# 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**

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|---|
| 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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## Disclosures

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