Special Report

Diagnosis of Stroke-Associated Pneumonia

Recommendations From the Pneumonia in Stroke Consensus Group

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Background and Purpose—Lower respiratory tract infections frequently complicate stroke and adversely affect outcome. There is currently no agreed terminology or gold-standard diagnostic criteria for the spectrum of lower respiratory tract infections complicating stroke, which has implications for clinical practice and research. The aim of this consensus was to propose standardized terminology and operational diagnostic criteria for lower respiratory tract infections complicating acute stroke.

Methods—Systematic literature searches of multiple electronic databases were undertaken. An evidence review and 2 rounds of consensus consultation were completed before a final consensus meeting in September 2014, held in Manchester, United Kingdom. Consensus was defined a priori as ≥75% agreement between the consensus group members.

Results—Consensus was reached for the following: (1) stroke-associated pneumonia (SAP) is the recommended terminology for the spectrum of lower respiratory tract infections within the first 7 days after stroke onset; (2) modified Centers for Disease Control and Prevention (CDC) criteria are proposed for SAP as follows—probable SAP: CDC criteria met, but typical chest x-ray changes absent even after repeat or serial chest x-ray; definite SAP: CDC criteria met, including typical chest x-ray changes; (3) there is limited evidence for a diagnostic role of white blood cell count or C-reactive protein in SAP; and (4) there is insufficient evidence for the use of other biomarkers (eg, procalcitonin).

Conclusions—Consensus operational criteria for the terminology and diagnosis of SAP are proposed based on the CDC criteria. These require prospective evaluation in patients with stroke to determine their reliability, validity, impact on clinician behaviors (including antibiotic prescribing), and clinical outcomes.

Key Words: consensus ■ C-reactive protein ■ pneumonia ■ respiratory tract infections ■ stroke

Infections frequently complicate stroke and have a significant impact on prognosis, length of stay, and healthcare costs.[1–3] Varying terminologies (eg, chest infection, stroke-associated pneumonia [SAP], aspiration pneumonia, poststroke pneumonia) and diagnostic approaches are used for the spectrum of lower respiratory tract infection (LRTI) complicating stroke.[4] Diagnosing pneumonia in acute stroke poses particular challenges,[4] and chest radiography may have

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limited use in the early stages.[5] Although diagnostic criteria for community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia are available,[6–9] there are currently no gold-standard or agreed criteria for categorizing LRTI or diagnosing pneumonia in acute stroke. Variations in the approach to diagnosing pneumonia complicating acute stroke are well-recognized in research and clinical practice,[4,10] which may lead to delayed or inappropriate antibiotic therapy. To address these issues, we convened a multidisciplinary group (Pneumonia in Stroke Consensus [PISCES] Group) with the aim of proposing consensus-based, standardized terminology and operational diagnostic criteria for the spectrum of LRTI complicating acute stroke for use in clinical practice and research.

Methods

Membership of the PISCES Group and Protocol Development

The PISCES group was convened by the Chair (C.J.S.) on the basis of collective multidisciplinary expertise across the spectrum of SAP, pneumonia, respiratory medicine, biomarkers, stroke unit management, systematic review, biomedical statistics, and clinical guidelines. The protocol was drafted by the chair and reviewed by the group to define the objectives, methodology, and statements for consensus.

Systematic Reviews

Two systematic reviews were undertaken to inform the consensus process. The first addressed the variation in terminology and diagnostic criteria of pneumonia complicating stroke and has been reported previously.[4] A second review was undertaken in multiple electronic databases using predefined search criteria and terms (Table I in the online-only Data Supplement). Published studies of hospitalized adults with ischemic stroke, intracerebral hemorrhage, or both, which related any biomarkers to diagnostic accuracy or prediction of pneumonia up to 1 March, 2014, were independently screened for eligibility (Table II in the online-only Data Supplement) by 2 investigators (A.K.K. and C.J.S.), using the study title and abstract. Ongoing studies/trials were also screened. In addition, 1 investigator (C.J.S.) hand-searched reference lists, and the PISCES group members were invited to provide any other potentially eligible articles. Studies not reporting infection/pneumonia during follow-up, studies of exclusively intubated and ventilated patients or studies including patients with pre-existing pneumonia were excluded. Lead/corresponding authors were contacted to resolve eligibility or data extraction issues, and discrepancies were resolved by discussion between the same 2 study investigators. Data extracted included study design, stroke subtype, sample size, mean age, mean National Institutes of Health Stroke Scale score, biomarker(s) measured, criteria used in diagnosis of pneumonia, clinical environment, country, proportion with pneumonia, and main findings with respect to diagnostic accuracy or prediction of pneumonia.

Consensus Process

Statements for consensus and an accompanying evidence review based on the systematic reviews were circulated to the group. Two rounds of consensus consultation were completed by e-mail, and collated by the chair, before a final consensus meeting on 24th to 25th September, 2014, held in Manchester, United Kingdom. The PISCES group independently ranked the statements and provided free-text comments. Consensus was approached using a modified Delphi technique[11] and defined a priori as ≥75% agreement between the consensus group members.

Results

The main recommendations of the consensus process are summarized in Table 1. The items considered and details of the preliminary and final consensus are summarized in Table III in the online-only Data Supplement.

Scope of Consensus

The need for operational diagnostic criteria and terminology which apply to both clinical care and research, excluding mechanically ventilated patients, was agreed by preliminary consensus. The group agreed that the remit would not include recommendations about the management of pneumonia (including initiation or choice of antimicrobial therapy) because of insufficient evidence in the stroke unit setting.

LRTI Complicating Stroke: Which Terminology and When?

The terminology covering the spectrum of LRTI in stroke is dominated by the concept of pneumonia, usually with accompanying chest x-ray (CXR) changes.[4] A spectrum of acute lower respiratory tract syndromes complicating stroke, which may or may not meet radiological criteria for pneumonia, and may even be noninfective (eg, aspiration pneumonitis), was considered. However, pneumonia was agreed as the starting-point for operational terminology given the widespread acceptance and familiarity of the concept of pneumonia in acute stroke care, and a lack of accepted definitions for alternative terms, such as stroke-associated chest infection, stroke-associated LRTI, and stroke-associated acute respiratory syndrome.

Pneumonia occurs most frequently within the first week of stroke onset,[12] probably reflecting the highest risk period in terms

Table 1. Summary of Pneumonia In Stroke ConsEnsuS (PISCES) Group Recommendations

SAP is the recommended terminology for the spectrum of pneumonia complicating the first 7 days after stroke onset in nonventilated patients
After 7 days from stroke onset, existing diagnostic criteria for hospital-acquired pneumonia should be followed for inpatients. Existing diagnostic criteria for ventilator-associated pneumonia are recommended for patients receiving mechanical ventilation
There is currently insufficient evidence about diagnostic accuracy of clinical symptoms (eg, cough, purulent sputum), signs (eg, fever, tachypnea), or laboratory investigations (eg, white blood cell count, C-reactive protein) for SAP. In the absence of validated clinical or laboratory criteria in the acute stroke setting, modified CDC criteria for clinically defined pneumonia are recommended for SAP
Categories of probable or definite SAP are recommended, based on the absence or presence of definitive appearances on chest radiographs, where the remaining CDC criteria are met. Where initial chest radiographs are negative (or inadequate) in probable SAP, the chest radiograph should be repeated 2 days later in the first instance
The modified CDC criteria for probable and definite SAP require rigorous prospective validation. The diagnostic accuracy of clinical variables, lung ultrasound, and biomarkers (routine or novel) for SAP, and their value in guiding antibiotic initiation and informing prognosis also requires further study

CDC indicates Centers for Disease Control and Prevention; and SAP, stroke-associated pneumonia.

of prevalence of dysphagia, immobility, impaired consciousness, and suppressed immune responses.[13,14] There was agreement that the diagnostic challenges associated with pneumonia in the setting of stroke were predominantly during this acute phase. A time-limited component to the terminology of SAP was therefore agreed, arbitrarily restricting SAP to the first 7 days after stroke onset. This is not based on pathological or microbiological grounds (as in the case of CAP and HAP), because of insufficient evidence, nor is it indicative of particular antibiotic requirements.

Recommendation

SAP is the preferred diagnostic terminology covering the spectrum of LRTI complicating stroke within the first week. For hospitalized patients beyond 7 days of stroke onset, HAP is the recommended terminology.

Role of the CXR in Diagnosing SAP: Probable and Definite SAP

Chest radiography is frequently normal in the early evaluation of both CAP and HAP.[15,16] In suspected SAP, typical diagnostic appearances on initial CXR were present in only 36%.[5] This raises the question as to whether typical CXR changes are mandatory for a diagnosis of SAP. Clinical suspicion of pneumonia, without diagnostic appearances on initial CXR, may represent (1) a different clinical or pathological LRTI syndrome; (2) an inadequate CXR; (3) a CXR undertaken before evolution of typical diagnostic appearances; (4) early antibiotic initiation averting the development of radiological changes. Consensus was reached that typical CXR changes of pneumonia were not mandatory for the diagnosis of SAP, but could be used as a criterion for differentiating probable from definite SAP, in the absence of routine use of additional imaging (eg, chest ultrasound or computed tomography).

Recommendation

Categories of probable SAP and definite SAP are recommended, differing in their requirement for typical diagnostic CXR changes.

Blood Biomarkers for Diagnosis of SAP

Five published studies of acute ischemic stroke (n=1106 participants; mean age, 71.0±1.4 years; mean NIHSS, 9.4±3.9) reporting an association between blood biomarkers with pneumonia, and prediction (area under the curve) of pneumonia, were identified (Figure I and Table IV in the online-only Data Supplement).[17–21] Several inflammatory/stress biomarkers (white blood cell [WBC] count [80%], C-reactive protein [CRP, 60%], procalcitonin [PCT, 60%], interleukin-6, glucose, copeptin, mHLA-DRII expression, normetanephrine, metanephrine) were evaluated, with sampling most frequently within 24 hours of stroke symptom onset. At least 2 sampling time points within the first 5 days of stroke were used in the majority (60%). None of the studies evaluated diagnostic performance of biomarkers sampled at the time of clinical suspicion of pneumonia, or their role in clinical decision-making (eg, initiation of antibiotics). Several biomarkers (eg, CRP, interleukin-6, PCT) were independently associated with pneumonia in some studies, but not others. Combination biomarker panels (WBC count, CRP, copeptin area under the curve 0.92; WBC count, CRP, PCT area under the curve 0.90) improved prediction of evolving pneumonia in 1 study.[19] Five ongoing or recently completed (unpublished) studies relating biomarkers to pneumonia diagnosis or prediction were also identified (Predictors of Sepsis [PRED-SEP], Predictors of Early Chest Infection in Acute Ischemic Stroke [PRECAST], Prediction of Stroke-Associated Pneumonia [PREDICT], Stroke Adverse Outcome Is Associated With Nosocomial Infections [STRAWINSKI], Copeptin and Risk Stratification in Patients With Ischemic Stroke and Transient Ischemic Attack [CoRisk]; Table V in the online-only Data Supplement).[22–26]

Recommendation

There is limited evidence for a diagnostic role of WBC count or CRP in discrimination of SAP. There is currently insufficient evidence for the use of other blood biomarkers in discrimination of SAP.

Which Diagnostic Criteria Should be Used for SAP?

No diagnostic clinical criteria have been validated in SAP. The options considered for consensus recommendation were to: (1) propose novel consensus diagnostic criteria; (2) apply existing diagnostic criteria for pneumonia (eg, Centers for Disease Control and Prevention [CDC][7] or Mann[27]); (3) modify existing diagnostic criteria. The concurrent validity of any symptoms or signs (or biomarkers) for definite SAP is not known, and it was agreed there was insufficient evidence to propose novel diagnostic criteria for SAP.

Recommendation

There is insufficient evidence to propose novel diagnostic criteria for probable or definite SAP.

The CDC and Mann criteria were proposed in the preliminary consensus process. Both share some components (Table VI in the online-only Data Supplement) but have important differences as follows: (1) The Mann criteria components are equally weighted (require ≥ any 3 from single list), whereas the CDC criteria have hierarchical arrangements of symptoms, signs, or investigations; (2) CXR changes are mandatory in CDC but not in Mann; (3) WBC count criteria and altered mental status appear in the CDC but not the Mann criteria; and (4) identification of a relevant pathogen appears in the Mann but not the CDC criteria. When considering the CDC or Mann as operational criteria for SAP, consensus was achieved in recommending modified CDC criteria for definite SAP and probable SAP (Table 2). The modifications were to use definite CXR changes to differentiate probable and definite SAP and removal of reference to increased ventilator demand.

Recommendation

Modified CDC criteria are recommended for the diagnosis of SAP:

Probable SAP

All CDC criteria met but in the absence of diagnostic changes on initial CXR AND repeat CXR (or where CXR not undertaken), and no alternative explanation or diagnosis.

Definite SAP

All CDC criteria met including diagnostic CXR changes on at least one CXR.

Table 2. Recommended Diagnostic Criteria for Definite and Probable SAP in Patients Not Receiving Mechanical Ventilation Based on the CDC Criteria[7]

At least 1 of the following:

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

And at least 2 of the following:

1. New onset of purulent sputum, or change in character of sputum over a 24 h period, or increased respiratory secretions, or increased suctioning requirements
2. New onset or worsening cough, or dyspnea, or tachypnea (respiratory rate>25/min)
3. Rales, crackles, or bronchial breath sounds
4. Worsening gas exchange (eg, O_2 desaturation [eg, $Pao_2/FiO_2 \leq 240$], increased oxygen requirements*)

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

New or progressive and persistent infiltrate, consolidation, or cavitation

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

Probable SAP: all CDC criteria met, BUT initial CXR and serial/repeat CXR nonconfirmatory (or not undertaken), and no alternative diagnosis or explanation. Definite SAP: ALL CDC criteria met, including diagnostic CXR changes (on at least one). CDC indicates Centers for Disease Control and Prevention; CXR, chest x-ray; FiO2, fraction of inspired oxygen; Pao_2, partial pressure oxygen; SAP, stroke-associated pneumonia; and WBC, white blood cell.

*Category of increased ventilator demand removed.

†CDC recommendation is for repeat CXR at days 2±7 if initial CXR negative.

Discussion

Our recommendations for SAP terminology and diagnostic criteria are intended as a starting point for both hospital-based clinical practice and research. In the absence of existing validated diagnostic criteria for SAP, we modified the CDC criteria,[7] which were originally developed for HAP. When applying these criteria to SAP, several aspects warrant further discussion and clarification.

First, the CDC criteria recommend that in patients with pre-existing cardiopulmonary disease, CXR is repeated on days 2 and 7 after the initial assessment. We acknowledge that serial CXR (especially if only to positively identify confirmatory changes compatible with pneumonia) may not reflect usual practice in many centres. We also acknowledge that interpretation of CXR changes may be a source of inter-rater and intersite reliability issues, and reporting by radiologists is recommended. Second, there is currently insufficient evidence for recommending particular thresholds for fever or WBC count in the diagnosis of SAP. This is confounded by the variability of the acute-phase response between individuals, including the influence of stroke severity, and timing of measurement.[28–30] In addition, the widespread use of antipyretics (aspirin and paracetamol) in acute stroke may mask fever. However, clinicians attach significance to leukocytosis/fever and CRP in the diagnosis of SAP,[10] and the thresholds for WBC count/fever in the CDC criteria were therefore considered acceptable in the absence of specific evidence in SAP. Third, the usefulness of confusion, delirium, or neurological deterioration when considering a diagnosis of SAP is uncertain. The criterion of altered mental status in the CDC criteria was felt to be acceptable, if measured objectively and other potential alternative causes excluded. Fourth, the diagnostic accuracy or performance of respiratory variables in isolation, or in combination, for discriminating SAP is unclear. The CDC thresholds for respiratory rate and gas exchange were deemed acceptable in the absence of data specifically in patients with stroke (the Pao_2/FiO_2 ratio can still be applied in patients not receiving mechanical ventilation). Finally, the absence of criteria for positive sputum (or blood) culture in the CDC criteria, when compared with the Mann criteria, was recognized. However, in patients with stroke not receiving ventilation, negative sputum cultures (31.4%–83.3%), and blood cultures (94.1%) are frequent.[30–34]

Definitions for CAP (pneumonia that is acquired outside hospital) and HAP (pneumonia that develops 48 hours or more after hospital admission) are based on data suggesting different causative micro-organisms in these groups. In addition, Healthcare-Associated Pneumonia (HCAP) has been proposed to incorporate individuals with prior hospitalization, residence in an institution, preceding intravenous antibiotics, chemotherapy or wound care, or hospital or hemodialysis clinic attendance.[35] Our use of the term SAP, and its restriction to the first 7 days after stroke, is arbitrary and does not imply specific pathophysiological or microbiological pathogenesis. The changes in oropharyngeal and nasopharyngeal flora after admission to the stroke unit setting from community or institutional settings, and the spectrum of culpable organisms in nonventilated stroke patients are not well characterized. LRTIs commonly precede stroke,[36] particularly in the 3 days preceding stroke onset,[37] and may therefore manifest at the time of stroke presentation or the days following. Organisms implicated from sputum culture/tracheal aspirates in nonventilated patients during the first 7 days after stroke suggest a predominance of organisms associated with HAP (*Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter sp., Escherischia coli*, and *Staphylococcus aureus*), but also organisms associated with CAP (*Streptococcus pneumoniae* and *Haemophilus sp.*), particularly within 48 hours.[31–34,38,39]

Our proposed diagnostic criteria require rigorous validation to establish their usefulness in clinical practice and research. One issue in evaluating concurrent validity of such criteria is the choice of a definitive gold-standard, although this is a similar issue in other classifications of pneumonia, even ventilator-associated pneumonia, where microbiological specimens are more accessible.[40] In nonventilated patients with stroke, definitive microbiological sampling (eg, bronchoalveolar lavage) is impractical. Use of serial CXR to confirm infiltrate, as recommended by the CDC criteria, may be of value. Additional imaging techniques, such as chest computed tomography and lung ultrasound, can increase diagnostic yield of pneumonia in various settings,[15,16,41,42] but have so far received little attention in SAP. A study evaluating paired CXR and lung ultrasound in patients with suspected SAP found that lung ultrasound increased the diagnostic yield of

radiologically confirmed SAP when the CXR was negative.[5] Thoracic computed tomography was undertaken when findings of CXR and ultrasound were discordant and confirmed the findings of ultrasound in these cases.

Conclusions

Consensus operational criteria for the terminology and diagnosis of definite and probable SAP are proposed based on the CDC criteria. These require prospective evaluation to determine their reliability, validity, impact on clinician behaviors (including antibiotic prescribing), and clinical outcomes.

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SUPPLEMENTAL MATERIAL

Diagnosis of stroke-associated pneumonia: a consensus statement from the Pneumonia In Stroke ConsEnsuS (PISCES) Group

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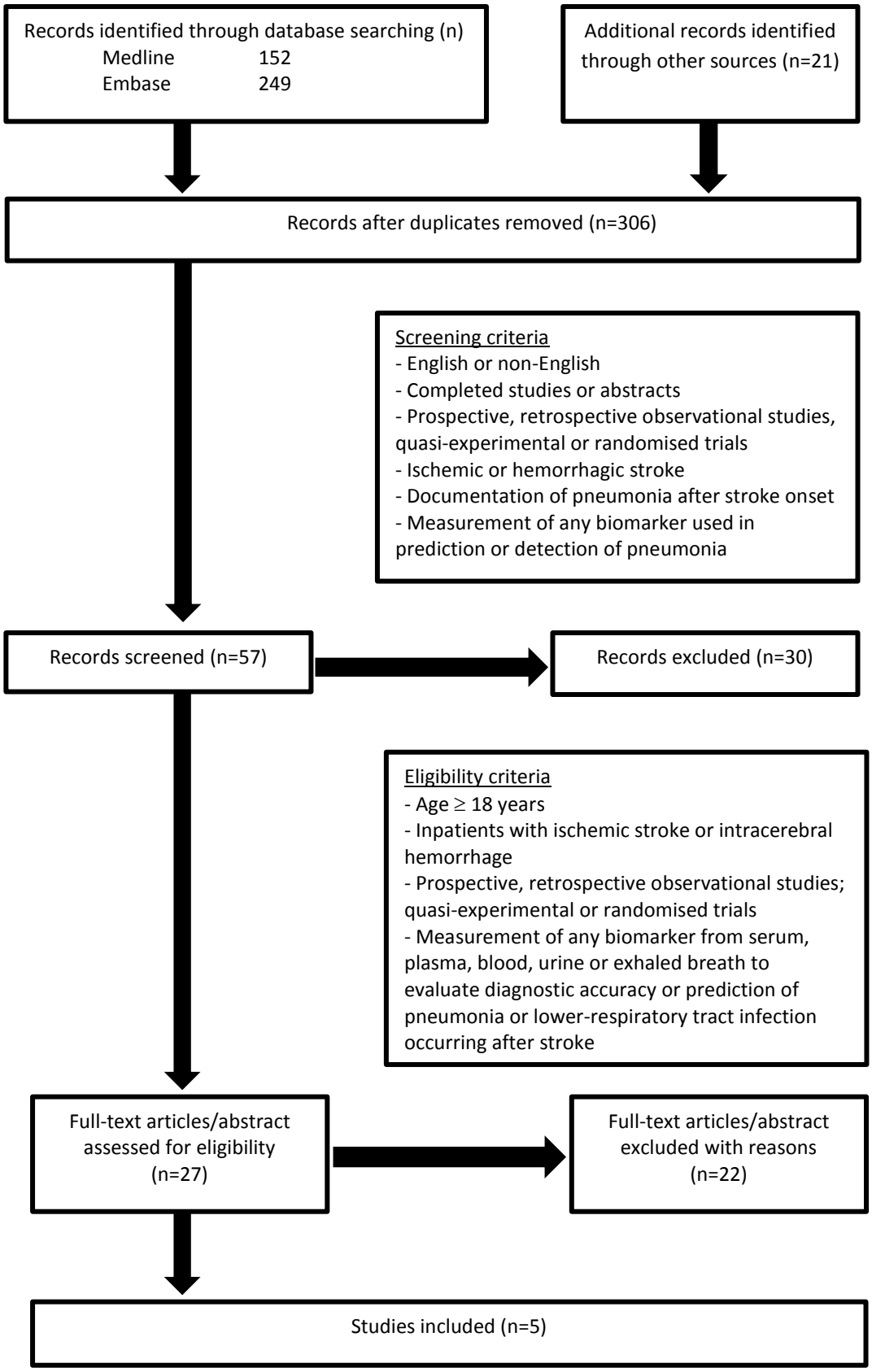
Cover title: Stroke-associated pneumonia consensus statement

Itemized list of figures and tables:

Online only Figure I: Flow diagram of search methodology and outcome



Online only Table I: Search terms

Search Areas	Thesaurus terms	Free Text Terms
MEDLINE	Subject Search in MESH: exp*Cerebrovascular disorders/; exp*Pneumonia/; exp*Cytokines/exp*Acute Phase Proteins/;exp*Biological Markers	Stroke*,Pneumonia*, respiratory tract infection*, chest infection*, hospital acquired pneumonia*, C reactive protein*, biological markers*, Cytokine*, Co-peptin*, Procalcitonin*, interleukin*, proadrenomedullin*, natriuretic peptide*, interleukin*, leukocyte*
EMBASE	Subject Search on EMTREE: exp*Cerebrovascular disease/ exp*Pneumonia/;exp * Marker/;exp* Cytokine/;exp*C reactive protein/;exp*Acute Phase Protein/;exp*Immune response	Stroke*, Pneumonia*, respiratory tract infection*, chest infection*, hospital acquired pneumonia*, biological marker*, cytokine*, C reactive protein*, Co-peptin*, Procalcitonin*, interleukin*, proadrenomedullin*, natriuretic peptide*, interleukin*, leukocyte*

Online only Table II: Inclusion/exclusion criteria

Inclusion criteria:
Inpatients with ischemic and/or hemorrhagic stroke
Age ≥ 18years
Measurement of any biomarker from plasma, serum, blood, urine or exhaled breath to evaluate diagnostic accuracy or prediction of pneumonia or lower-respiratory tract infection
Prospective or retrospective observational studies, quasi-experimental or randomised trials reviews
Completed studies or published abstracts
English or non-English language

Exclusion criteria:
Infection and/or pneumonia/ respiratory tract infection not recorded during follow-up
Frequency of pneumonia or respiratory tract infection not reported separately from frequency of infection
Exclusively intubated/ventilated patients*
Exclusively pneumonia preceding index stroke
Publication after March 1st 2014

Online only Table III: Summary of consensus items and process

Item	% agreement	
	Preliminary consensus	Final consensus
Scope of consensus		
Operational criteria required for spectrum of LRTI	100	100
For clinical care	92.3	100
For stroke research	100	100
Patients not receiving mechanical ventilation	100	100
What is the preferred terminology for confirmed pneumonia complicating stroke?		
Stroke-associated pneumonia	84.6	
Aspiration pneumonia	0	
Post-stroke pneumonia	7.7	
Hospital acquired pneumonia	7.7	
Other	0	
Definite stroke-associated pneumonia		100
Would a diagnostic category for suspected or probable pneumonia be useful?	84.6	100
What should the proposed terminology be?		
Suspected stroke-associated pneumonia	53.8	0
Probable stroke-associated pneumonia	23.1	100
Stroke-associated chest infection	7.7	0
Other	7.7	0
An abnormal CXR is mandatory for diagnosis of pneumonia	46.2	0
Should existing published standard diagnostic criteria be applied?		
Mann criteria	7.7	12.5
CDC criteria	38.5	87.5
Unsure which	23.1	0
No	30.8	0
Modifications to CDC criteria proposed		100
Is there sufficient evidence to support proposing de novo diagnostic criteria?		
Yes		0
No		100
Should operational criteria proposed be used to inform initiation of antibiotics?	61.5	0
Should there be a time-limited component when defining pneumonia complicating stroke?		
Within first 72h	15.4	
Within first 4d	15.4	
Within first 7 d	7.7	100
Unsure	61.5	
What threshold would you recommend for fever?		
> 37.5°C	7.1	
≥ 37.5°C	14.3	
> 38°C	28.6	
≥ 38°C	7.1	
> 38.5°C	0	
≥ 38.5°C	7.1	
Uncertain or threshold unknown	35.7	100
What threshold would you recommend for WBC count?		
> 12,000 or < 4000 x10^9/l	20.0	6.7
> 11,000 or < 4000 x10^9/l	20.0	0
Above reference range for laboratory	13.3	0
Uncertain or threshold unknown	46.7	93.3
What threshold would you recommend for CRP?		
> 50mg/ml	7.1	0
≥ 50mg/ml	14.3	6.7
Uncertain or threshold unknown	78.6	93.3
What threshold would you recommend for procalcitonin?		
> 0.5ng/ml	0	
≥ 0.5ng/ml	13.3	
Uncertain or threshold unknown	86.7	100
Is there currently any evidence supporting use of any other biomarkers?		
No	100	100
Yes	0	0

LRTI indicates lower respiratory tract infection; CXR, chest x-ray; CDC, Centers for Disease Control and Prevention; WBC, white blood cell; CRP, C-reactive protein

Online only Table IV: Biomarkers in pneumonia complicating stroke

Study	Design and country	Participants	Mean age± SD (y)	Median NIHSS	Biomarker(s)	Definition of pneumonia	Occurrence of pneumonia/infections	Main findings
Harms et al, 2013[1]	Prospective observational Germany	Ischemic stroke MCA territory <24h onset n=335	69.9 ± 13.4	NR	WBC count, glucose <24h of admission	CDC	31.3% pneumonia From admission to d7	WBC>11.000/μL independently associated with pneumonia (OR 5.99; 95% CI 2.68 to 13.37) WBC count incorporated in PANTHERIS score (AUC 0.85)
Zhang et al, 2012[2]	Prospective observational China	Ischemic stroke Diabetic <24h onset n=106	70.3*	11*	WBC count, body temperature, IL-6, CRP <24h + 8h fasting	Not reported	30.2% pneumonia	Age, NIHSS, CRP and IL-6 independently associated with pneumonia
Fluri et al, 2012[3]	Prospective observational Switzerland	Ischemic stroke <72h onset n=383	71.4 ±13.7	5 (IQR 2-10)	WBC/monocyte count, CRP, PCT, copeptin <72h + 24h + 72h	CDC	5.2% pneumonia 6.5% UTI 5.5% other infection From admission + d5	WBC, CRP, PCT, copeptin all associated with pneumonia in bivariate analyses Combination of WBC, CRP and copeptin optimised discrimination of pneumonia (AUC 0.92)
Hug et al, 2011[4]	Prospective observational	Ischemic stroke < 12h onset n=50	73.28*	12.2*	PCT, WBC, HLA-DRII d1 and d4	Objective, *ad hoc*	36% pneumonia 14% UTI	Infarct volume strong discriminator of pneumonia (AUC 0.96) PCT, WBC, HLA-DRII not independently associated with pneumonia d4 PCT AUC 0.79 for pneumonia; d4 cut-off >0.25ng/ml specificity 96% for pneumonia
Walter et al, 2010[5] PRECAST interim analyses‡	Prospective observational Germany	Ischemic stroke <24h onset n=232	70.2±13.2	5 (IQR 2-14)	WBC count and differential, surface markers, PCT, CRP, IL-10, metanephrine, normetanephrine, <24h + next 0800-0900	CDC	19% chest infection >24h from admission to d7	NIHSS≥10, normetanephrine>90ng/l and eosinophil count <53/μl independent predictors of pneumonia

MCA indicates middle cerebral artery; NR, Not recorded; WBC, White blood cell; CDC, Centers for Disease Control and Prevention; OR, Odds ratio; AUC, Area under the receiver operating characteristic curve; PANTHERIS, Preventive Antibacterial THERapy in acute Ischemic Stroke; IL-6, Interleukin-6; CRP, C-reactive protein; NIHSS, National Institutes of Health Stroke Scale; UTI, Urinary tract infection; PCT, procalcitonin; HLA-DRII, Human leucocyte antigen-DRII; PRECAST, Predictors of chest infection in acute ischemic stroke; IL-10, interleukin-10

*‡Abstract; *weighted mean difference calculated from mean for those with and without pneumonia*

Online only Table V: Ongoing or recently completed (unpublished) studies evaluating biomarkers in stroke-associated infections

Study	Design	Eligibility	Intervention	Biomarkers/variables	Primary outcome measure	Secondary endpoints	Planned sample size
Brämer et al, 2014[6] PRED-SEP DRKS00003392 Planned: Feb 2012-May 2014	Prospective observational Single-centre	MCA territory ischemic stroke NIHSS ≥ 8 Age≥ 18y	N/A	Heart rate variability Copeptin, PCT, CRP, IL-6, IL-10, mHLA-DR, TNF-α A^2DS^2 score	Stroke-associated infection (pneumonia, UTI, no focus identified) to d5	SIRS Severe sepsis to 5d Survival, mRS, BI at 3mo	n=240
PREDICT[7] NCT01079728 Planned: Mar 2010-Jun 2013	Prospective Observational Multicentre	Ischemic stroke Age≥ 18y <36h onset	N/A	IL-6, IL-8, IL-10, mHLA-DR, *ex vivo* monocyte cytokine induction, C5a, PCT, acetylcholinesterase	Stroke-associated pneumonia to d7	Neurological outcome at 3mo	n=486
PRECAST[8] NCT00906542 Planned: May 2009-Feb 2010	Prospective observational	Ischemic stroke Age≥ 18y < 24h onset	N/A	CRP, WBC count and differential, surface markers, metanephrine, normetanephrine, PCT, IL-10 <24h onset +next 0800-0900	Chest infection >24h from admission to d7	Any infection, sepsis, chest infection during hospitalisation	n=530
Ulm et al, 2012[9] STRAWINSKI NCT01264549 Planned: May 2009-Feb 2010	Randomised, open-label trial Multicentre	MCA territory ischemic stroke NIHSS ≥9 Age≥ 18y	PCT-guided infection surveillance and antibiotic therapy guidance v standard care	Daily blood PCT	mRS at 3mo	Mortality, rehospitalisation, recurrent stroke, infections, days with fever to d7	n=200
De Marchis et al, 2013[10] CoRisk Study NCT00878813 Planned:March 2009-Apr 2011	Prospective observational Multicentre	AIS< 24h onset; ± thrombolysis TIA< 24h onset	N/A	Copeptin<24h Repeat copeptin at 24h if thrombolysis	AIS: mRS/survival 3mo TIA: Recurrent cerebrovascular event	AIS: Symptomatic ICH, aspiration pneumonia, seizures, cerebral oedema	AIS + IA/IV thrombolysis n=220 AIS no thrombolysis=506 TIA n=200

PRED-SEP indicates Predictors of sepsis; MCA, Middle cerebral artery territory; NIHSS, National Institutes of Health Stroke Scale; PCT, Procalcitonin; CRP, C-reactive protein; IL-6, interleukin-6; IL-10, interleukin-10; mHLA-DR, Monocyte human leucocyte antigen-DR; TNF-α, Tumour necrosis factor-α; A^2DS^2, Age, Atrial fibrillation, Dysphagia, Stroke severity, Sex; *UTI, Urinary tract infection; SIRS, Systemic inflammatory response syndrome; mRS, modified Rankin Scale; BI, Barthel Index; PREDICT, PREDICTion of stroke-associated pneumonia; IL-8, Interleukin-8; PRECAST, PREdictors of early Chest infection in Acute ischemic STroke; STRAWINSKI, STRoke Adverse outcome is associated With NoSocomial Infections; CoRisk, Copeptin Risk stratification study; AIS, Acute ischemic stroke; TIA, Transient ischemic attack*

Online only Table VI: Comparison of CDC and Mann criteria

Component	CDC criteria	Mann criteria
Symptoms		
Cough	✓	✓
Dyspnea	✓	
Purulent sputum	✓	✓
Altered mental status*	✓	
Clinical signs		
Fever (>38°C)	✓	✓
Respiratory rate	✓ (>25/min)	✓ (>22/min)
Abnormal chest examination	✓	✓
Tachycardia		✓
Laboratory findings		
Relevant pathogen		✓
WBC count	✓	
Hypoxia	✓	✓
Radiology		
Chest X-ray criteria	Mandatory	✓

CDC indicates Centers for Disease Control and Prevention; WBC, white blood cell

*≥70 years old

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