mario Di Napoli[6] MD, Lalit Kalra[7] PhD, Peter Langhorne[8] PhD, Christine Roffe[9] MD, Willeke Westendorp[10] MD, Paul J Nederkoorn[10] PhD, Javier Garau[11], PhD, Diederik van de Beek[10] PhD, Joan Montaner[12,13] PhD, Mark Woodhead[14] DM, Andreas Meisel[15] MD, Craig J Smith[1]MD, on behalf of Pneumonia In Stroke ConsEnsuS (PISCES) Group.

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

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 ≥ 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	
Chamorro[1]	48	Yes	9.5	Excluded	17.6	16.9	12.5	NR	63.2	22.8	0
Hassan[2]	NR	No	NR	NR	NR	NR	NR	NR	NR	NR	0
Vargas[3]	42	NR	10	4.3	16.1	16	NR	NR	60	19	0
Ros[4]	NR	NR	NR	NR	12.4	NR	13.2	12.8	63.2	35.3	0
Harms[5]	66	Yes	7.5	8.8	11.4	11.4	37.2	34.1	64.5	31.6	8.8
Sui[6]	47	NR	NR	NR	NR	49	32	NR	NR	44	2.2
Yeh[7]	73	No	NR	NR	NR	NR	NR	NR	NR	NR	12.2
Fluri[8]	NR	NR	NR	NR	NR	NR	34	19.4	80	19.3	0
Chen[9]	58	NR	NR	NR	NR	NR	NR	NR	82	39	0.3
Chen[10]	NR	NR	25.5*	14*	31.4*	43*	27.5*	NR	70.6 *	29.4*	23.5*
Satou[11]	100	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Becker [12]	NR	No	NR	Excluded	35.3	37	24	NR	53.1	24	NR
Warusevitane[13]	100	No	16	NR	NR	NR	NR	60	66	28	0
Li[14]	NR	NR	NR	NR	NR	40	NR	NR	74	20	NR
Westendorp[15]	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*

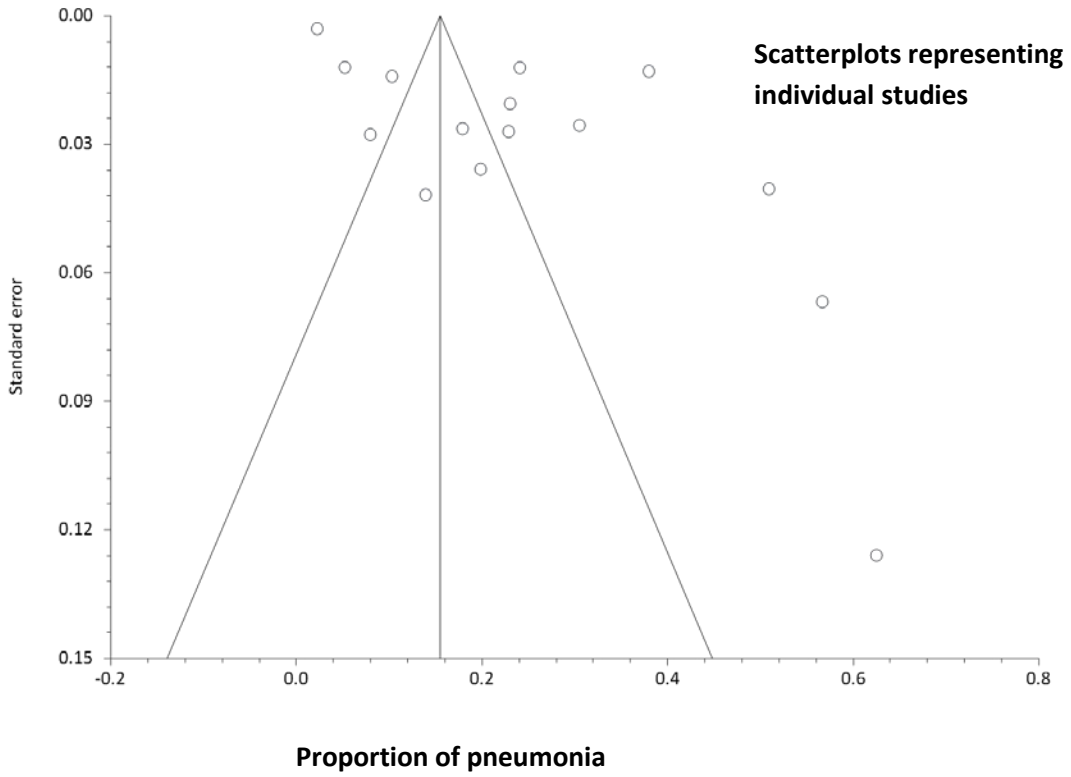
Online only Table IV: The eight most commonly isolated organisms in positive cultures (%) in the included studies

	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															
Staphylococcus aureus	11	×	5	36.3	5	22.2	11.7	1.7	9.3	19.2	6.8	20	11.7	24.1	1.9
Streptococcal pneumoniae	3.7	2.4	×	9	×	×	×	1.7	0.5	1.2	10.7	×	3.9	2.8	1
GRAM NEGATIVE BACILLI															
Klebsiella pneumoniae	×	×	5	×	×	11.1	11.7	×	8.8	51	18.2	10	3.9	15.4	23.5
Escherichia coli	×	7.3	×	×	×	×	5.8	×	7.7	9	21.7	×	1.9	2.8	10
Enterobacter cloacae	×	7.3	1.7	×	×	×	5.8	×	×	9.6	×	×	1.9	3.8	10
Pseudomonas aeruginosa	×	2.4	×	×	×	11.1	×	×	6.6	4.8	8.2	×	11.7	6.7	3.9
Haemophilus influenzae	3.7	21.9	×	×	5	11.1	×	×	6.6	×	×	×	3.9	11.5	7.8
Acinetobacter baumanii	×	×	×	×	×	×	×	×	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, TsaiWS, 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, Huckabeee 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 EmergencyMedicine.*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 Thrombolyzed 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, Patejdla R, Steinhagena 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, Hodsoll J, Simpson M, Gulliford G, Smithard D, et al, on behalf of the STROKE-INF InvestigatorsProphylactic 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.