

European stroke organisation guideline on stroke-associated pneumonia

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Abstract

Stroke-associated pneumonia (SAP), which occurs in approximately 12%, is the most frequent infectious complication after acute stroke and a major contributor to morbidity and mortality. Despite its clinical importance, high-quality evidence to guide the diagnosis, prediction, prevention and treatment of SAP remains limited, underscoring the need for structured, consensus-based recommendations in stroke care. This guideline was developed following the standard methodology of the European Stroke Organisation (ESO): an interdisciplinary working group identified 15 clinically relevant questions, conducted systematic literature reviews and meta-analyses, appraised the quality of the available evidence and formulated evidence-based recommendations. Notably, only 3 of 15 questions were supported by predominantly low-quality evidence, and most guideline statements therefore rely on expert consensus rather than evidence-based recommendations. For clinical practice, standardised diagnostic criteria are recommended, while chest CT and plasma C-reactive protein may provide additional diagnostic value. Clinical prediction scores and biomarkers demonstrate moderate to good discriminative performance. However, their routine use will depend on the availability of effective preventive measures. Prevention strategies include positioning, early mobilisation and individualised nutritional approaches. Dysphagia screening and swallowing management are established components of post-stroke care for SAP prevention and are addressed in a separate ESO guideline. Adjunctive therapies are not part of standard care but may be considered in selected patients. Preventive antibiotic therapy is not recommended due to a lack of benefit on SAP incidence or clinical outcomes, whereas empirical antibiotic treatment should be initiated promptly after diagnosis and guided by local protocols targeting aspiration-associated pathogens. In addition, this guideline provides a framework for future randomised trials aimed at improving the evidence base for SAP management.

Keywords aspiration, biomarker, diagnostic criteria, dysphagia, guideline, pneumonia, positioning, preventive antibiotics, scores, stroke

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Plain language summary

Pneumonia is one of the most common complications following a stroke, affecting around 1 in 8 patients and is associated with poorer recovery and survival. This guideline aims to support healthcare professionals in diagnosing, preventing and treating stroke-associated pneumonia. As robust scientific evidence remains limited, many recommendations are based on expert consensus. The guideline recommends the use of standardised diagnostic criteria and the prompt initiation of antibiotic treatment when pneumonia is suspected, while preventive antibiotic use is not advised. Preventive care should focus on simple measures such as appropriate patient positioning, safe nutrition and early mobilisation where suitable. Additional treatments may be considered in selected patients. Overall, these recommendations are intended to support stroke teams in everyday clinical practice and highlight the need for further research to improve care and outcomes for patients after stroke.

Key recommendations/suggestions of the guideline

In patients hospitalised, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset

Use a standardised algorithm-based approach for SAP diagnosis

Consider using validated clinical prediction scores or biomarkers to identify patients at increased risk of SAP, to better target preventive standard measures.

Do not use preventive antibiotic therapy, as it does not reduce SAP incidence or improve clinical outcomes. Initiate antibiotic therapy promptly upon confirmed diagnosis of SAP.

Do not use metoclopramide, statins, beta-blockers, ACE inhibitors/angiotensin receptor blockers, acid-suppressive drugs (PPIs or H₂-receptor antagonists), antacids, or benzodiazepines for the prevention of SAP. Continue or initiate statins or beta-blockers these drugs if indicated for other conditions before or after stroke.

Use the feeding method with which the clinical team is most familiar if nasogastric feeding is required, without preference for intermittent or continuous enteral feeding.

Consider respiratory physiotherapy as part of an early post-stroke rehabilitation programme to improve respiratory function and potentially reduce respiratory complications.

Initiate mobilisation (in or out of bed) within 48 hours of symptom onset to prevent SAP but avoid very early (<24 hours) and prolonged out-of-bed mobilisation in patients with severe stroke.

Treat SAP with empirical antibiotic therapy as early as possible after clinical diagnosis, ideally within a few hours, and perform routine microbiological diagnostics prior to initiation where feasible.

Treat SAP with empirical antibiotic therapy according to local or regional protocols, primarily following aspiration pneumonia recommendations and targeting aerobic Gram-negative bacilli and Gram-positive cocci, including *Pseudomonas* coverage where relevant risk factors are present.

Determine the duration of antibiotic treatment on clinical response and treat for at least 5 days.

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Introduction

Infections are among the most common medical complications in the acute phase after stroke, with pneumonia and urinary tract infections representing the 2 most frequent entities.¹ Stroke-associated pneumonia (SAP) is reported in approximately 5%–30% of acute stroke patients with the incidence depending on diagnostic criteria, timing, methods of assessment, stroke severity, as well as on patient- and care-related factors.^{2–4} In a recent meta-analysis including more than 32 million stroke patients, SAP remained the most frequent infectious complication (12.1%) and was associated with substantial in-patient mortality (rate 21.6%).⁵ Despite an overall decline in post-stroke infection rates over the past decade, SAP continues to constitute the leading infectious burden and a major clinical hazard in acute stroke care.^{1–3}

SAP results from a multifactorial disruption of protective airway and immune mechanisms. Major contributing factors are aspiration due to post-stroke dysphagia, a reduced level of consciousness, diminished cough and airway clearance reflexes, as well as stroke-induced immunodepression, which compromises antibacterial defence and increases vulnerability to respiratory infections.^{1,6,7} SAP usually becomes clinically apparent between the second and fifth day after stroke onset, providing an important window of opportunity for early risk stratification and the timely implementation of targeted preventive measures.¹ This temporal pattern has stimulated the development of both non-pharmacological and pharmacological strategies aimed at reducing SAP occurrence,⁸ alongside considerable efforts to establish biomarkers and clinical prediction scores for identifying patients at highest risk.^{9,10}

SAP has a profound impact on both short- and long-term outcomes after stroke. It is strongly associated with respiratory failure, prolonged hospital and intensive care stays, poorer

functional recovery, increased rates of institutionalisation, stroke recurrence and mortality.^{1,10–12} Emerging evidence further suggests that stroke-associated infections (SAI), including SAP, may contribute to subsequent vascular cognitive impairment and dementia.^{13,14} Beyond its direct physical complications, SAP therefore imposes a substantial burden on patients, reduces independence and increases healthcare costs.¹⁵ Given its high epidemiological relevance and its role as a major determinant of post-stroke morbidity and mortality, SAP represents a key target for improved prevention and management in contemporary stroke care.

Despite its clinical importance, there is currently no dedicated evidence-based guideline specifically addressing the diagnosis, prediction, prevention and treatment of SAP. Although SAP management and preventive measures and treatment are embedded within broader acute stroke care guidelines, such as those issued by the American Heart Association/American Stroke Association AHA/ASA and within the ESO dysphagia guideline, detailed evidence-based guidance specifically addressing SAP management remains lacking.^{16,17} The *Pneumonia In Stroke ConsEnsuS* (PISCES) group has provided important proposals on diagnostic criteria, microbiological aetiologies and potential preventive and therapeutic strategies.^{18–20} However, these were largely based on limited evidence, highlighting the need for updated, structured and evidence-based guidance.

Dysphagia is a key risk factor for SAP, and dysphagia screening and swallowing management are established components of post-stroke care with proven relevance for SAP prevention. These topics were intentionally excluded from the current PICO (Population, Intervention, Comparator and Outcome) framework, as they have been comprehensively addressed in the 2021 ESO guideline on Post-Stroke Dysphagia, to which readers are referred for detailed recommendations.¹⁷

Given these unmet needs, the European Stroke Organisation (ESO), in collaboration with relevant multidisciplinary partners, has decided to compile guidelines on the management of SAP. These recommendations are based on the systematic evaluation of evidence from randomised controlled trials (RCTs), observational studies and expert consensus where evidence is limited. They were developed according to the ESO standard operating procedure (SOP) for guideline development and were agreed through consensus among the involved authors using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.²¹ The guideline document has received approval from the ESO Executive Committee.

The aim of this guideline is to provide practical recommendations for physicians, stroke nurses, speech-and-language therapists and all members of the multidisciplinary stroke care team on how to diagnose SAP, identify patients at risk, implement evidence-based preventive interventions and optimise treatment strategies in order to reduce SAP-related complications and improve outcomes after stroke.

Methods

Composition and approval of the module working group

These guidelines were initiated by the ESO. One chairperson (AM) was selected to assemble and coordinate the Guideline Module Working Group (MWG). The expert panel comprised a multidisciplinary group of 9 specialists from 6 European countries, primarily from the fields of neurology and stroke medicine, complemented by expertise in neurorehabilitation, cardiovascular and clinical neuroscience, stroke epidemiology and guideline methodology within the ESO. The ESO Guideline Board and Executive Committee reviewed the intellectual and financial disclosures of all MWG members and approved the composition of the group. The full details of all MWG members and their disclosures is included in [Supplemental Material 1](#).

Development and approval of clinical questions

This guideline was prepared according to the ESO SOPs,²¹ which are based on the GRADE framework.²² The MWG developed a list of topics and corresponding questions of greatest clinical interest. Questions were formatted using the PICO approach and reviewed by 2 external reviewers as well as members of the ESO Guideline Board and Executive Committee. The outcomes were rated by members of the MWG as: critical, important or of limited importance according to GRADE criteria. Final decision on outcomes used a Delphi approach. Results of the outcomes rating for each PICO question are included in the [Supplementary Material 1](#).

For the literature search, the MWG defined the search criteria with regard to (1) general eligibility criteria for the populations of interest (see [Table S3](#)), (2) the intervention and comparator (see [Table S3](#)) and (3) the outcomes. To determine the outcome-related search terms for the individual PICO questions, we first compiled a comprehensive list of clinically relevant outcomes, complications and healthcare-related measures from a clinical practice perspective. Critical clinical outcomes included functional

status (modified Rankin Scale, analysed as dichotomised outcome and/or shift analysis), activities of daily living (Barthel Index), survival and quality of life. Relevant complications comprised recurrent vascular events (stroke, transient ischaemic attack, myocardial infarction, intracerebral haemorrhage [ICH]), seizures, sepsis, recurrent infections, venous thromboembolism (deep vein thrombosis and pulmonary embolism) and antibiotic-related adverse events such as antibiotic-associated diarrhoea, *Clostridioides difficile* infection and antimicrobial resistance. Healthcare-related outcomes included length of hospital stay, hospital readmission, discharge destination and antibiotic use. All candidate outcomes were then rated anonymously by members of the MWG on a 9-point rating scale according to their importance for decision-making. Outcomes rated as critical for decision-making (mean score 7–9) were included in the literature search. The general outcomes and complication-related outcomes of further interest are summarised in [Table S4](#) and [Figure S1](#). These outcomes were subsequently incorporated into the search strategy for the respective PICO questions.

Literature search

For each PICO question, search terms were developed by the MWG and ESO methodologist (SH). Where a validated search strategy was available, this was used or adapted. Where there was a recent relevant systematic review on the question of interest, the corresponding search strategy and results were used and updated as necessary. Search strategies are described in [Supplementary Material 1](#).

The search was performed by the ESO Guideline methodologist (SH). The following databases were searched: Medline and EMBASE from 1946 to February 2023. Reference lists of review articles, the authors' personal reference libraries and updated non-structured searches were also done up to March 2026.

Search results were loaded into the web-based Covidence platform (Health Innovation, Melbourne, Australia) for assessment by the MWG. Two or more MWG members were assigned to independently screen the titles and abstracts of publications registered in Covidence and then assess the full text of studies determined to be potentially relevant. All disagreements were resolved by discussion between the 2 reviewers or by a third MWG member.

We prioritised fully published RCTs; where data were limited, we also considered health registry analyses, large observational studies and systematic reviews or meta-analyses. Only studies in humans were included, while conference abstracts without full publication and animal studies were excluded.

Data analysis

Data extraction and analysis was performed by the MWG members and ESO methodologist (AP). Where appropriate, random-effects meta-analyses (Mantel–Haenszel method) were conducted using Review Manager (RevMan) online or MedCalc software. Results were presented as estimates of effect with associated 95% CIs (Wald method). Statistical heterogeneity across studies was assessed using the tau² statistics (DerSimonian and Laird method) and I² statistic, and classified as moderate (≥30%), substantial (≥50%) or considerable (≥75%).³ Funnel plot or Eggers test were used for the assessment of publication bias.^{23,24} Where appropriate, subgroup analyses based on medication group were performed (PICO 7).

Table 1 Formatting based on strength of recommendations.

Strength of recommendation	Balance of desirable and undesirable consequences	Recommendation formatting
Strong recommendation for intervention	The desirable consequences clearly outweigh the undesirable consequences in most settings	“We recommend”
Strong recommendation against intervention	The undesirable consequences clearly outweigh the desirable consequences in most settings	“We recommend...not”
Weak recommendation for intervention	The desirable consequences probably outweigh the undesirable consequences in most settings	“We suggest”
Weak recommendation against intervention	The undesirable consequences probably outweigh the desirable consequences in most settings or when the balance between desirable and undesirable consequences is closely balanced or uncertain	“We suggest...not”
Ungraded consensus-based statement	The desirable consequences probably outweigh the undesirable consequences in most settings, but there is little evidence	“We suggest”

Evaluation of the quality of evidence and formulation of recommendations

The risk of bias of each included randomised trial was assessed with the Cochrane Rob2 tool,²⁵ observational studies by ROBINS-I²⁶ and diagnostic accuracy with the PROBAST tool.²⁷ The robvis tool was used for visualisation.²⁸ As recommended, the evidence synthesis did not use a quality “score” threshold but classified overall risk of bias at study level and then in aggregate.²⁹

The results of data analysis were imported into the GRADE-pro Guideline Development Tool (McMaster University, 2015; developed by Evidence Prime, Inc.) For each PICO question, and each outcome, the following were considered: risk of bias based on the type of available evidence (randomised or observational studies); considerations on inconsistency of results; indirectness of evidence, imprecision of results and other possible bias. GRADE evidence profiles/summary of findings tables were generated and used to prepare recommendations. “Evidence-based Recommendations” were based on the GRADE methodology. The direction, strength and formulation of the recommendations were determined according to the GRADE evidence profiles and the ESO-SOP.^{21,22}

Finally, Expert Consensus Statements were added whenever the PICO group considered that there was insufficient evidence available to provide Evidence-based Recommendations and where practical guidance is needed for routine clinical practice. The Expert Consensus Statements were based on voting by all expert MWG members. Importantly, these Expert Consensus Statements should not be regarded as evidence-based recommendations, since they only reflect the opinion of the writing group.

Drafting of the document, revision and approval

Each PICO question was addressed in distinct sections, in line with the updated ESO SOP.²¹ First, “Analysis of current evidence”

summarised current pathophysiological considerations followed by a summary and discussion of the results of the identified RCTs and other studies. Second, “Additional information” was added when more details on the studies referred to in the first section were needed to provide information on key subgroup analyses of the included studies, on ongoing or future RCTs, and on other studies which can provide important clinical guidance on the topic. Third, an “Expert consensus statement” paragraph was added whenever the MWG considered that insufficient evidence was available to provide evidence-based recommendations for situations in which practical guidance is needed for everyday clinical practice. The Guideline document was reviewed several times by all MWG members and modified using a Delphi approach until consensus was reached.

Results

Overall, 13,888 non-duplicate records were screened. Details of the study selection process are summarised in the PRISMA flow diagram (see [Figures S27–S29](#)).

PICO 1

In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, does use of any standardised diagnostic criteria for SAP, compared to non-standardised clinician-based diagnosis, improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there are insufficient data to support recommendations on whether the use of standardised diagnostic criteria for SAP improves clinical outcomes. Consequently, no evidence-based recommendation can be made. Please see the Expert Consensus Statement below.	-	-

Expert consensus statement

In the absence of appropriately designed RCTs, and on the basis of observational studies and secondary analysis of RCTs, we suggest to use an algorithm-based approach for SAP diagnosis (for example PISCES) guided by a minimum set of agreed criteria. This may improve diagnostic accuracy and require further evaluation in research in clinical practice.

Voting: 8/8

Analysis of current evidence

In hospitalised adult patients with acute ischaemic or haemorrhagic stroke (non-ventilated) there is continued uncertainty over the most accurate approach for diagnosing SAP, because of the lack of a validated gold standard.

No included studies.

Additional information

The PISCES group proposed a pragmatic approach recommending the use of adapted Centers for Disease Control and Prevention (CDC) criteria for the diagnosis of SAP. Probable SAP is defined as fulfilment of the CDC criteria without typical chest X-ray findings despite repeated imaging, whereas confirmed SAP requires fulfilment of the CDC criteria including typical chest X-ray changes.¹⁸

In a secondary analysis of the multicentre STROKE-INF randomised trial,³⁰ the diagnostic utility of an algorithm-defined approach to pneumonia, compared to physician-diagnosed pneumonia, was evaluated in 1088 patients within 14 days of stroke onset. The algorithm-defined diagnosis was based on CDC criteria and performed by the study statistician independent of treating physicians at trial centres. Adjudicated diagnosis of pneumonia by 2 independent experts was used as the reference standard when there was discrepancy between the physician and algorithm-defined diagnosis. Physician-diagnosed pneumonia occurred in 176 of 1088 (16%) and algorithm-defined pneumonia in 123 of 1088 (11.3%) patients. Diagnosis was concordant in 885 of 1088 (81.3%) patients (κ 0.22, 95% CI, 0.14–0.29). On a blinded review, 129 of 1088 (11.8%) patients were adjudicated as having pneumonia. The algorithm (97%, 95% CI, 96–98) and the physician diagnosis (90%, 95% CI, 88–92) both had high specificity, but only moderate sensitivity ((72%, 95% CI, 64–80) and (65%, 95% CI, 56–73), respectively) in diagnosing pneumonia. The algorithm-defined approach had better positive predictive value (PPV; (76%, 95% CI, 67–83) vs (48%, 95% CI, 40–55)), diagnostic OR ((80, 95% CI, 42–136) vs (18, 95% CI, 12–27)) and agreement ((κ 0.70, 95% CI, 0.63–0.78) vs (0.48, 95% CI, 0.41–0.54)) than physician diagnosis with adjudicated pneumonia. These findings illustrate that physician diagnosis, and algorithm-based approaches are very good at excluding patients who do not have post-stroke pneumonia (<5% false-negative rate). Both the physician diagnosis and algorithm-defined approach over-diagnosed pneumonia, although the algorithm-defined approach had greater diagnostic utility. However, these different diagnostic approaches were not related to clinical outcomes.³⁰

PICO 2

In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset,

does use of chest ultrasound or computed tomography to diagnose SAP, compared to chest X-ray alone, increase diagnostic accuracy and improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, uncertainty remains regarding the most accurate diagnostic approach for SAP when using chest ultrasound or computed tomography compared with chest X-ray alone. The potential benefits and risks of these procedures in relation to clinical outcomes are also unclear. Therefore, no evidence-based recommendation can currently be made. Please see the Expert Consensus Statement below.	-	-

Expert consensus statement

We suggest to consider a pulmonary CT scan if SAP is suspected and the diagnosis uncertain, particularly where there is a need to inform further antibiotic/ medical therapy and/or exclude other pathologies (e.g. pulmonary embolism).

Voting: 8/8

Analysis of current evidence

An observational study aimed to evaluate the diagnostic accuracy of chest X-ray (CXR) in the setting of SAP and the use of pulmonary computed tomography (CT) as a reference standard for final diagnosis.³¹ The study found that CXR had limited diagnostic value in clinically suspected SAP when using pulmonary CT as a diagnostic reference standard. Only 13 out of 40 CXRs (32.5%) were reported as suggestive of pneumonia by the independent thoracic radiologist, while pulmonary CT confirmed pneumonia in only 12 out of 35 patients (34%). Compared to the pulmonary CT reported by the independent thoracic radiologist as the reference standard for diagnosis of SAP, CXR had a sensitivity of 58.3%, a specificity of 73.9%, a PPV of 53.8%, a negative predictive value (NPV) of 77.2%. The inter-rater reliability of reported CXR interpretation of pneumonia between the local radiologists and independent thoracic radiologist was moderate (k = 0.42), while the inter-rater reliability for CXR diagnosis of pneumonia between the 4 stroke physicians (independent thoracic radiologist as standard) was weak (k = 0.35). The utility of CXR or CT was not related to outcome, and the interpretation was limited by relatively small numbers and lack of external validation.

Additional information

Another observational study aimed to evaluate lung ultrasound (US) in 70 patients with clinically suspected pneumonia occurring after stroke.³² This study is discussed here rather than under the analysis of current evidence, as no performance metrics were reported to assess the diagnostic accuracy of CXR compared with lung US. Pneumonia was adjudicated using standardised CDC-based criteria, although the interval of pneumonia following stroke onset was not defined. Lung US and CXR were both undertaken within 24 hours of onset of the clinical manifestation of pneumonia, and a non-contrast pulmonary CT was planned only if the CXR or lung US were inconclusive. CXR was negative for signs of pneumonia in 44 (63%). Lung US and CXR were concordant in 42 out of 63 cases, 66.7 % (P = .001). Pulmonary CT was only performed in 9 of 21 patients where there was disagreement between lung US and CXR, but in this situation always confirmed

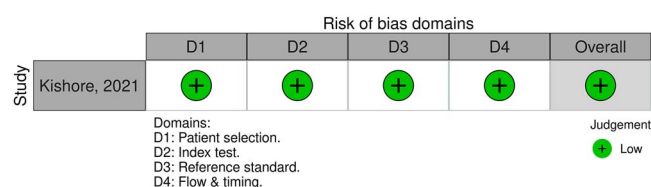


Figure 1 Risk of bias profile for study included in PICO 1.

lung US results. However, the reference standard was unclear and diagnostic accuracy for CXR or lung US was not reported (Figure 1). Accordingly, there are currently no specific recommendation supporting its use in acutely unwell stroke patients.

PICO 3

In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, does incorporation of any diagnostic (blood) biomarker, compared to not making use of diagnostic (blood) biomarkers, increase diagnostic accuracy and improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is insufficient data to make an evidence-based recommendation and continued uncertainty of the role of blood inflammatory or stress biomarkers in the diagnostic approach to SAP. Please see the Expert Consensus Statement below.	-	-

Expert consensus statement

We suggest considering the addition of CRP to standardised diagnostic algorithms for SAP to improve diagnostic accuracy in afebrile patients, with available data indicating cut-off values between 30 and 40 mg/L.

Voting: 8/8

Improved diagnostic accuracy may influence clinical decision-making, particularly with regard to the timely initiation of antibiotic therapy, and may thereby impact downstream outcomes such as infection control. Importantly, as SAP is associated with increased mortality and morbidity after stroke, more accurate and timely diagnosis may also contribute to improved survival and functional recovery. In this context, the incorporation of biomarkers into diagnostic algorithms may be helpful in enhancing diagnostic performance.

Analysis of current evidence

In the study “Ex vivo synthesized cytokines as a biomarker of stroke-associated pneumonia,”³³ 20 out of 279 patients (7%) prospectively recruited patients with ischemic stroke had a diagnosis of SAP. Patients with SAP exhibited lower ex vivo release of blood TNF α , IL-1 β , IL-12, IP-10, and higher levels of circulating IL-6 compared to those without pneumonia. Specifically, the odds ratios for pneumonia were 0.27 (95% CI, 0.11–0.65) for TNF α , 0.31 (95% CI, 0.14–0.67) for IL-1 β , 0.06 (95% CI, 0.01–0.33) for IL-12, 0.11 (95% CI, 0.03–0.47) for IP-10 and 2.02 (95% CI, 1.45–2.79) for plasma IL-6 in univariate logistic regression. In multivariate analysis, cytokines with *P*-values below 0.1 included ex vivo IL-12

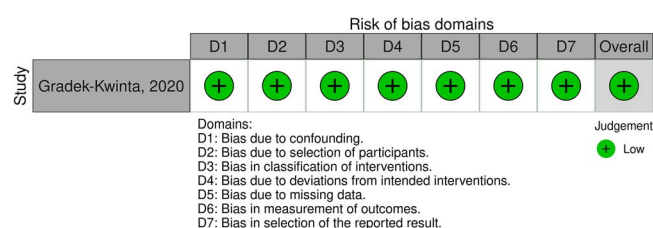


Figure 2 Risk of bias profile for study included in PICO 3.

(OR 0.09, 95%CI, 0.01–0.75), IP-10 (OR 0.32, 95% CI, 0.09–1.13) and plasma IL-6 (OR 1.70, 95% CI, 1.18–2.45). The multimarker score comprising IL-12, IP-10 and IL-6 showed good sensitivity (0.89) and specificity (0.88) for SAP, outperforming individual cytokines (Figure 2). These findings suggest the potential of cytokines as biomarkers for early detection of SAP, emphasising the importance of a multimarker approach for improved diagnostic accuracy and patient care. However, these cytokines were not related to clinical outcomes and the clinical value of assessment of ex vivo cytokine production from blood samples remains unclear.

Additional information

In a secondary analysis of the single centre MAPS (metoclopramide to prevent pneumonia in stroke patients fed via nasogastric tubes) randomised trial,³⁴ plasma C-reactive protein (CRP) was evaluated as a diagnostic biomarker for development of pneumonia up to 21 days after stroke onset in 60 dysphagic patients with acute ischaemic or haemorrhagic stroke. Post-stroke pneumonia was diagnosed in 33 patients (44 episodes) using modified British Thoracic Society criteria, with a median (IQR) interval from stroke onset to the first pneumonia of 3.5 days (3.0–5.0 days). For patients with no incident pneumonia, the mean of all available CRP values over the first week was used, whereas the CRP value on the day of, or the closest to the day of, the diagnosis of pneumonia was used in patients with confirmed pneumonia. The area under the ROC curve for CRP was 0.83 (95% CI, 0.72–0.93). The diagnostic cut-off for CRP with an acceptable sensitivity (>0.8) was 25.6 mg/L (Youden index (J) 0.52; sensitivity 0.85; specificity 0.67). A cut-off of 64.7 mg/L had the highest diagnostic accuracy (J 0.56; sensitivity 0.64; specificity 0.93). A CRP cut of ≥ 40 had an acceptable sensitivity of 0.69 and a specificity of 0.75. In summary, CRP could be a useful biomarker in diagnosing SAP with different cut-off values offering trade-offs between sensitivity and specificity but needs further evaluation of utility and external validation.

In a secondary analysis of the multicentre STROKE-INF randomised trial, the addition of plasma CRP to a CDC-based diagnostic algorithm for pneumonia occurring up to 14 days after stroke onset was evaluated in 1088 dysphagic patients with acute ischaemic or haemorrhagic stroke.³⁰ Expert adjudicated pneumonia was used as a reference standard and occurred in 123 patients. Plasma CRP was collected at baseline, day 2, 4, 7, 10 and 14. The inclusion of elevated CRP ≥ 30 mg/L (from any of the 6 timepoints) as an additional criterion to the full algorithm did not increase its overall diagnostic accuracy or agreement with adjudicated pneumonia. In afebrile patients (*n* = 965), elevated CRP ≥ 30 mg/L with chest and laboratory findings had sensitivity of 0.84 (95% CI, 0.67–0.93), specificity of 0.99 (95% CI, 0.98–1.00), and kappa 0.80 (95% CI, 0.70–0.90). The modified algorithm of pyrexia or elevated

CRP ≥ 30 mg/L and chest signs with infiltrates or leucocytosis had sensitivity of 0.94 (95% CI, 0.87–0.97), specificity of 0.96 (95% CI, 0.94–0.97) and kappa of 0.88 (95% CI, 0.84–0.93) compared to adjudicated pneumonia.

In summary, while adding CRP to the full CDC algorithm did not improve overall diagnostic accuracy, a modified algorithm incorporating CRP showed high sensitivity and specificity for diagnosing SAP. Available study data indicate that supplementing standardised diagnostic algorithms with plasma CRP measurements, using a cut-off value between 30 and 40 mg/L, may improve diagnostic accuracy. However, external validation is required, including confirmation of clinical utility and evidence of impact on patient related outcomes.

PICO 4

In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, does use of clinical prediction scores or biomarkers, compared to not using clinical prediction scores or biomarkers, identify patients who will develop SAP?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, clinical prediction scores and selected biomarkers may help identify individuals at increased risk of developing SAP, with moderate to good discriminatory performance. However, there is currently insufficient evidence to support the routine combination of biomarkers with existing clinical prediction tools for risk stratification. Continued uncertainty remains regarding the incremental clinical value of these approaches, and their implementation will ultimately depend on the availability, feasibility, and effectiveness of targeted preventive interventions. Please see the Expert Consensus Statement below.	⊕	↑?

Expert consensus statement

We suggest using validated clinical prediction scores or biomarkers to identify patients at increased risk of SAP and to better target preventive standard measures. However, their clinical utility is currently limited by only moderate to good discriminatory performance and is likely to depend on the availability of more effective preventive treatment strategies.

Voting: 8/8

Analysis of current evidence

Prediction scores

We extracted data from 49 studies and identified 5 most common clinical risk scores for SAP (A2DS2, ISAN, AIS-APS, PANTHERIS, PASS) that each have been evaluated in more than 3 studies. A2DS2-score and AIS-APS score, PANTHERIS score and PASS score were developed for ischaemic stroke, ISAN for both ischaemic and haemorrhagic stroke. Included scores vary in the number and type of predictors included (Table 2). In total, we included 29 studies which validated ISAN in 13, A2DS2 in 22,^{35–56} modified A2DS2 in 8,^{35,42,43,45,49,53,55,56} AIS-APS in 6,^{37,40,41,46,47,52} PANTHERIS in 4^{37,39,41,52} and PASS in 4 studies.^{52,57–59} The majority of included studies focused exclusively on ischaemic stroke ($n = 20$,

69%), while 8 studies (28%) included both ischaemic and haemorrhagic stroke populations, and one study (3%) examined haemorrhagic stroke exclusively. The meta-analysis of all predictive risk scores with ROC values ranging from 0.725 to 0.881 (Table 2, Figure 3, Table S6, Figures S1–S10). Considerable heterogeneity was present between included studies and there is no publication bias (Table 2).

Risk of bias

We assessed 29 individual studies examining various prediction scores for SAP. Risk of bias was low in 17% (5 studies), indicating high-quality studies with robust methodology, moderate in 59% (17 studies), indicating generally good studies with some methodological concerns, and high in 24% (7 studies), indicating significant methodological concerns (Table 4).

Biomarkers

While individual biomarkers may have both diagnostic and prognostic capacity in SAP, this section focuses specifically on their role in prediction. In contrast to PICO 3, which examined biomarkers as adjuncts to improve diagnostic accuracy, PICO 4 evaluates their ability to identify patients at increased risk of SAP. For example, procalcitonin (PCT) increases in response to bacterial infection and may support diagnostic decision-making. However, it may also indicate the early development of SAP before clinical symptoms become apparent, thereby allowing early identification of patients at increased risk.

We extracted data from 37 studies^{34,35,42,50,56,64–95} that evaluated prognostic value of one or more of biomarkers. A total 41 candidate biomarkers (assessed within 24 hours of admission) for SAP were identified by search of the literature and considered for meta-analysis (Table S7). Most biomarkers are specific immune cell types or ratios, cytokines or acute phase proteins. Predictive values were investigated and reported in a way allowing for pooled ROC meta-analysis in 3 or more studies, these were: C-reactive protein (CRP) (7 studies),^{34,35,42,56,69,73,96} interleukin-6 (IL-6; 4 studies),^{69,76–78} neutrophil-to-lymphocyte-ratio (NLR; 8 studies)^{35,55,56,73,84,86,87,90} and neutrophils (4 studies).^{35,56,73,82} The prognostic value (AUC ROC) ranged between 0.787 and 0.808 (Table 5). Considerable heterogeneity was present between included studies and for NLR and neutrophils a potential publication bias exists (Table 5).

Risk of bias

We assessed 15 individual studies examining various biomarkers for post-stroke pneumonia prediction. Overall risk of bias was low in 40% of studies ($n = 6$), moderate in 53% ($n = 8$), and high in 7% ($n = 1$), indicating that most studies were of moderate methodological quality with some risk of bias concerns (Table 6).

Combining prediction scores and biomarkers

For the current analysis we focused on individual predictive value of prediction scores and biomarkers separately. Adding biomarkers to existing prediction scores has the potential to improve diagnostic value. Limited data is present on different combinations of the above-mentioned scores and biomarkers for prediction of SAP. Four studies report on the combination of the A2DS2 score with either IL-6 or NLR and show an additive predictive value of 0.02 to 0.10 (Table 6). In addition, one other study with pooled clinical data of 2 acute stroke studies

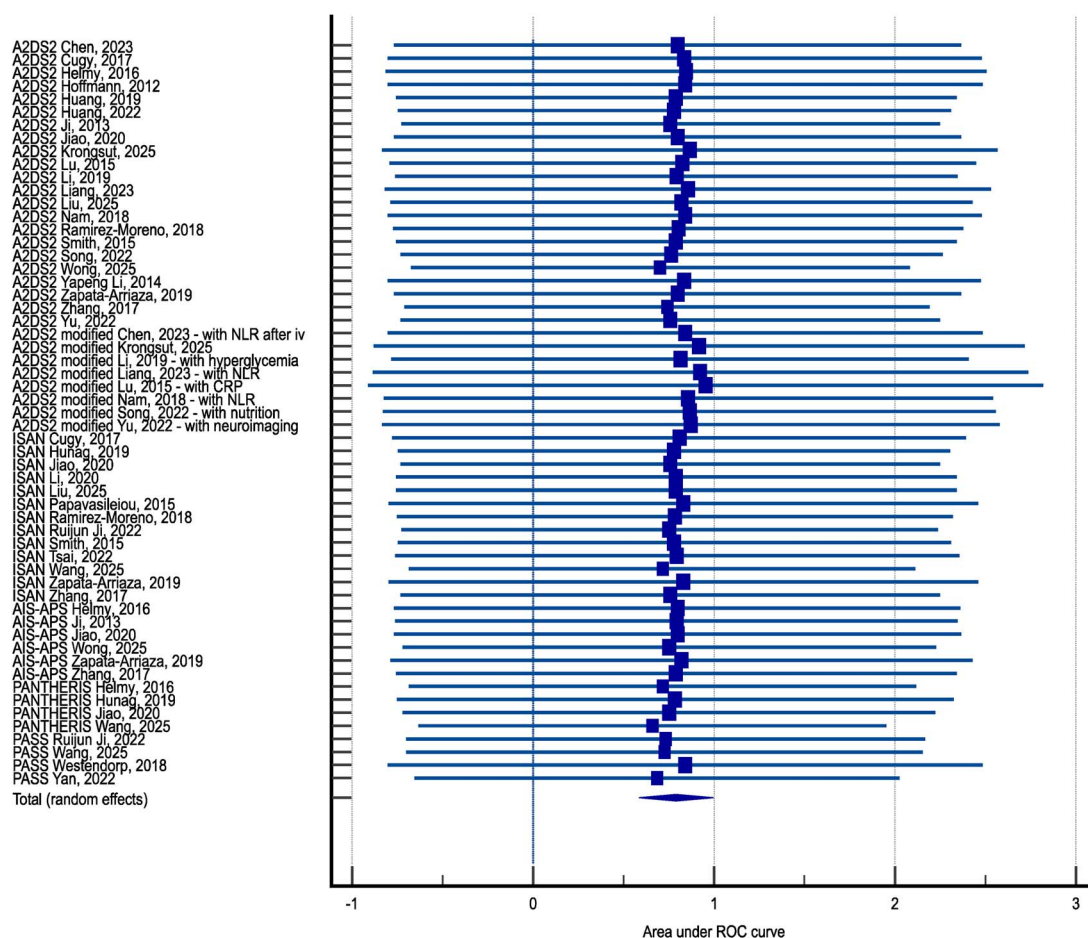


Figure 3 Forest plot of the area under ROC curve for studies evaluating prediction scores for SAP.

Table 2 Components of clinical risk scores for predicting SAP (modified from⁹).

	ISAN	A2DS2	AIS-APS	PANTHERIS	PASS
Age	✓	✓	✓	✓	✓
NIHSS	✓	✓	✓		✓
GCS			✓	✓	
Sex	✓	✓			✓
Dysphagia		✓	✓		✓
OCSF subtype			✓		
Increase in systolic BP > 200 mmHg				✓	
Pre-stroke dependence (mRS)	✓		✓		✓
Atrial fibrillation		✓	✓		
Congestive cardiac failure			✓		
COPD			✓		✓
Current smoking			✓		
Diabetes					✓
Blood glucose (mmol/l)			✓		
WBC count/ μ l				✓	
Stroke type (ischaemic/haemorrhagic)					✓

involving 683 patients, describes the external validation of 5 scores (Friedant pneumonia predict score, PASS pneumonia rule, ISAN score, A2DS2 score, Kwon pneumonia score) together with the additional value of selected biomarkers (ultrasensitive

procalcitonin—PCT-us, mid-regional pro-adrenomedullin, mid-regional pro atrial natriuretic peptide, ultrasensitive copeptin, C-terminal proendothelin-1). It was found that all scores predicted diagnosis of SAP with fair to strong abilities, and diagnostic value increased when stricter criteria for SAP were used. In this study, biomarkers improved discrimination of these scores as measured by area under the receiver operating characteristic curve (AUROC) by 0.05–0.1, although these findings are not yet externally validated and the authors state that it is possible that collinearity is present.⁹⁷ In conclusion, limited data exists on the combination of specific prediction scores with biomarkers. The available data show that predictive value might be slightly increased, but external validation of findings is lacking. The downside of adding a biomarker to the clinical use of a prediction score are the additional costs and the delay in time associated with the assessment of the biomarker. It will depend on the future application whether the slight increase in diagnostic value will be worth the additional costs and time.

Additional information

Use of prediction scores and biomarkers can help to identify the patients at the highest risk of SAP, but they are currently not part of clinical practice. At this stage, they may help the treating physician to identify patients at high risk of SAP and can also be used as inclusion criteria in trials investigating SAP prevention. The future use of these prediction rules and biomarkers will depend on possible future preventive strategies. In a previous review on

Table 3 Meta-analysis of the predictive performance of SAP risk scores in external validation.

Score	Number of Study Arms	ROC	SE	95% CI	Q	I ²	Egger's Test
A2DS2	22 (35–56)	0.800	0.00978	0.780 to 0.819	331.6643	93.67%	<i>P</i> = 0.5055
A2DS2 modified	8 (35, 42, 43, 45, 49, 53, 55, 56)	0.881	0.0159	0.850 to 0.912	61.2397	88.57%	<i>P</i> = 0.8329
ISAN	13 (36, 39, 41, 44, 46, 47, 51, 52, 54, 57, 60–62)	0.779	0.00974	0.760 to 0.798	69.9041	82.83%	<i>P</i> = 0.4408
AIS-APS	6 (37, 40, 41, 46, 47, 52)	0.783	0.00899	0.766 to 0.801	11.4343	56.27%	<i>P</i> = 0.9491
PANTHERIS	4 (37, 39, 41, 52)	0.725	0.0278	0.671 to 0.780	29.3483	89.78%	<i>P</i> = 0.2702
PASS	4 (52, 57–59)	0.745	0.0288	0.689 to 0.801	100.0979	97.00%	<i>P</i> = 0.1903

Abbreviations: I² = I-squared; Q = Cochran's Q; ROC = receiver operating characteristic.

Table 4 PROBAST—risk of bias assessment for studies examining prediction scores for SAP.

Study	Participants	Predictors	Outcome	Analysis	Overall Risk of Bias	Applicability Concerns
Chen, 2023(35)	Low	Low	Low	Low	Low	Low
Cugy, 2017(36)	Low	Low	Low	High	High	Low
Helmy, 2016(37)	Low	Low	Low	Low	Low	Low
Hoffmann, 2012(38)	Low	Low	Low	High	High	Low
Huang, 2019(39)	Low	Low	Low	Low	Low	Low
Huang, 2022(50)	Low	Low	Low	Low	Low	Low
Ji, 2013(40)	Low	Low	Low	Low	Low	Low
Jiao, 2020(41)	Low	Low	Low	Low	Low	Low
Ji, 2022 (Ruijun)(57)	Low	Low	Low	Low	Low	Low
Kongsut, 2025(53)	Low	Low	Low	Low	Low	Low
Li, 2014 (Yapeng)(48)	Low	Low	Low	High	High	Low
Li, 2019(43)	Low	Low	Low	Low	Low	Low
Li, 2020(61)	Low	Low	Low	Low	Low	Low
Liang, 2023(55)	Low	Low	Low	Low	Low	Low
Liu, 2025(54)	Low	Low	Low	High	High	Low
Lu, 2015(42)	Low	Low	Low	High	High	Low
Nam, 2018(56)	Low	Low	Low	Low	Low	Low
Papavasileiou, 2015(62)	Low	Low	Low	Low	Low	Low
Ramirez Moreno, 2018(51)	Low	Low	Low	Low	Low	Low
Smith, 2015(44)	Low	Low	Low	Low	Low	Low
Song, 2022(45)	Low	Low	Low	Low	Low	Low
Tsai, 2022(61)	Low	Low	Low	Low	Low	Low
Tu, 2017(63)	Low	Low	Low	High	High	Low
Wang, 2025(52)	Low	Low	Low	Low	Low	Low
Westendorp, 2018(58)	Low	Low	Low	Low	Low	Low
Yan, 2022(59)	Low	Low	Low	Low	Low	Low
Yu, 2022(49)	Low	Low	Low	Low	Low	Low
Zapata-Arriaza, 2018(46)	Low	Low	Low	Low	Low	Low
Zhang, 2017(47)	Low	Low	Low	High	High	Low

Legend: High (Red), Moderate (Yellow), Low (Green)

prediction scores and biomarkers an insightful example is given: if you would use the A2DS2 score with a cut-off of ≥ 4 as selection criterium for a preventive strategy, the sensitivity will be 91% and the specificity 57%.⁹ This means that almost half of the patients would be incorrectly classified as high risk for SAP. In case of a low-risk preventive strategy this will be acceptable, but not for a preventive strategy with moderate or high risks.

PICO 5

In hospitalised adults with stroke associated pneumonia (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, does antibiotic treatment guided by clinical prediction scores or biomarkers, compared to standard clinical practice, improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there are currently insufficient data to support an evidence-based recommendation regarding the routine use of clinical prediction scores or blood biomarkers to guide antibiotic treatment of SAP. Please see the Expert Consensus Statement below.	Low	Weak

Expert consensus statement

Due to insufficient evidence, we suggest not using clinical prediction scores or biomarkers to guide antibiotic treatment of SAP. For information on the start and duration of antibiotic therapy, the choice of antibiotic, and the role of microbiological tests, please refer to PICO questions 12 to 14.

Voting: 8/8

Analysis of current evidence

The search identified one German multicentre randomised clinical trial (STRAWINSKI trial) investigating whether PCT-us guided antibiotic therapy for SAP could improve functional outcome after stroke (modified Rankin Scale ≤ 4 vs > 5).⁹⁹ In total, 227 patients were included in the intention-to-treat analysis, 197 completed 3-month follow-up and adherence to PCT-guided treatment algorithm was moderate (65%). PCT-us guided therapy did not improve functional outcome at 3 months (OR 0.79, 95% CI, 0.45–1.35; *P* = .47), nor did it reduce pneumonia rates or mortality compared with standard care (Figures 4 and 5). Antibiotic use was higher in the PCT group (63% vs 45%), with a trend towards fewer days with fever, but no clinically relevant benefit on major outcomes. A post-hoc analysis showed that PCT levels on the first day of infection were significantly higher in patients with SAP or sepsis than in those with urinary tract infections (UTIs) or no infections, supporting its potential diagnostic value. However, the study also highlighted frequent clinical overdiagnosis of SAP and possible overtreatment with antibiotics. Overall, this trial does not support routine use of PCT-guided antibiotic treatment for SAP, although the moderate adherence to the treatment algorithm may have led to an underestimation of any potential benefit. The study further underscores the importance of standardised operational

Table 5 Meta-analysis of the performance of biomarkers for SAP risk prediction in external validation.

	Number of Studies Included	ROC	SE	95% CI	Q	I ²	Egger's test
NLR	8 (35,55,56,74,84,86,87,90)	0.803	0.0246	0.755 to 0.852	80.1075	91.26%	0.0184
CRP	7 (34,35,42,50,56,69,73)	0.800	0.0295	0.742 to 0.858	67.1831	91.07%	0.2704
IL-6	4 (69,76–78)	0.808	0.0327	0.744 to 0.872	8.2440	63.61%	0.1570
Neutrophils	4 (35,56,73,82)	0.787	0.0326	0.723 to 0.851	39.8361	92.47%	0.0031

Abbreviations: CRP = C-Reactive Protein; IL-6 = Interleukin-6; I² = I-squared; NLR = neutrophil-to-lymphocyte ratio; Q = Cochran's Q; ROC = receiver operating characteristic.

Table 6 PROBAST—risk of bias assessment for studies examining biomarkers for SAP.

Study	Primary Biomarker(s)	PROBAST Domains (Modified for Biomarkers)				Overall Risk of Bias	Applicability
		Participants	Biomarker Measurement	Outcome	Analysis		
Cao, 2021 (82)	Neutrophil count	+	+	+	-	-	+
Chen, 2023 (35)	NLR, CRP, Neutrophil, Lymphocyte, Monocyte, Leukocyte	+	+	+	+	+	+
Gens, 2021 (86)	NLR	+	+	+	-	-	+
Hasse, 2022 (78)	Clinical markers, IL-6, LBP	+	+	+	+	+	+
Hoffman, 2017 (76)	IL-6	-	+	+	-	-	-
Huang, 2022 (50)	CRP, Albumin	+	+	+	+	+	+
Kochetov, 2022 (29)	CRP, IL-6	+	+	+	-	-	+
Li, 2023 (84)	NLR, PLR, MLR	+	+	+	+	+	+
Liang, 2023 (55)	NLR	+	+	+	+	+	+
Lu, 2015 (42)	CRP, Iron, PCT, Ferritin	-	-	-	+	+	-
Nam, 2018 (56)	NLR, CRP, Neutrophil, Lymphocyte	+	+	+	-	-	+
Wang, 2021 (87)	NLR	+	+	+	-	-	+
Wang, 2023 (90)	NLR, PLR	+	+	+	+	+	+
Warusevitane, 2016 (34)	CRP	-	+	-	-	-	-
Wu, 2021 (29)	NLR, CRP, Neutrophil	+	+	+	-	-	+

⊕ High, ⊖ moderate, ⊕ low. Abbreviations: CRP = C-reactive protein; IL-6 = interleukin-6; LBP = lipopolysaccharide-binding protein; MLR = monocyte-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; PCT = procalcitonin; PLR = platelet-to-lymphocyte ratio.

diagnostic criteria for SAP and highlights the need for additional research to refine biomarker-guided approaches and optimise antibiotic stewardship in acute stroke care.

Additional information

The role of serial biomarker assessment (eg, PCT or CRP) for guiding discontinuation of antibiotic therapy and improving antibiotic stewardship was not a primary focus of this guideline. However, current guidelines on Community Acquired Pneumonia (CAP), Hospital Acquired Pneumonia (HAP) and Ventilation-Associated Pneumonia (VAP) were considered for potential implications for SAP.^{100–102} Across these guidelines, PCT is generally favoured over CRP due to greater specificity, as CRP is more susceptible to non-infectious elevations. For severe CAP, the European guideline provides a conditional recommendation (low quality evidence) for the use of PCT to shorten the duration of antibiotic therapy, although its added value appears limited when clinical stability is achieved and treatment duration is already between 5 and 7 days. Similarly, the CAP guideline of the Infectious Disease Society of America (IDSA) suggests that serial

Table 7 Diagnostic value of combination of A2DS2 score with IL-6 and NLR.

Author, Year	No. of Patients	A2DS2 Score	A2DS2 + IL-6	A2DS2 + NLR
Yang, 2020 (98)	398	0.82 (0.77–0.88)	0.92 (0.89–0.95)	-
Chen, 2023 (35)	388	0.80 (0.74–0.86)	-	0.84 (0.079–0.90)
Nam, 2018 (56)	1317	0.84 (0.82–0.86)	-	0.86 (0.84–0.88)
Liang, 2023 (55)	1505	0.86 (0.82–0.88)	-	0.92 (0.90–0.94)

PCT measurement may be useful primarily in settings with longer-than-standard treatment durations (5–7 days). For VAP/HAP, the European guideline does not recommend routine serial PCT measurement when anticipated duration is 7–8 days, except in selected circumstances (eg, severe immunosuppression or highly resistant pathogens). The IDSA guideline recommends combining PCT levels with clinical criteria to guide discontinuation of antibiotic therapy but acknowledges uncertainty regarding benefit when standard treatment is already 7 days or less. As standard antibiotic treatment duration in SAP is generally less than 7 days, extrapolation of serial PCT-guided discontinuation approaches from CAP and HAP/VAP guidelines is likely limited.

PICO 6

In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, does preventive antibiotic treatment compared to no preventive antibiotic treatment reduce SAP frequency and improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, we suggest not using preventive antibiotic therapy, as it has not been shown to reduce the incidence of SAP.	⊕⊕	1?
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, we recommend not using preventive antibiotic therapy, as it has not been shown to improve clinical outcomes.	⊕⊕⊕	1?

Preventive antibiotic therapy for SAP is theoretically attractive given the high early risk of infection after stroke, driven by aspiration due to dysphagia and stroke-induced immunodepression,

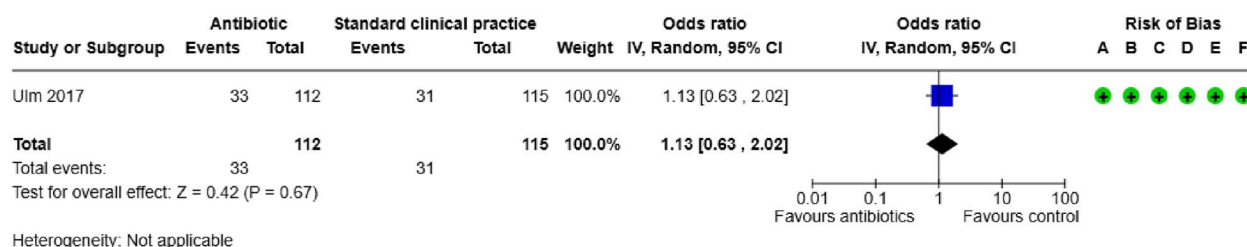


Figure 4 Forest plot and risk-of-bias assessment of biomarker-guided antibiotic treatment for SAP incidence. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, ● low, ○ No information.

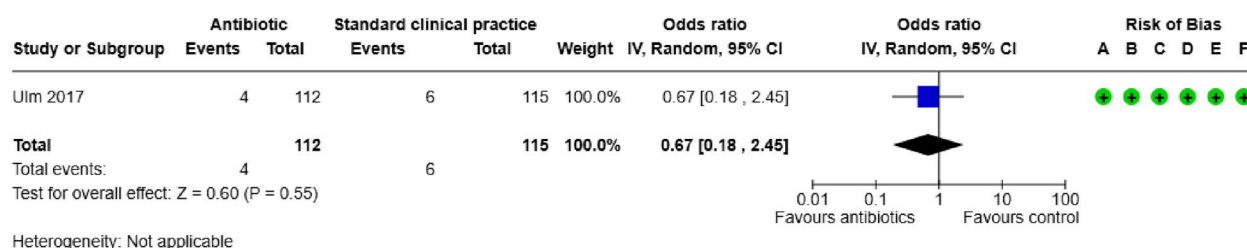


Figure 5 Forest plot and risk-of-bias assessment biomarker-guided antibiotic treatment for all-cause mortality. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, ● low, ○ No information.

the strong association of SAP with poor functional outcome and mortality, and the limited effectiveness of standard preventive measures. Since SAP typically becomes clinically apparent several days after stroke onset (most commonly around day 3),¹⁰³ it has been hypothesised that this window could be used to administer prophylactic antibiotics to prevent infection and potentially improve post-stroke recovery.

Analysis of current evidence

All trials on preventive antibiotic therapy were included in a systematic review and meta-analysis on individual patient level in 2021.⁸ Since this publication in 2021, one randomised clinical trial was published.¹⁰⁴ Below we will summarise the data for the different endpoints.

Physician-diagnosed SAP

Six trials (ESPIAS, MISS, PANTHERIS, PASS, PRECIOUS and STROKE-INF),^{104–109} including 5941 participants, reported on physician-diagnosed pneumonia. Of these, 2774 were assigned to preventive antibiotic therapy and 2614 to the control group (Figure 6). Preventive antibiotic therapy did not reduce the incidence of physician-diagnosed pneumonia, which occurred in 8.3% of patients in the antibiotic group compared with 8.2% in controls (OR 0.92, 95% CI, 0.69–1.10; $P = .55$). There was no evidence of substantial heterogeneity across studies ($\text{Tau}^2 = 0.03$, $I^2 = 27\%$; Figure 6).

Panel-diagnosed SAP

Three studies reported on panel-diagnosed pneumonia: the PANTHERIS, PASS and STROKE-INF trials. In total, 3705 patients were included, 1871 in the experimental vs 1834 in the control group (Figure 7). Preventive antibiotic therapy did not show an effect on the incidence of panel-diagnosed pneumonia (5.2% [97/1871] vs.

5.1% [94/1834], OR 0.81, 95% CI 0.42 to 1.57; $P = .54$). Substantial heterogeneity existed between the studies ($\text{Tau}^2 = 0.21$, $I^2 = 69\%$; Figure 7).

Favourable functional neurological outcome (mRS 0–2) at 90 days

Four studies reported on mRS at 90 days: the PASS, STROKE-INF, PRECIOUS and MISS trials.^{104,107–109} Three studies included patients with both ischaemic and haemorrhagic stroke, 1 study only ischaemic stroke patients. Preventive antibiotics consisted of 4 days iv. Ceftriaxone (a 3rd generation cephalosporin) in the PASS and PRECIOUS trial, local antibiotic policy in the STROKE-INF (in 78% co-amoxiclav or amoxicillin + clarithromycin) and prophylactic mezlocillin plus sulbactam (3 × 2 g/1 g for 4 days) in the MISS trial as compared to standard medical care in all control arms, without placebo treatment.

In the updated meta-analysis of these 4 studies 4836 patients were included (Figure 8): 2486 patients were randomised to preventive antibiotic therapy vs. 2368 patients to standard care (no placebo treatment was given). Preventive antibiotic treatment was not associated with favourable functional outcome at 90 days: 31% (766/2486) in the experimental group vs 32% (755/2368) of patients in the control group had a favourable clinical outcome (OR 0.96, 95% CI, 0.85–1.09). There was no heterogeneity between the studies ($\text{Tau}^2 = 0.00$, $I^2 = 0\%$; Figure 8).

Improved outcome on total range of mRS at 90 days

Three studies^{104,107,109} evaluated improved outcome on the total range of the mRS in ordinal analyses at 90 days (Figure 9): STROKE-INF, PRECIOUS and the PASS trial. No difference was found between the 2 treatment groups. The pooled adjusted odds ratio was 1.0 (95% CI, 0.87–1.21; $P = .50$), with moderate heterogeneity and low risk of bias ($I^2 = 47.9\%$, $Q = 3.84$; $P = .15$; Figures 9 and 10).

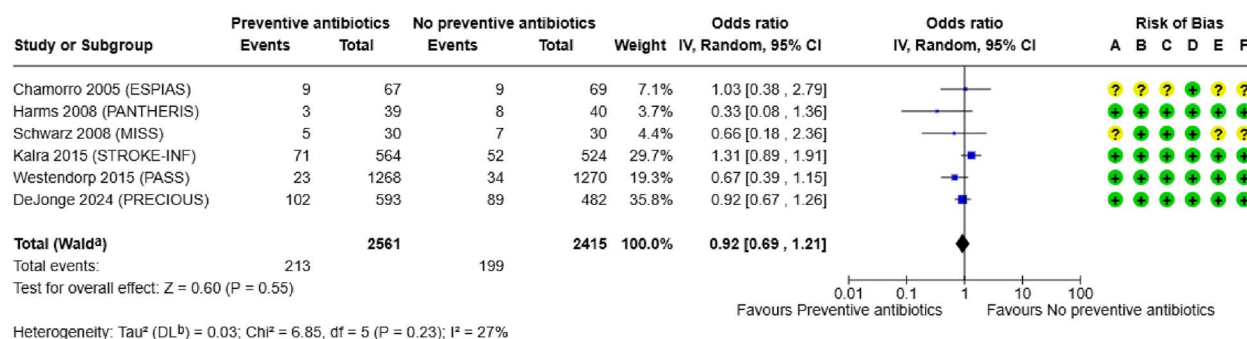


Figure 6 Forest plot and risk-of-bias assessment of preventive antibiotic therapy for physician-diagnosed SAP. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, ● low, ○ No information.

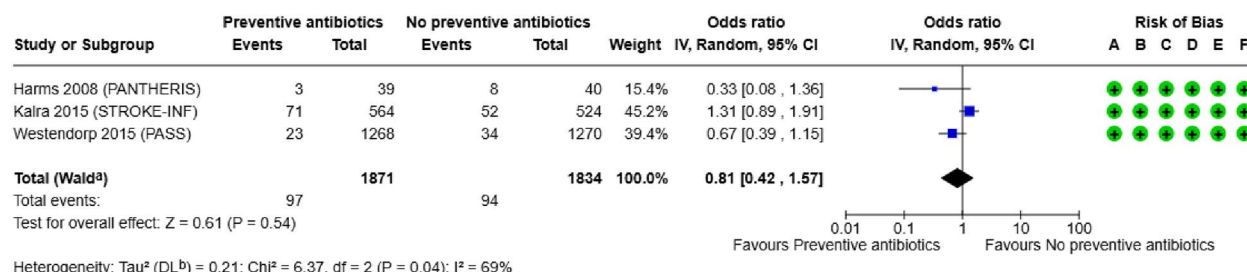


Figure 7 Forest plot and risk-of-bias assessment of preventive antibiotic therapy for panel-diagnosed SAP. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, ● low, ○ No information.

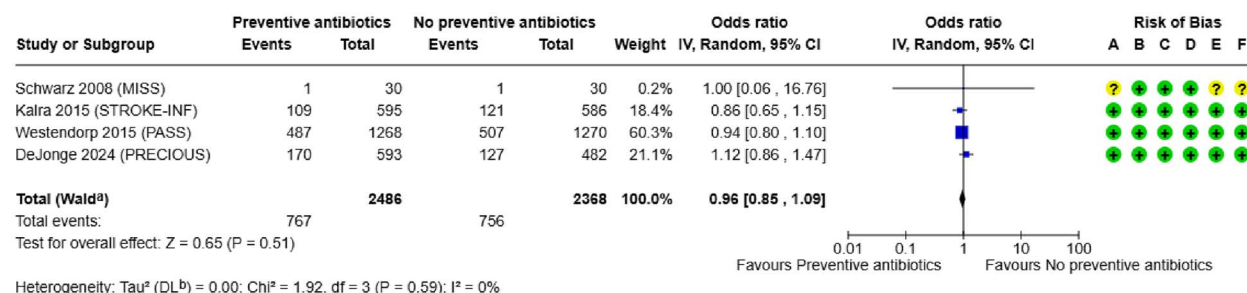


Figure 8 Forest plot and risk-of-bias assessment of preventive antibiotic therapy for favourable functional neurological outcome (mRS 0-2) at 90 days. Schwarz 2008 (MISS) had 0/30 in both arms, to allow meta-analysis the data was supplemented by one. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, ● low, ○ No information.

Mortality at 90 days

Six studies,^{104–109} including 5941 participants, reported mortality at 90 days. Of these, 3054 (51.4%) were allocated to preventive antibiotic therapy and 2887 (48.6%) to the control group (Figure 11). Mortality was 18.3% in the preventive antibiotic group compared with 17.2% in the control group, with no significant difference between groups (OR 1.07, 95% CI, 0.9–1.26; $P = .44$). There was no evidence of substantial heterogeneity across studies (Tau² = 0.01, I^2 = 11%; Figure 11).

Additional information

As shown above, preventive antibiotic therapy did not improve functional outcome nor decrease pneumonia rate. In the 3 largest trials (PASS, STROKE INF, PRECIOUS) and 2 smaller trials (MISS,

PANTHERIS), preventive antibiotic therapy did strongly decrease infection rate overall, mostly driven by the reduction of UTIs.

Possible explanations for the lack of effect of preventive antibiotic therapy on physician and panel-diagnosed pneumonia include the following. First, one possible explanation is that preventive antibiotic therapy—administered in most studies at a mean of approximately 24 hours after stroke onset—may have been initiated too late to effectively prevent SAP. Experimental models in mice suggest that SAP develops as early as 6–12 hours following the ischemic insult.^{110,111} Secondly, the question is whether the chosen antibiotics covered the pathogens responsible for pneumonia adequately. Based on a review¹⁹ it seems that ceftriaxone treats most pathogens adequately, although possible anaerobic pathogens are not covered. However, these

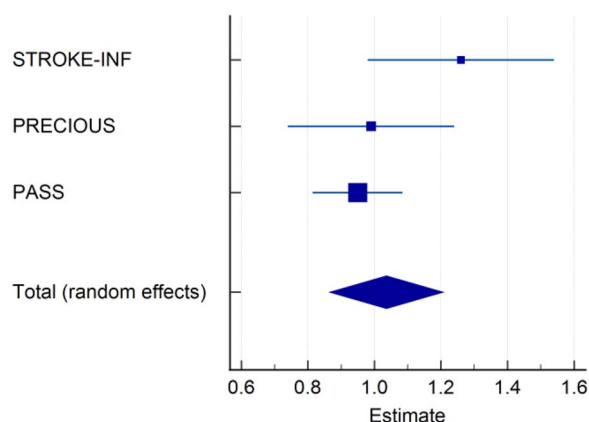


Figure 9 Pooled odds ratio of preventive antibiotic therapy for improved outcome on total range of mRS.

were covered in the antibiotic therapy of the STROKE-INF, and this trial also failed to show an effect. Thirdly, the open-label design of the 3 largest trials could have lowered the threshold for start of antibiotics in patients randomised to the control group. However, both in the PASS and STROKE-INF trial, more patients received antibiotic therapy than the control group (PASS: 4979 defined daily doses vs 2120 defined daily doses in the control group; STROKE-INF 87% vs 10% in the control group was treated with antibiotic therapy), although this does not completely exclude a lower threshold for treatment in the control group. Fourthly, preventive antibiotic therapy could not add to the high level of stroke unit care, which has been shown to improve outcome after stroke. Finally, it is possible that panel and physician defined pneumonia is not a true bacterial infection that can be prevented with antibiotic therapy, but merely an aspiration pneumonitis, or that other pulmonary diseases such as pulmonary oedema, atelectasis or lung cancer, mimic pneumonia.³¹

Based on the current evidence, the expert group recommends against the use of prophylactic antibiotic therapy to prevent SAP, as it does not reduce SAP incidence nor improve clinical outcomes. The prophylactic antibiotic use is therefore not warranted, even in the framework of antibiotic-stewardship. The expert group recommends initiating antibiotic therapy promptly upon confirmed diagnosis of SAP.

PICO 7

In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, does usage of specific drugs (eg, antiemetics, beta-blockers, statins, acid-suppressing medication) compared to no usage of these specific drugs affect SAP frequency and clinical outcomes?

Antiemetics

Aspiration of oropharyngeal content is the most common cause of SAP. The aspirate can come from oral intake, oropharyngeal secretions or gastric contents regurgitated or vomited into the oropharyngeal space. Stroke delays gastric emptying,^{112,113} increases residual volume,¹¹⁴ reduces lower oesophageal sphincter closure pressures and gastro-oesophageal reflux partly due to the neurological injury itself and partly to circulating stress hormones that affect gastric motility.¹¹⁵ Lower oesophageal sphincter

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is currently insufficient evidence to make an evidence-based recommendation regarding the use of antiemetics for the prevention of SAP. Please see the Expert Consensus Statement below.	-	-

Expert consensus statement

We suggest not to administer antiemetics for the prevention of SAP hospitalized, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset outside of clinical trials, as there is insufficient evidence for this indication. However, we suggest using these drugs for the treatment of nausea and vomiting, guided by local guidelines and clinical judgement. A large phase 3 randomised controlled trial investigating metoclopramide for preventing SAP in the first two weeks after stroke is currently ongoing.

Voting: 8/8

dysfunction is exacerbated by a nasogastric tube, further increasing the risk of reflux, regurgitation and micro-aspiration.¹¹⁶ Prevention of vomiting and regurgitation by antiemetic treatment could therefore reduce the risk of SAP.

Analysis of current evidence

Four randomised controlled studies have investigated antiemetics for the prevention of SAP, 3 using metoclopramide and one domperidone.^{104,117–119} Duration of treatment differed between 4 and 21 days.^{104,117–119} All patients in one study were receiving nasogastric tube feeding at enrolment,¹¹⁷ whereas only a small proportion of patients in the other studies were fed via a nasogastric tube at baseline.^{104,118} The meta-analysis of these 4 studies included 1622 participants, 913 were randomised to antiemetics, and 917 to control. Antiemetic treatment was not associated with a significant reduction in pneumonia (165 vs 182; OR 0.38, 95% CI, 0.08–1.91) or mortality (Figures 12 and 13). There was substantial heterogeneity between the studies ($\tau^2 = 2.45$, $I^2 = 94\%$; Figures 12 and 13) for pneumonia, with significant benefit in the 2 studies with longer treatment duration,^{117,118} but not in the studies where the antiemetic was used for 7 days or less. There was no significant difference in the effect on mortality between the 4 studies. The GRADE assessment is weakly in favour of antiemetics but given that there is very substantial heterogeneity between the studies, we consider the evidence insufficient for a recommendation.

Additional information

Since the risk of aspiration pneumonia is highest in stroke patients with nasogastric tubes in situ,^{120,121} it is possible that this subgroup derives the greatest benefit from preventive interventions. This may help to explain why a trial exclusively enrolling patients with nasogastric tubes reported a positive effect,¹¹⁷ whereas another study including only a smaller proportion of tube-fed patients (329; 24%) did not demonstrate benefit.¹²² However, subgroup analysis restricted to participants with nasogastric tubes did not demonstrate a benefit of 4 days of metoclopramide treatment.¹²² It therefore remains uncertain whether the heterogeneity across the available antiemetic trials reflects the small sample sizes of some studies or differences in

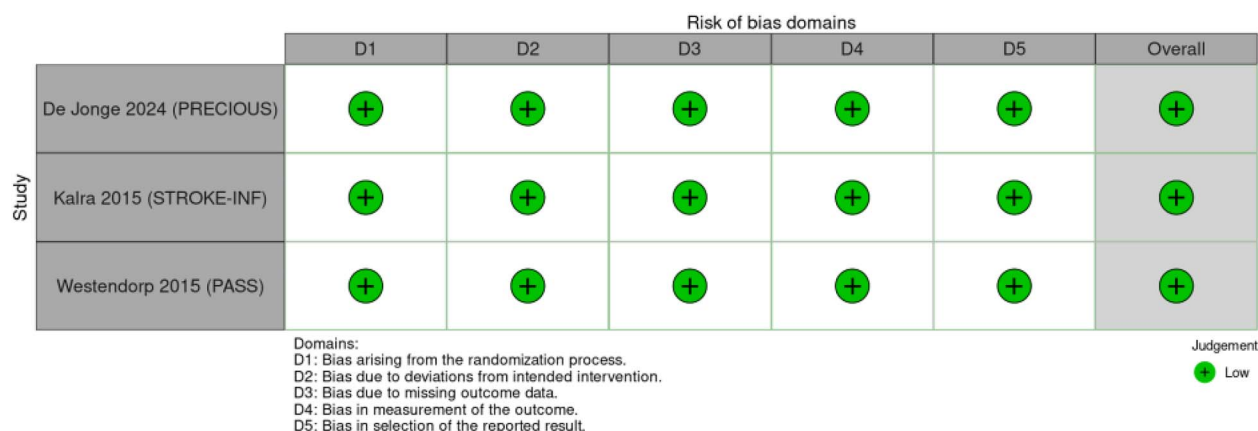


Figure 10 Risk of bias profile for studies included in PICO 6 (improved outcome on total range of mRS).

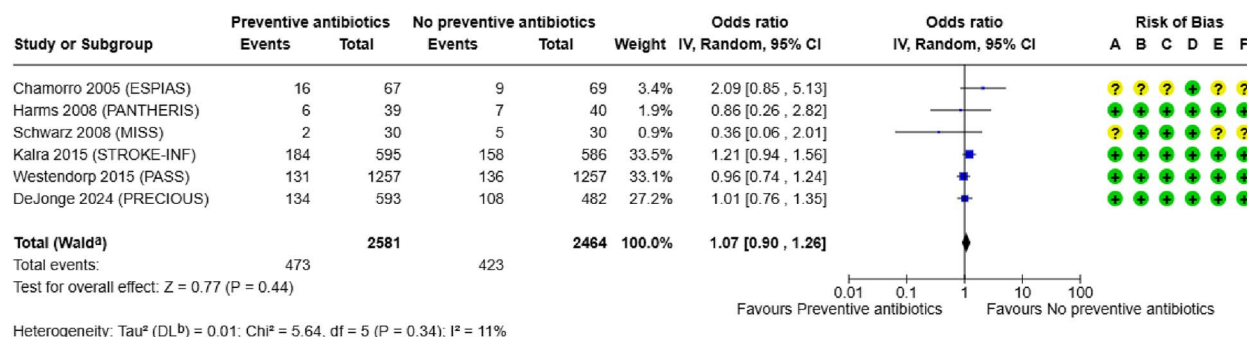


Figure 11 Forest plot and risk-of-bias assessment of preventive antibiotic therapy for all-cause mortality. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, + low, ! No information.

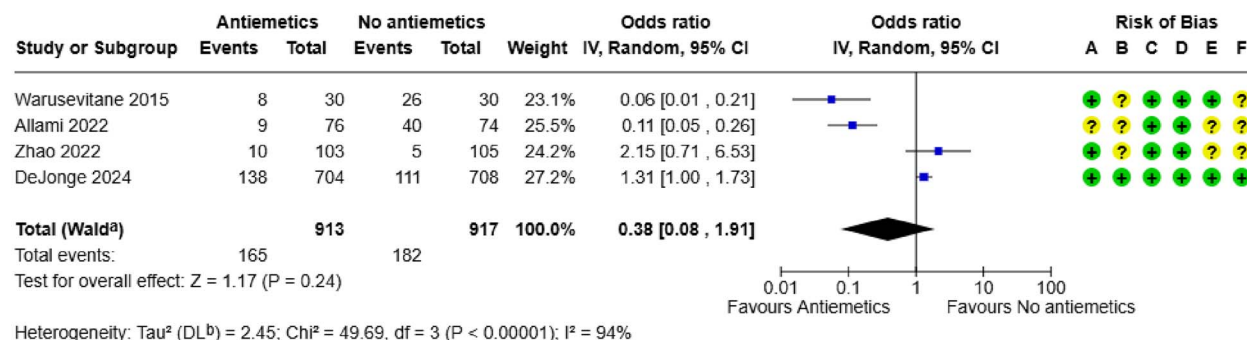


Figure 12 Forest plot and risk-of-bias assessment of antiemetics for SAP incidence. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, + low, ! No information.

treatment duration. A larger, adequately powered randomised trial (MAPS-2) is currently ongoing (ISRCTN40512746).

Beta-blockers

In animal models of cerebral ischemia beta-blockers decreased the risk of infections by counteracting stroke-induced immunosuppression.^{110,123}

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is no evidence from RCTs or observational studies to determine whether starting beta-blockers after stroke prevents pneumonia. We are therefore unable to make an evidence-based recommendation. Please see the Expert Consensus Statement below.	-	-

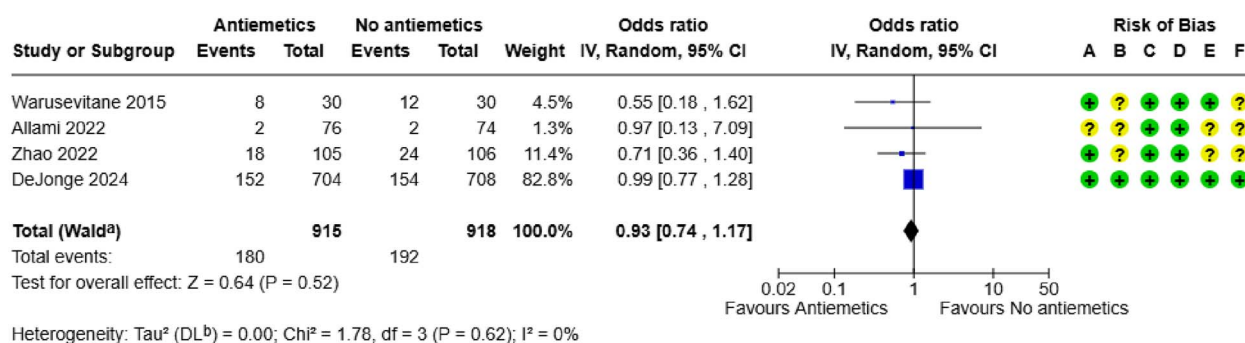


Figure 13 Forest plot of antiemetics and risk-of-bias assessment for all-cause mortality at 90 days. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, ● low, ! No information.

Expert consensus statement

In hospitalised, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset, we suggest not to initiate beta-blockers for the prevention of SAP. However, if patients are taking beta-blockers for other reasons after the stroke, these should be continued, as there is no reason to stop them and weak evidence for a reduction in mortality.

Voting: 8/8

Analysis of current evidence

There were no RCTs devoted to this topic. There were also no prospective observational studies evaluating patients that were started on beta-blockers after stroke. We therefore conducted an exploratory analysis summarising evidence from mostly retrospective studies with patients taking betablockers already prior to stroke. These are discussed in the additional information section.^{124–127}

Additional information

In a retrospective study including 841 consecutive patients with acute ischaemic stroke, 88 patients (10.6%) were treated with a beta-blocker during hospitalisation.¹²⁷ Almost 94% of them received a beta-blocker prior to stroke. The incidence of SAP was lower in patients treated with beta-blockers compared with those without beta-blockers (4.5% vs 11.4%; $P = .05$). Three other studies investigated an association between beta-blocker therapy during the acute phase of stroke and pneumonia. However, these papers did not differentiate patients who were beta-blocker naive prior to stroke and received this class of medication after admission from those who received a beta-blocker before stroke and continued this therapy during hospitalisation. An analysis of 5212 ischemic stroke patients and found that on-stroke beta-blocker use was associated with a reduced risk of pneumonia (adjusted RR 0.49, 95%CI, 0.25–0.95).¹²⁶ In the observational study that included 138 consecutive patients with hypertensive ICH, the frequency of SAP was lower in patients treated with atenolol in the acute phase of stroke compared with those without atenolol (8.9% vs 30.5%; $P = .002$).¹²⁴ No association was observed between the use of either cardio selective or non-selective beta-blockers during the first 3 days after admission with ischaemic stroke and pneumonia.¹²⁸ After propensity matching, the frequency of SAP was 5.5% in patients treated with beta-blockers and 3.1% in patients without beta-blockers ($P = .16$). Three papers reported

no association between the beta-blocker use and functional outcome at discharge or 3 months after stroke.^{124,126,128} Three studies reported lower in-hospital or 90-day mortality in stroke patients treated with beta-blockers,^{124,126,127} whereas one another study did not find any association. The meta-analysis showed no significant difference of SAP between patients treated with beta-blockers compared to those non-treated with beta-blockers (OR 0.51, 95% CI, 0.20–1.29; Figure 14), however, the risk of death was reduced in patients treated with beta-blockers (OR 0.46, 95% CI, 0.24–0.91; Figure 15). There was considerable heterogeneity between studies (Figures 14 and 15). These results should be interpreted with caution because they are based on only observational studies which varied in beta-blocker type (selective vs non-selective) and doses, a treatment duration and diagnostic criteria of SAP. Overall, there is no consistent evidence from these studies to support the use of beta-blockers for SAP prevention.

Statins

In an experimental model of cerebral ischemia, simvastatin decreased the stroke-associated lung susceptibility to spontaneous bacterial infections.¹²⁹ It is possible that similar protective effects are seen in humans.

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is insufficient evidence to make an evidence-based recommendation regarding the use of statins for the prevention of pneumonia. Please see the Expert Consensus Statement below.	-	-

Expert consensus statement

In hospitalised, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset, we suggest not to initiate statins for the purpose of preventing SAP. Where statins have been started for other indications, they should be continued.

Voting: 8/8

Analysis of current evidence

To address this PICO question, we considered only patients in whom statin therapy was initiated de novo in the acute phase of stroke. The literature search identified only 1 study relevant for this PICO question. A retrospective analysis of 1258 consecutive patients with ischaemic stroke excluded individuals who had

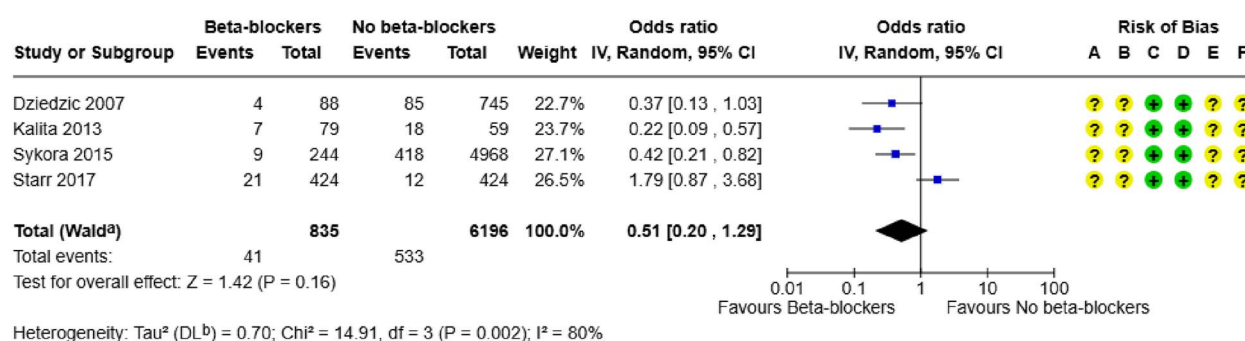


Figure 14 Forest plot of beta-blockers and risk-of-bias assessment for SAP incidence. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, ● low, ○ No information.

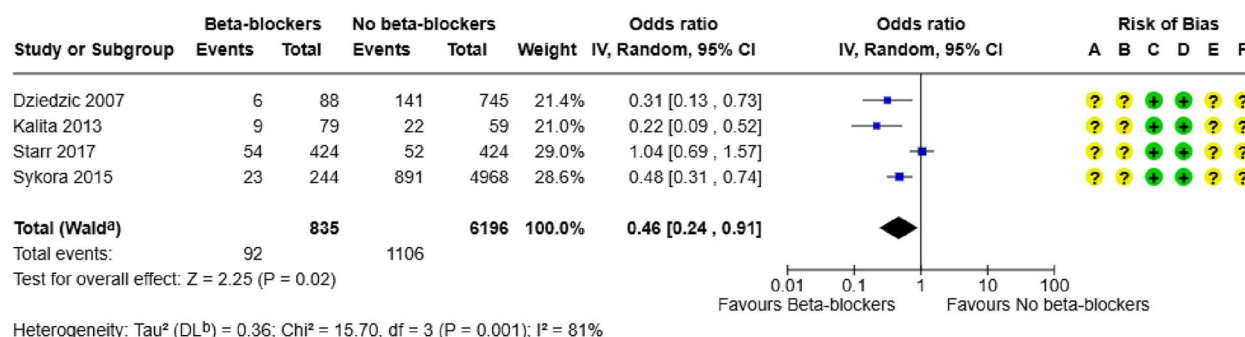


Figure 15 Forest plot of beta-blockers and risk-of-bias assessment for all-cause mortality at 90 days. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, ● low, ○ No information.

received statin therapy prior to stroke onset.¹³⁰ The frequency of SAP was lower in patients treated with statins in the acute phase of stroke compared with those without statins (19.4% vs 34.6%; $P < .01$; OR = 0.45, 95% CI, 0.32–0.64); however, this association was no longer significant in multivariate analysis (OR 1.51, 95% CI, 0.85–2.67). The other 2 studies in the Forest plot are not used as evidence here, as they report continuation of pre-existing statin treatment, but discussed in additional information.^{130–132}

Additional information

A retrospective analysis of 481 consecutive ischemic stroke patients treated with thrombolysis evaluated the association of statin therapy with post-stroke outcomes.¹³¹ Statin treatment was defined as prior use before stroke onset and continuation for at least the first 3 days after hospital admission. Patients receiving statins were less likely to develop SAP compared with those not receiving statins (5% vs 13%; $P = .04$; adjusted OR 0.31, 95% CI, 0.10–0.94). However, no significant associations were observed between statin use and 90-day mortality or functional outcome. A retrospective analysis of 2045 patients with acute ischaemic stroke found no significant difference in the frequency of SAP between those receiving statin therapy prior to stroke onset and during the acute phase compared with patients not treated with statins (7.8% vs 10.2%).¹³² The meta-analysis showed that the use of statins in the acute phase of ischaemic stroke was associated with a reduced risk of SAP (OR 0.54, 95% CI, 0.36–0.81; Figure 16). The risk of death did not differ between groups (OR 0.78, 95% CI,

0.51–1.19 Figure 17). These results are, however, limited by the observational, mostly retrospective, design of included studies, treatment timing (pre-stroke with continuation post-stroke vs post-stroke only) and varied diagnostic criteria of SAP (Figures 16 and 17). Thus, no firm conclusions could be drawn about the utility of statins for SAP prevention.

Other preventative treatments

In this section, we have summarised pharmacological interventions for which published evidence suggests a potential influence on the development of SAP. These include both active treatment strategies, such as modulation of the inflammatory response via angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs),¹³³ and of medications that may increase the risk of aspiration or pneumonia, such as gastric acid suppressants,¹³⁴ as well as drugs with potentially beneficial (neuroprotection) and adverse (sedation) effects (diazepam).¹³⁵ No RCTs specifically addressing these approaches were identified. Given the heterogeneity and absence of a shared mechanism of action,

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is insufficient evidence to recommend the use/avoidance of ACEIs/ARBs, antacids, PPIs and H2 RAs, and benzodiazepines for the prevention of stroke-associated pneumonia. Please see the Expert Consensus Statement below.	⊕	-

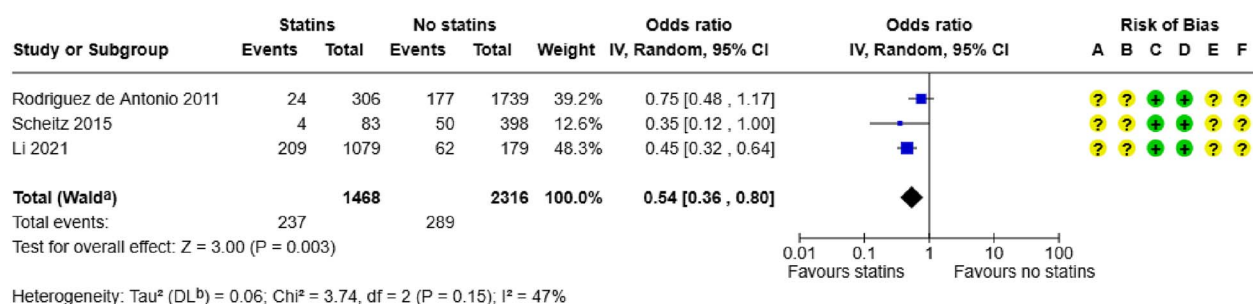


Figure 16 Forest plot and risk-of-bias assessment of statins for SAP incidence. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, + low, ! No information.

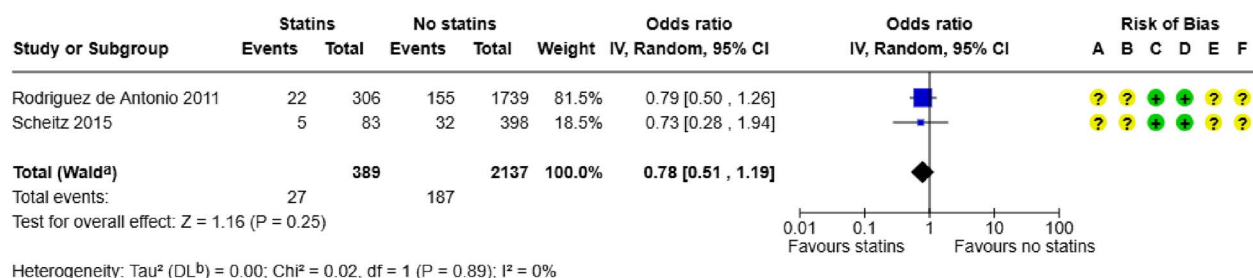


Figure 17 Forest plot and risk-of-bias assessment of statins for all-cause mortality at 90 days. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, + low, ! No information.

Expert consensus statement

In hospitalised, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset, concomitant medications prescribed for other indications may influence the risk of SAP. Acid-suppressive therapy may increase SAP risk, whereas treatment with ACEIs or ARBs in patients with intracerebral haemorrhage may be associated with reduced pneumonia and mortality risk. Given the limited evidence, we suggest considering these potential effects and using these medications strictly according to their primary indications, i.e. PPIs/H2 antagonists for the prevention and treatment of peptic ulceration, and ACEIs or ARBs for the management of hypertension.

Voting: 8/8

no meta-analysis was performed. The above mentioned studies are discussed in additional information.

Additional information

Suppression of gastric acid may influence gastrointestinal motility and alter the enteral microbiome, potentially increasing susceptibility to respiratory infections. A cohort study including 1676 hospitalised stroke patients compared individuals who received acid-suppressive therapy during admission—histamine-2 receptor antagonists (H2RAs) and/or proton pump inhibitors (PPIs) ($n = 1,340$)—with those who were not exposed to these agents ($n = 336$).¹³⁴ Pneumonia occurred significantly less frequently in the non-exposed group (12/336, 3.6%) than in the exposed group (277/1,340, 20.7%). Within the exposed cohort, the highest risk was observed among patients receiving combined H2RA and PPI therapy. However, given the relatively small number of unexposed individuals, residual confounding and bias due to

unmeasured factors cannot be excluded. Mortality outcomes were not reported.

The impact of benzodiazepines on pneumonia and functional outcome after stroke was addressed in an analysis of the virtual trials archive (VISTA).¹³⁵ SAP occurred in 218/1708 (12.8%) benzodiazepine exposed and 561/4138 (13.6%) non-exposed of controls ($P = .9$). There was also no difference in mortality and functional recovery at 90 days.

The association between ACEIs or ARBs and the SAP frequency was evaluated in a cohort of 635 patients with ICH.¹³³ SAP occurred less frequently in patients receiving ACEI/ARB therapy than in those who were not exposed (164/281 [58.4%] vs 236/354 [66.7%]; $P = .03$). Mortality was likewise lower in the exposed group (14/281 [5.0%] vs 42/354 [11.9%]; $P = .002$). In contrast, functional outcomes at 90 days did not differ significantly between groups.

PICO 8

In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset who require nasogastric feeding, does intermittent feeding via the nasogastric tube, compared to continuous feeding via the nasogastric tube, reduce SAP frequency and improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset who require nasogastric feeding, there is continued uncertainty regarding the balance of benefits and risks of intermittent feeding compared with continuous enteral feed delivery. Please see the Expert Consensus Statement below.	-	-

Expert consensus statement

Given the limited evidence for intermittent versus continuous nasogastric feeding, with no clear evidence favoring either approach, we suggest to use the feeding mode with which clinicians and their teams are most familiar.

Voting: 8/8

Pneumonia is a common complication in stroke patients fed via nasogastric tubes^{136,137} and may be due to disruption of gastroesophageal sphincter by the nasogastric tube, or to wider effects of tube feeding on gastric emptying and gastrointestinal motility. Within Europe continuous nasogastric feeding using a pump for delivery is most common, because of concerns that intermittent feeding may cause gastrointestinal bloating, diarrhoea and vomiting, but in China standard of care is intermittent feeding.¹³⁸ Most studies if intermittent feeding are done late after insertion of the feeding tube, when gastrointestinal motility has already adapted to lower feeding load. In studies of healthy volunteers feeding pattern does not affect gastric emptying and the rate of reflux.¹³⁹

Analysis of current evidence

We have found 3 RCTs and one observational study comparing intermittent with continuous feeding in acute stroke patients^{140–143} including a total of 255 patients. A study included 61 patients with ischaemic or haemorrhagic stroke. Although the timing of enrolment was not reported beyond acute stroke, but description of the gradually increased feed volumes suggested that they were enrolled when feeding was started.⁸⁴ The details of the randomization procedure were not reported. There was no significant difference in the incidence of pneumonia (11/31(35%) vs 9/31 (29%)), mortality (1/32 (3%) vs 3/31 (10%)), or gastrointestinal complications between intermittent and continuous feeding, but nurses found continuous feeding easier to deliver. Wang et al.¹⁴² enrolled 53 patients with acute stroke, exact timing was not given, but the trial intervention was started immediately after insertion of the nasogastric tube, suggesting that this would have been within less than 7 days from onset. Randomization was by random number table. Pneumonia occurred in 10/25 (40%) and 9/28 (32%) in the intermittent and continuous groups respectively, with no significant differences. There was more diarrhoea (52 vs 25%, $P = .04$) in the intermittent group. Mortality was not reported.

In a study using alternate envelope allocation, 69 Chinese patients with acute stroke were assigned to intermittent or continuous feeding (including a 7-hour overnight break). Intermittent feeding was associated with a lower incidence of pneumonia compared with continuous feeding (33% vs. 58%; $P = .04$), while nutritional intake was similar between groups and no differences were observed in gastrointestinal complications, including diarrhoea, gastric retention or gastrointestinal bleeding.¹⁴³ This study was only reviewed using the English abstract, and the risk of bias was considered high. In an observational registry study 71 out of 118 consecutive Japanese patients with acute stroke were included after excluding patients those who resumed oral feeding or required parenteral nutrition within the first 7 days after stroke onset.¹⁴⁰ Choice of treatment was determined by the nutritional team, based on clinical considerations, and this may have introduced bias and confounding by indication. There was no significant difference in pneumonia rates between intermittent and continuous feeding (7% [3/45] vs 15% [4/26]; $P = .40$), nor in

any of the other complications (diarrhoea, vomiting). None of the 4 studies reported functional recovery.

There is significant risk of bias in all 4 studies significant heterogeneity ($I^2 = 42\%$), and all but one of the studies are based in Eastern Asia, where feeding practice may not reflect European preferences (Figures 18 and 19). While the GRADE assessment is weak in favour of intermittent feeding, we do not consider the evidence sufficient to make such a recommendation.

Additional information

One further study¹⁴⁴ addressed gastrointestinal complications in acute stroke patients fed continuously or intermittently, but did not report pneumonia, and therefore was not included in the meta-analysis.

PICO 9

In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, do physical treatments to improve lung function, compared to no physical treatments to improve lung function, reduce SAP frequency and improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is currently insufficient evidence to support an evidence-based recommendation regarding the use of physical treatments to improve lung function for the prevention of SAP or improvement of outcome. Please see the Expert Consensus Statement below.	-	-

Expert consensus statement

In hospitalised, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset, we suggest respiratory physiotherapy as part of an early post-stroke rehabilitation programme to prevent SAP. This is based on evidence suggesting improvements in respiratory function and reductions in respiratory complications when delivered over several weeks—primarily during the rehabilitation phase and often in combination with other interventions—as well as a trend towards reduced SAP and mortality in a meta-analysis of two small studies.

Voting: 8/8

In addition to limb weakness stroke also affects respiratory and trunk muscles. This contributes to the risk of aspiration stroke patients with dysphagia. Respiratory physiotherapy increases strength of respiratory muscles¹⁴⁵ and could potentially prevent pneumonia.

Analysis of current evidence

In the former study, patients with acute ischaemic or haemorrhagic stroke (<2 weeks from onset) underwent respiratory muscle training using a threshold load method. Participants were randomised to 4 weeks of daily expiratory training ($n = 27$), inspiratory training ($n = 26$) or sham training ($n = 25$). Baseline characteristics were comparable across groups.

The search identified 2 RCTs evaluating respiratory muscle training in patients with acute stroke. One trial enrolled patients within 2 weeks of stroke onset,¹⁴⁶ whereas the second provided only limited detail beyond the acute stroke setting.¹⁴⁷ In the former study, patients with acute ischaemic or haemorrhagic

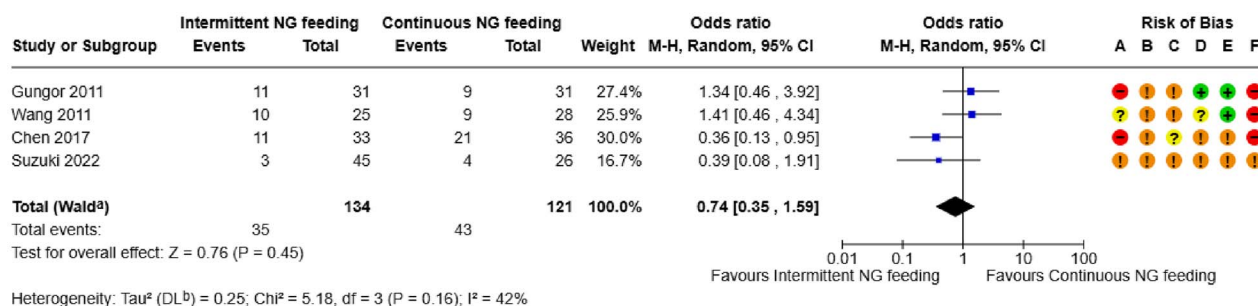


Figure 18 Forest plot and risk-of-bias assessment of intermittent vs continuous nasogastric (NG) tube feeding for SAP incidence. ^aConfidence interval (CI) calculated with Wald-type method. ^b τ^2 calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ● some concerns, ● low, ● No information.

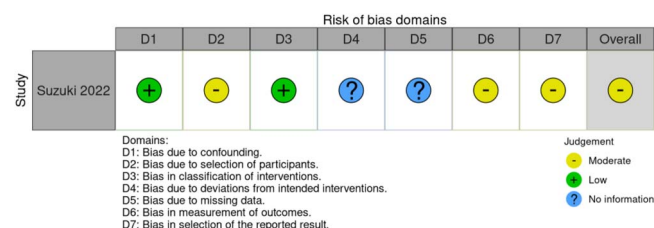


Figure 19 ROBINS-I risk of bias profile for non-randomised studies included in PICO 8.

stroke (<2 weeks from onset) underwent respiratory muscle training using a threshold load method.¹⁴⁶ Participants were randomised to 4 weeks of daily expiratory training ($n = 27$), inspiratory training ($n = 26$) or sham training ($n = 25$). Baseline characteristics were comparable. There was a high drop-out rate (6, 5 and 4, respectively) by day 28. The primary outcome was peak expiratory cough flow (PECF) at 28 days, with secondary outcomes including PECF of capsaicin-induced involuntary cough and maximal mouth pressures. There were no significant differences in respiratory muscle strength or cough flow between the intervention and control groups at any time point. There were 6 (22%), 3 (11%) and 4 (16%) pneumonias, respectively, at 90 days ($P = .65$). Two participants died (one in each intervention group). Functional recovery was not recorded. A second trial randomised 181 patients with acute ischaemic stroke (although no specific definition of “acute” was provided) to receive respiratory physiotherapy—consisting of therapist-supported breathing exercises—for 30 min, 3 times per week over 12 weeks, or to receive no respiratory physiotherapy.¹⁴⁷ There was a significant reduction of pneumonia (5 (2.8%) with active treatment and 11 (6.1%) in controls, $P = .043$) and admission to intensive care (1 (1%) vs 5 (6.2%), $P = .04$), but no significant difference in NIHSS (National Institute of Health Stroke Scale), mRS and mortality at 90 days. Randomization was by card, and no reason was given for the unequal numbers in both groups. No information is given on drop-outs, or what happened when the patients were discharged from hospital. There is significant heterogeneity between the 2 studies, with the higher high risk of bias in the larger study supporting use of breathing exercises. Despite the GRADE assessment of the evidence as weak in favour of the intervention we consider the evidence insufficient to make an evidence-based recommendation, as there are only 2 small

studies, with unclear timing of the intervention (acute rather than within 7 days), small sample size, significant heterogeneity and high risk of bias (Figures 20 and 21).

Additional information

There is some evidence to support the use of respiratory rehabilitation in stroke patients, which did not fit the criteria for the metanalysis because the intervention was part of a wider program of rehabilitation¹⁴⁸ or was delivered in the rehabilitation phase, rather than the acute phase of stroke.

A prospective randomised trial in 80 patients with moderate-to-severe acute ischemic stroke after thrombolysis compared conventional rehabilitation with comprehensive pulmonary rehabilitation (CPR), a multimodal program combining respiratory therapy, respiratory muscle training and mobilisation. Initiated on the first day after stroke, CPR significantly improved fatigue, motor and balance scores and reduced the incidence of SAP (10% vs. 25%). These findings suggest that CPR might enhance functional recovery and lower respiratory complication rates in the acute phase of stroke.¹⁴⁸ We did not include this study in the metanalysis or respiratory rehabilitation, as it is not possible to distinguish the effect of respiratory physiotherapy from the other rehabilitation modalities administered.

One further study¹⁴⁹ was not included, because the intervention started only during the rehabilitation phase at a mean of 35 and 39 days after onset. A high proportion of participants did not complete the study, with 36 and 28 patients allocated to respiratory physiotherapy 5 times a week for one month or control (no respiratory therapy), but only 22 in each group included in the outcomes. They reported significant improvement in 2/7 respiratory outcomes assessed at 4 weeks and a reduction of deaths (1/22 vs 3/22, $P = .16$) at 1 year after the stroke. Two meta-analyses including mostly patients treated in the rehabilitation setting confirm improvements in respiratory function and reductions in respiratory complications. One included 9 RCT ($n = 308$) across acute to chronic stages showed that respiratory muscle training significantly improved respiratory muscle strength, lung function, walking ability and reduced respiratory complications, with benefits lasting up to 12 weeks.¹⁵⁰ The other included 11 RCTs ($n = 523$) and confirmed reduced respiratory complication risk (RR 0.51) and improved

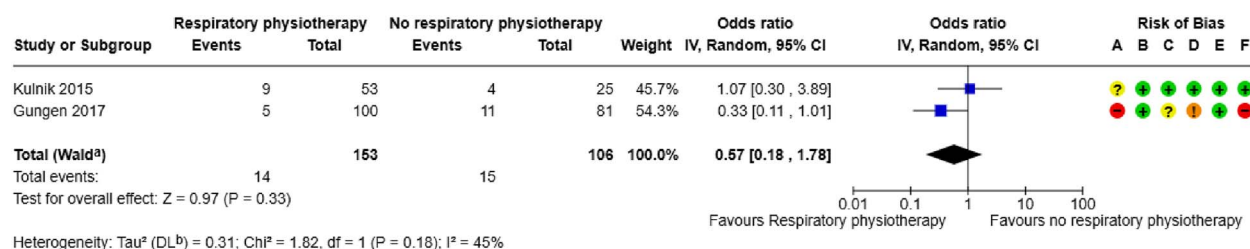


Figure 20 Forest plot and risk-of-bias assessment of physical interventions for SAP incidence. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, ● low, ! No information.

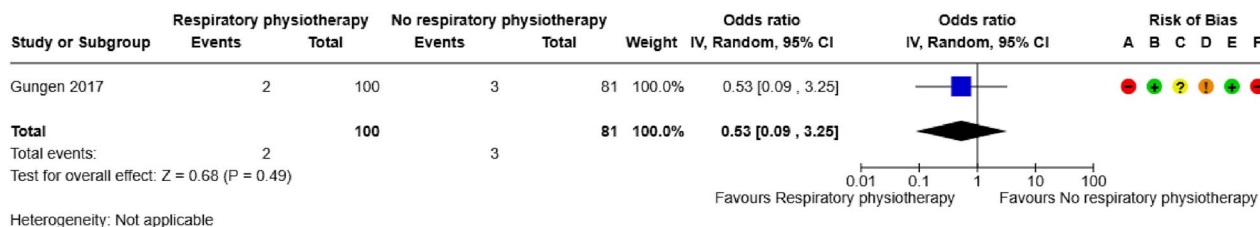


Figure 21 Forest plot and risk-of-bias assessment of physical interventions for all-cause mortality. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, ● low, ! No information.

swallowing function.¹⁵¹ In addition, a randomised trial of 44 acute stroke patients demonstrated that a 4-week comprehensive RMT program not only improved pulmonary function and muscle strength but also lowered the 1-year incidence of pneumonia and other respiratory complications.¹⁴⁹ These studies suggest that respiratory physiotherapy, given as part of a comprehensive stroke rehabilitation program can improve respiratory function and reduce pneumonia, if given over several weeks in rehabilitation.

PICO 10

In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, do early physical treatments to address mobility, compared to no early physical treatments to address mobility, reduce SAP frequency and improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, we suggest that physical interventions to promote mobilization, either within bed or out of bed, should be initiated early (within 48 hours) to prevent SAP. Please see the Expert Consensus Statement below.	⊕	1?

Expert consensus statement

In hospitalised, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset, we therefore suggest to mobilise within the 48 hour window for the prevention of SAP. However, based on the results of the AVERT study very early (within less than 24 h of onset) and prolonged mobilisation out of bed should be avoided in patients with severe strokes, as it is associated with worse outcomes in that group.

Voting: 8/8

Early mobilisation within 24–48 hours is one of the key aspects of acute stroke care and associated with reductions in death, disability and institutionalisation.^{152,153} It is widely thought that this is due to a reduction of complications, such as pneumonia.¹⁵⁴

Analysis of current evidence

Two RCTs^{155,156} and 2 observational studies^{157,158} fitted the selection criteria and were included in the meta-analyses.¹⁵⁹ The 4 included studies were small (71–392 participants) and conducted in different stroke populations. All 4 studies were restricted to ischaemic strokes. Definition of “early” intervention varied across trials, ranging from within 12 hours of symptom onset in one study, to within 24 hours in another, and within 48 hours in the remaining 2 studies.^{155–158} Mobilisation interventions differed across studies: in 3 trials, out-of-bed mobilisation was delivered by stroke unit staff, whereas in 1 study (turn-mob) mobilisation was limited to in-bed activity and was provided by the patient’s family.¹⁵⁶

Four studies reported pneumonia incidence. A random effects meta-analysis of these trials included 1011 participants.^{155–158} Among those 24 of 445 (5.4%) had pneumonia in the experimental group and 74 of 566 (13.1%) in the control group (Figure 22). This difference was statistically significant (OR 0.41, 95% CI, 0.18–0.96; $P = .04$). There is evidence of moderate heterogeneity between the studies (Tau² = 0.36, $I^2 = 50\%$) caused by one small study, which only recruited 71 participants, and had some baseline imbalance favouring the control group (Figures 22 and 23).

Two studies reported on death.^{155,158} Random effects meta-analysis of 2 studies included 285 participants; among those, 8 out of 145 (5.5%) died in the experimental group and 5 out of 140 (3.6%) in the control group (Figure 23). The analysis revealed no statistically significant difference between groups (OR 1.04, 95% CI, 0.091–12.12; $P = .98$). There is evidence of moderate

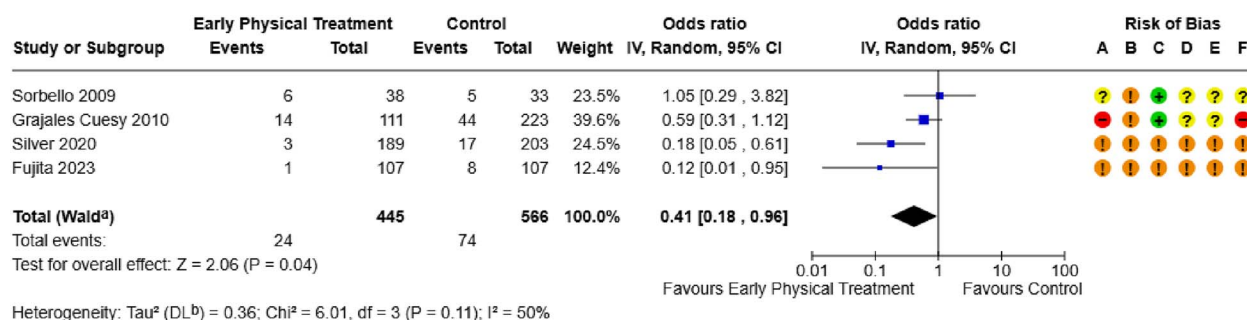


Figure 22 Forest plot and risk-of-bias assessment of mobilisation for SAP incidence. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend: (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, ● low, ! No information.

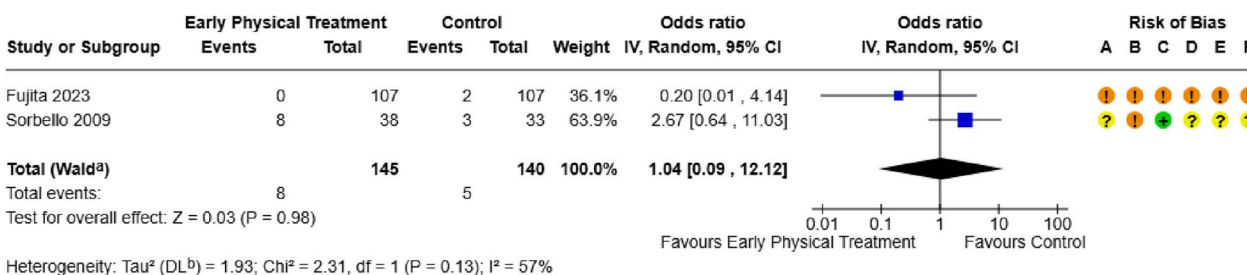


Figure 23 Forest plot and risk-of-bias assessment of mobilisation for all-cause mortality. ^aConfidence interval (CI) calculated with Wald-type method. ^bTau² calculated with DerSimonian and Laird method. Risk of bias legend (A) bias arising from the randomization process, (B) bias due to deviations from intended interventions, (C) bias due to missing outcome data, (D) bias in measurement of the outcome, (E) bias in selection of the reported result, (F) overall bias. ● High, ? some concerns, ● low, ! No information.

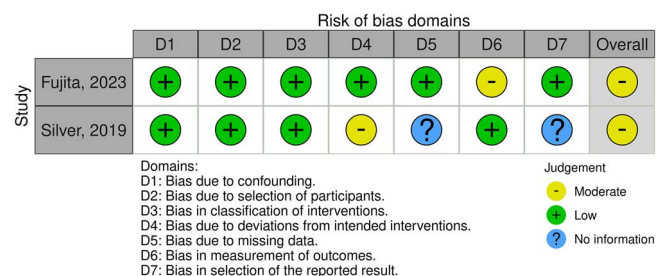


Figure 24 ROBINS-I risk of bias profile for non-randomised studies included in PICO 10.

heterogeneity between the studies (Tau² = 1.93, I² = 57%; Figures 23 and 24).

Only one study¹⁵⁸ reported functional outcomes after discharge, with no difference in good outcome between groups (mRS 0-2 at discharge 72/107 (67%) for early mobilisation vs 73/107(68%) for control, P = .88).

Overall, early mobilisation, including very early initiation (<24 hours), may be associated with reduced pneumonia after stroke; however, evidence is limited, with moderate risk of bias and low to very low GRADE certainty.

Additional information

The largest RCT comparing early mobilisation with very early and intensive mobilisation (<24 hours from onset) out of bed, the AVERT II study, enrolled 2083 participants, but is not included in the meta-analysis, as pneumonia was reported as an adverse event and only separately quantified from other complications

when it was listed as a cause of death.¹⁵⁹ The key finding of the study was that very early (within less than 24 hours) frequent and intensive mobilisation out of bed was not associated with lower mortality, better recovery or fewer complications, and worse outcomes in those with severe strokes. A Cochrane meta-analysis of RCTs comparing very early (within 24 hours of onset) with early mobilisation including 2958 participants confirmed these findings, and suggested that 24 hours after onset was the optimal, with both earlier and later start associated with worse outcomes.¹⁶⁰ More research is needed to inform decisions about patient selection timing and dose of early mobilisation. A large multicentre study (AVERT dose) is currently ongoing.¹⁶¹

A large Japanese nationwide cohort study analysed 426,508 patients aged ≥75 years with acute ischaemic stroke who received early rehabilitation/mobilisation within 3 days of onset. Multivariable logistic regression demonstrated a dose-dependent reduction in pneumonia risk with increasing daily rehabilitation duration up to day 7, with adjusted odds ratios from 0.78 (20–39 minutes/day) to 0.46 (≥80 minutes/day; all P < .001). This study was not included in the meta-analysis as it compared different doses of physical therapies, and because it was impossible to determine which form of physical therapy (mobilisation, respiratory training, speech and language therapy) was delivered. The results suggest that longer early rehabilitation in the first week of hospitalisation may substantially reduce pneumonia incidence in elderly stroke patients.¹⁶²

PICO 11

In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset

who have reduced level of consciousness, does positioning in the recovery position, compared to no specific positioning, reduce SAP frequency and improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset and a reduced level of consciousness, there is currently no clinical trial evidence to support recommendations on the use of the recovery position for preventing SAP. Please see the Expert Consensus Statement below.	-	-

Expert consensus statement

Based on the results of a single small study (turn-mob) we suggest that patients, including those with reduced level of consciousness, should be turned from supine to the left and right lateral recumbent position every 2 hours during the day and mobilized passively in bed to prevent SAP, if they are unable to change position independently. In line with clinical practice and guidance for enteral feeding, we suggest that during and after enteral feeds patients should be nursed in the 30–45 degree head-up position to avoid aspiration. Guided by the results of the HeadPost study, we suggest that alert patients with mild strokes and without enteral tubes in place should maintain any position they find comfortable.

Voting: 8/8

Aspiration is a major mechanism of post-stroke pneumonia, particularly in patients with a reduced level of consciousness. European Resuscitation council guidance for basic life support are that adults and children with decreased level of consciousness, due to medical illness or nonphysical trauma, that do not meet criteria for the initiation of rescue breathing or chest compressions should be nursed in a lateral, side-lying recovery (lateral recumbent) position as opposed to leaving them supine.¹⁶³ It is unclear whether this recommendation should continue for the hospital stay, where other considerations, such as the ability to observe the patient easily and the need to change position to prevent skin damage in pressure areas need to be considered for inpatient care.

Analysis of current evidence

Our search did not identify any studies comparing the recovery position with no specific positioning in patients with acute stroke.

Additional information

There are a number of studies which examine positioning of patients in bed, but none uses the recovery position as the intervention. The most relevant is the turn-mob RCT,¹⁵⁶ discussed in PICO 6, which tested a combination of positioning in bed and passive mobilisation in bed, initiated within 48 hours of admission, and found a significant reduction in pneumonia (14/111 (12.6%) vs 30/112 (36.8%), $P = .008$) in a patient population with mostly moderate to severe strokes (NIHSS > 7 68.6%, Glasgow Coma Scale [GCS] < 12 64.1%). Nursing staff instructed family members to reposition the patient from supine to alternating lateral recumbent positions every 2 hours during daytime; however, the duration of the intervention was not specified.¹⁵⁶

The HeadPoST Study¹⁶⁴ included 11,093 patients with acute stroke. They were randomised to remain lying flat (any flat position) or the head up position (at least 30-degree elevation of the head), which had to be maintained for at least 24 hours. There was no difference in pneumonia rates, mortality and functional outcomes at 30 days. This study suggests that head position early

after the stroke does not affect outcome, but this study examined lying flat in general, rather than the recovery position, and was therefore not included. Furthermore, it included a high proportion of very mild strokes with low National Institutes of Health Stroke Scale scores (median 4/42). As HeadPoST enrolment was biased towards mild strokes, the findings cannot be extrapolated to suggest that flat or head up positioning do not matter for patients with severe strokes. A recent RCT of flat (0 degree) versus 30 degree head up positioning of patients awaiting mechanical thrombectomy¹⁶⁵ was terminated early by the safety monitoring committee after only 92/182 planned patients were enrolled, as neurological deterioration was significantly more likely in participants nursed in the 30 degree head up position (hazard ratio 34.4, $P < .001$). No pneumonias were reported. However, the groups were not well matched, and the primary outcome could not be blinded. More research will be needed to guide clinical practice. As the study did not address recovery versus supine positioning it is not relevant for this PICO question.

For patients fed via enteral tubes positioning in in 30–45 degree head up position is widely recommended by professional bodies to prevent reflux and aspiration,¹⁶⁶ but this is based on clinical practice rather than evidence. Except for patients awaiting thrombectomy there is, however, also no evidence to suggest that this position is detrimental. A recent large RCT including 2143 sedated patients following extubation after surgery (different types including thoracic, lung, major abdominal surgery, planned and emergency procedures) showed that nursing in the lateral rather than the supine position significantly reduced the incidence and severity of hypoxaemia, but did not report on pneumonia.¹⁶⁷

PICO 12

In hospitalised adults with stroke associated pneumonia (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, does longer duration of antibiotic treatment (> 7 days), compared to standard duration of antibiotic treatment (≤ 7 days), improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, uncertainty remains regarding the effect of antibiotic treatment duration on clinical outcomes following acute stroke. Consequently, no evidence-based recommendations can currently be made. Please see the Expert Consensus Statement below.	-	-

Expert consensus statement

There is consensus in the group that the duration of the antibiotic treatment should depend on the clinical response and should generally be at least five days.

Voting: 8/8

Analysis of current evidence

The optimal duration of antibiotic therapy for SAP remains uncertain and may impact clinical outcomes, adverse events and antimicrobial stewardship. Clarifying whether prolonged treatment offers additional benefit is important to guide clinical

practice and avoid unnecessary antibiotic exposure. There are no clinical studies comparing different duration of antibiotic therapy for SAP.

Additional information

There is no evidence that the duration of antibiotic treatment in adults with SAP influences clinical outcomes. However, excessive antibiotic use in SAI has been linked to higher in-hospital mortality among patients with ICH. This study included 570 ICH patients, 162 of whom were diagnosed with SAI, and applied an antibiotic use index (PAUD: personal antibiotic use density) to evaluate this relationship. Patients who died had significantly higher PAUD scores, larger ICH volumes, higher NIHSS (National Institute of Health Stroke Scale) and ICH scores, lower GCS scores and shorter hospital stays ($P < .05$). PAUD was identified as an independent risk factor for in-hospital death (OR 2.396, $P = .001$), with mortality rates significantly lower in patients with low or moderate PAUD compared to those with high PAUD. Additionally, cumulative survival was notably higher in the low and moderate PAUD groups ($P < .001$). These findings indicate that higher PAUD may be associated with an increased risk of death, emphasising the potential importance of optimising antibiotic use in this patient population.¹⁶⁸ However, interpretation should be cautious, as the evidence is based on a single retrospective study and may be confounded by indication.

The duration of antibiotic treatment for acute bacterial pneumonia in other clinical areas depends on the severity, the causative pathogen and the clinical course. No validated severity scoring system exists specifically for SAP. CAP-derived tools such as CURB-65 and the ATS/IDSA severe CAP criteria may support severity assessment once SAP is diagnosed^{20,169}; however, both have important limitations in stroke populations and are not validated for SAP. Patients meeting ATS/IDSA criteria for severe CAP should generally be managed in an intensive care setting. Empiric antibiotic therapy should include a β -lactam plus either a macrolide or a respiratory fluoroquinolone; monotherapy is not recommended. In severe cases, extended microbiological diagnostics are recommended, including blood cultures, sputum cultures and urinary antigen testing for *Streptococcus pneumoniae* when indicated. Antibiotic treatment duration should be at least 5 days and is typically extended to 7–10 days or longer in complicated infections, delayed clinical response or when difficult-to-treat pathogens (eg, Methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*) are suspected or confirmed.²⁰

The recommendations of the PISCES group were based on the recommendations for the treatment of CAP and HAP. A distinction was made between whether the SAP occurred on or before day 3 after the stroke or later.²⁰ For early SAP, the PISCES group recommended following the CAP guidelines, which recommend a treatment duration of at least 5 days^{18,170} if clinical stability (eg, no fever, improved breathing, normalised inflammatory markers) is achieved within 48–72 hours.¹⁷¹ A systematic meta-analysis for CAP confirms that a shorter treatment duration (5–7 days) is just as effective as longer treatment in stable patients.¹⁷² They reduce side effects, the risk of antibiotic-related complications (eg, *Clostridioides difficile* infections) and the development of resistance. Longer treatment times offer no additional benefit unless

complications or certain pathogens (eg, *P. aeruginosa*) are present. For severe cases, a duration of 10–14 days may be necessary, especially if complications arise.¹⁸ If pneumonia occurs more than 3 days after stroke, especially more than 7 days after stroke, it is more likely to involve HAP pathogens.²⁰ For HAP, the PISCES group recommended a 7-day course of antibiotics, even for multidrug-resistant pathogens. Longer treatment periods (10–14 days) are reserved for complications or slow recovery. In the absence of clinical studies evaluating the optimal duration of antibiotic therapy for SAP, the PISCES group has previously recommended that treatment duration should be guided by clinical response, with a minimum of 7 days.²⁰

In contrast to the PISCES group, the guideline group considers SAP occurring within the first 7 days after stroke to be a direct consequence of stroke-related pathophysiological mechanisms, particularly aspiration, and—based on the available data on the pathogen spectrum—to represent aspiration pneumonia. The *British Thoracic Society Clinical Statement on Aspiration Pneumonia* recommends at least 5 days of antibiotic treatment, with extension depending on clinical progress.¹⁷³ As no study data addressing this question have emerged to date, we recommend that treatment duration should be guided by clinical response, with a minimum of 5 days. In case it becomes clear that diagnosis of SAP is incorrect the treatment should be stopped earlier due to antibiotic stewardship.

PICO 13

In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, does using broad spectrum antibiotics, compared to narrow spectrum antibiotics in pneumonia treatment (including choice of specific subclasses), improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, there is currently no clinical trial evidence to support recommendations on the use of broad-spectrum versus narrow-spectrum antibiotics to improve clinical outcomes. Please refer to the Expert Consensus Statement below.	-	-

Expert consensus statement

In patients with SAP, we suggest initiating empirical antibiotic therapy in accordance with local or regional protocols, with primary reference to recommendations for aspiration pneumonia, targeting aerobic Gram-negative bacilli and Gram-positive cocci. Even in the presence of dysphagia or confirmed aspiration, extended antimicrobial treatment is not justified. Where relevant risk factors exist, empirical therapy should include coverage for *Pseudomonas* spp. For pneumonia developing more than 7 days after stroke onset, the group suggests following local or regional HAP protocols.

Voting: 8/8

SAP is a frequent and serious complication in the first week after stroke, associated with increased mortality and poorer recovery. Antibiotics are central to treatment, yet the optimal spectrum remains uncertain. Broad-spectrum therapy may better cover aspiration-related or polymicrobial infections but carries risks such as resistance and adverse effects, whereas narrow-spectrum regimens may be safer but potentially inadequate.

Robust evidence is therefore needed to guide effective and safe antibiotic choices in this vulnerable population.

Analysis of current evidence

There are no clinical studies comparing the use of broad vs. narrow spectrum antibiotics for SAP.

Additional information

The current evidence base is insufficient to guide the selection of optimal antibiotic regimens in SAP. This is particularly relevant to the question of whether broad-spectrum antibiotics offer superior efficacy compared to narrow-spectrum agents. The PISCES group has established evidence-based recommendations for standardised empirical antibiotic management in SAP. Given the incomplete characterisation of SAP's microbiological profile, this consensus opinion focusses on anticipated pathogen distribution while emphasising judicious antimicrobial stewardship practices. The recommendations emerged from comprehensive literature synthesis and rigorous evidence evaluation, and a structured multidisciplinary consensus process utilising modified Delphi methodology with 75% agreement as the consensus threshold.¹⁷⁴

As outlined in the additional information for PICO 12, the PISCES group assumes that SAP may be caused by pathogens typically associated with either CAP or HAP. Early-onset SAP occurring within 72 hours after stroke was therefore considered to warrant CAP-directed therapy. SAP developing between 72 hours and 7 days after stroke is generally managed according to CAP recommendations, with additional consideration of Gram-negative enteric organisms and *Pseudomonas* species in the presence of relevant risk factors.²⁰ Importantly, pneumonia that clearly began prior to stroke onset (eg, fever, chest radiograph changes and markedly elevated inflammatory markers at admission) and without signs of post-stroke aspiration should be considered community-acquired and treated accordingly. PISCES further recommends that late-onset SAP beyond 7 days should follow institutional HAP treatment protocols, that dysphagia or witnessed aspiration does not necessitate modified antimicrobial coverage, and treatment duration should extend for a minimum of 7 days across all scenarios.¹⁷⁴

However, SAP must be assumed to result primarily from (micro) aspiration, with dysphagia as the key clinical risk factor, alongside other relevant mechanisms such as stroke-induced immunosuppression.¹ While pathogens originating from the oropharynx and outside the hospital setting may contribute to SAP in the first few days after stroke, thereby resembling CAP, aspiration is only a minor factor in typical CAP cases. Even within the first 72 hours after stroke onset, the underlying mechanisms and microbiological profile are more consistent with aspiration pneumonia than with early CAP. The pathogens typically involved—predominantly aerobic Gram-negative bacilli and Gram-positive cocci¹⁹—closely resemble those seen in hospital-acquired or ventilator-associated pneumonia, with a higher likelihood of polymicrobial infection and only a very low likelihood of atypical pathogens. Consequently, classifying SAP as a CAP-like entity in the early post-stroke period is misleading, and antibiotic selection should be guided by recommendations for aspiration pneumonia or HAP rather than CAP. The British Thoracic Society Clinical Statement on Aspiration Pneumonia

recommends treating aspiration pneumonia with at least a 5-day antibiotic course, using co-amoxiclav as first-line therapy. In penicillin allergy, a fluoroquinolone such as levofloxacin (or moxifloxacin) is appropriate; amoxicillin plus metronidazole is an alternative if co-amoxiclav cannot be used. Routine coverage for or atypical pathogens as well as for anaerobes is not indicated, except in cases of massive aspiration.¹⁷³

Empiric regimens should be guided by local epidemiology and individual risk factors, with a β -lactam/ β -lactamase inhibitor combination or an antipseudomonal β -lactam as the standard approach, providing coverage for common gram-negative organisms including *Klebsiella* species, while taking into account the potential presence of resistant strains (eg, ESBL-producing isolates). MRSA coverage (vancomycin or linezolid) should be added in patients with relevant risk factors. Combination therapy is reserved for patients with septic shock or high risk of multidrug-resistant pathogens, whereas monotherapy is preferred in most cases.¹⁷¹ The recommended treatment duration is 7–8 days, with early de-escalation based on microbiological results and a rapid switch from intravenous to oral therapy whenever feasible.^{101,175,176} While specific antimicrobial class recommendations could not be definitively established due to limited high-quality evidence, emerging data suggests potential differential outcomes based on antibiotic choice. Retrospective analysis of 2708 ischaemic stroke patients from the VISTA Acute registry demonstrated that macrolide therapy was independently associated with improved functional outcomes at 3 months, as measured by modified Rankin Scale and Barthel Index scores, for both general SAI and pneumonia specifically. Conversely, treatment with carbapenem agents, cephalosporin or monobactam antibiotics, beta-lactamase inhibitor combinations with penicillins, and aminoglycosides correlated with less favourable functional recovery. These findings suggest potential immunomodulatory properties of macrolides in post-stroke infections, though the retrospective nature of this analysis and inherent methodological limitations underscore the critical need for prospective RCTs to validate these observations.¹⁷⁴

For SAP with onset beyond 7 days after stroke onset, empiric antibiotic therapy should follow the principles of HAP management, as recommended by the PISCES group.²⁰

Prior pneumococcal vaccination could impact the microbiological landscape, with important implications for antibiotic choice in SAP, with emerging multi-drug-resistant non-vaccine serotype but there was insufficient evidence in SAP.¹⁷⁷

PICO 14

In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, does antibiotic treatment guided by identification of microbiologic aetiology, compared to empirical antibiotic treatment, improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, there is currently no clinical trial evidence to support recommendations on the use of pathogen-directed antibiotic therapy guided by microbiological identification compared with empirical antibiotic treatment. Please refer to the Expert Consensus Statement below.	-	-

Expert consensus statement

In patients with SAP, we suggest initiating empiric antibiotic therapy as early as possible, ideally within a few hours of clinical diagnosis. Where feasible, the group also suggests performing routine microbiological diagnostics (e.g., sputum cultures) prior to starting antibiotic treatment to enable subsequent targeted antibiotic therapy based on pathogen identification.

Voting: 8/8

Due to ongoing uncertainty regarding the optimal empirical antibiotic spectrum for SAP, this question examines whether microbiology-guided, individually tailored therapy improves clinical outcomes compared with empirical treatment alone. Clarifying the value of pathogen-directed approaches is important to maximise treatment efficacy while minimising unnecessary broad-spectrum antibiotic exposure in this vulnerable population.

Analysis of current evidence

There are no clinical studies comparing targeted antibiotic therapy for SAP based on identification of the microbiological cause with empirical antibiotic therapy.

Additional information

The prompt initiation of antibiotic therapy following the diagnosis of SAP is widely regarded as the cornerstone of its treatment. Although this therapeutic principle has never been formally validated in clinical trials, it is supported by both ethical considerations and pathophysiological rationale. In CAP, antibiotics should be given as soon as the diagnosis is likely and initial diagnosis is finished, ideally within a few hours after initial evaluation, but rigid “≤4 hours” targets are no longer supported by guidelines.^{170,178} In HAP/VAP, both timing and adequacy of initial therapy are decisive: inappropriate or delayed treatment markedly increases mortality, and empiric therapy should therefore start promptly once suspected, with de-escalation at 48–72 hours.¹⁷⁹ Aspiration pneumonia should be managed like CAP or HAP/VAP depending on setting. In contrast, aspiration pneumonitis after witnessed macro-aspiration, a very rare condition in acute stroke, is a chemical injury antibiotics should be withheld initially and only started if bacterial infection is evident after 24–48 hours.¹⁷³ Sepsis develops in roughly 2% of patients after acute stroke. In cases of sepsis without shock, current guidelines recommend initiating antimicrobial therapy within 3 hours of recognition, whereas in septic shock, immediate administration—ideally within 1 hour—is essential, as each hour of delay is associated with an approximately 4% increase in mortality risk.^{180–182} Thus, the urgency of therapy depends on severity: the greater the instability, the more every hour counts. Beyond the immediate, life-threatening risks associated with untreated or delayed bacterial pneumonia, the presence of fever and a systemic proinflammatory response—both of which are known to negatively affect neurological outcomes—further support early antibiotic administration.¹

Conversely, there is currently strong evidence against routine prophylactic use of antibiotics to prevent SAP (see PICO 6).⁸ This is notable, as phase III trials on SAP prevention have employed antibiotics identical to those used in standard clinical treatment. As such, the optimal timing for initiating antibiotic therapy in

cases of suspected or confirmed SAP remains uncertain. However, immediate empirical antibiotic treatment following diagnosis is generally considered appropriate, in line with CAP guideline recommendations.²⁰

Recommendations for empirical therapy are based on the relatively limited data available on the causative pathogens of SAP, as analysed in a systematic review. Fifteen studies involving 7,968 hospitalised adults with ischaemic stroke and/or ICH were analysed according to Cochrane and PRISMA guidelines. The reported frequency of SAP varied widely (2%–63%), with most cases (78%) occurring within the first week after stroke. Sputum samples were the predominant diagnostic method, either alone or in combination with tracheal aspirates or blood cultures. Culture positivity ranged from 15% to 88%, with aerobic Gram-negative bacilli (38%) and Gram-positive cocci (16%) being the most commonly isolated organisms. The most frequently identified pathogens were Enterobacteriaceae (21.8%; *Klebsiella pneumoniae* 12.8% and *Escherichia coli* 9%), *Staphylococcus aureus* (10.1%), *P. aeruginosa* (6%), *Acinetobacter baumannii* (4.6%) and *S. pneumoniae* (3.5%).¹⁹ Despite limitations due to the heterogeneity of the studies and the small number of cases, this study currently provides the best overview of the causative pathogens of SAP.

While viral aetiologies were not reported in this study, contemporary rapid molecular diagnostic methods have shown that viral agents such as influenza, respiratory syncytial virus and SARS-CoV-2 often represent the initiating pathogens in severe/hospitalised community-acquired pneumonia.¹⁸³ In another systematic review and meta-analysis of respiratory viral pathogens identified in adults with community-acquired pneumonia in Europe, the pooled proportion of patients with identified respiratory viruses was 22.0% (95% CI, 18.0–27.0), rising to 29.0% (25.0%–34.0%) in studies where polymerase chain reaction (PCR) diagnostics were performed raising the possibility of mixed viral-bacterial aetiology. Influenza virus was the most frequently detected virus in 9% (7%–12%) of adults with CAP. Molecular diagnostic methods have not yet been reported in suspected SAP patients.¹⁸⁴ However, respiratory viral pathogens, including SARS-CoV, influenza and RSV, have been identified as established triggers of cerebrovascular events. This association is of clinical significance, as the burden of stroke attributable to such infections may be mitigated through effective vaccination strategies.^{11,185} In summary, it is unclear whether and to what extent viral pathogens play a role in SAP, as no relevant data are available. Therefore, no treatment recommendations can be given with regard to viral pathogens.

PICO 15

In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, does use of adjuncts (eg, cough assisted device, breathing therapy), compared to treatment without adjuncts, improve clinical outcomes?

Evidence-based Recommendations	Quality of evidence	Strength
In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, uncertainty remains regarding whether the use of adjunctive therapies improves clinical outcomes. Consequently, no evidence-based recommendation can currently be made. Please see the Expert Consensus Statement below.	-	-

Expert consensus statement

In patients with SAP, we suggest that adjunctive measures, such as cough-assist devices or breathing therapies, may be considered on an individual basis within an interdisciplinary stroke unit setting, although they are not part of standard treatment. These interventions may be particularly beneficial in patients with relevant comorbidities, such as COPD.

Voting: 8/8

Analysis of current evidence

No included studies. There are no clinical studies investigating adjuncts in the treatment of SAP and their impact on stroke outcome.

Additional information

Hypoxia is common after stroke, most often due to pneumonia, aspiration or respiratory muscle dysfunction, and is associated with worse outcomes. While supplemental oxygen is a key element in correcting hypoxia, excessive use may be harmful, and randomised trials have not shown benefit when given to non-hypoxic patients. Current evidence does not support routine oxygen therapy after stroke,¹⁸⁶ but rapid identification and treatment of underlying causes of hypoxia remain essential.¹⁸⁷ In patients who develop SAP with respiratory compromise, optimised oxygen delivery strategies may be relevant.

A large, randomised trial of 8003 acute stroke patients found that routine low-dose oxygen supplementation, whether given continuously or nocturnally, did not reduce death or disability at 3 months compared with control. These results indicate that prophylactic oxygen provides no functional benefit in nonhypoxic stroke patients. In summary, SpO₂ levels should be monitored regularly in stroke units, with oxygen only administered to correct hypoxia (target value $\geq 94\%$), while routine supplementation is not recommended for non-hypoxic patients.¹⁶

Appropriate monitoring plays a key role in identifying hypoxia early. A Cochrane review of 3 small studies ($n = 354$) compared continuous with intermittent monitoring of physiological variables, including oxygen saturation, in acute stroke. Continuous monitoring was associated with a reduction in deaths and disabilities at 3 months or at discharge, but the results were heavily weighted towards 1 study with high bias. The authors conclude that continuous monitoring in the first 2–3 days may improve outcomes, but high-quality studies are still needed to define its role.¹⁸⁸

A retrospective study in 87 elderly patients with SAP and moderate respiratory failure compared high-flow nasal cannula (HFNC) with Venturi mask oxygen therapy. HFNC significantly improved oxygenation and reduced the need for invasive ventilation within 72 hours, although 28-day mortality did not differ between groups.¹⁸⁹

Beyond oxygen therapy, adjunctive respiratory interventions such as cough-assist devices or respiratory therapy may hold potential in the management of SAP. In acute stroke, reductions in functional residual capacity, inspired cough volume and peak cough flow likely contribute to the increased risk of chest infections.¹⁹⁰ While traditional airway clearance techniques remain in use, growing evidence supports device-based approaches including cough assist, vacuum techniques and airflow modulation, often applied in combination.¹⁹¹ In addition,

respiratory muscle training and early rehabilitation may improve lung function and potentially improves in both SAP and stroke. While oxygen therapy for hypoxia and HFNC are highly relevant in SAP management, they do not represent adjunctive airway clearance or respiratory therapies as addressed by this PICO. However, their clinical importance underscores the relevance of optimising respiratory function and indirectly supports the potential role of such adjunctive approaches. However, no studies to date have specifically evaluated these interventions for SAP with respect to clinical outcomes, although some evidence exists for improvements in lung function in the acute phase of stroke.

Discussion

SAP remains a major challenge in acute stroke care and is among the most frequent and serious complications in patients hospitalised within the first days after stroke onset.^{1,192} SAP has been consistently associated with adverse outcomes, including increased mortality, poorer functional recovery (modified Rankin Scale, both dichotomised and shift analyses), reduced independence (Barthel Index), lower quality of life, prolonged hospitalisation and a higher likelihood of institutionalisation.¹ These outcome domains therefore formed the core evaluative framework for all PICO questions, ensuring that recommendations were anchored in clinically meaningful and patient-relevant endpoints.

Despite its clinical relevance, no dedicated evidence-based guideline has been available. This guideline, developed according to ESO methodology, addressed 15 questions, of which only were supported by predominantly low-quality evidence, necessitating consensus procedures.

The resulting recommendations emphasise a pragmatic, clinically oriented approach. Standardised diagnostic criteria are recommended, while chest CT and plasma C-reactive protein may serve as useful adjuncts in selected cases. Clinical prediction scores and biomarkers show moderate to good discrimination, but their clinical utility depends on effective risk-adapted preventive interventions. Preventive antibiotic therapy is not supported. Prevention should focus on supportive care, including positioning, mobilisation and feeding strategies. Pharmacological prevention is not recommended.

Once SAP is clinically diagnosed (eg, definite or probable according to PISCES criteria), empiric antibiotic therapy should be initiated promptly and guided by local protocols. Microbiological diagnostics should be obtained where feasible, and treatment duration guided by clinical response (generally ≥ 5 days). Adjunctive respiratory interventions are not part of standard care but may be considered in selected patients, particularly those with relevant comorbidities such as chronic lung disease. All Evidence-based Recommendations and Expert Consensus Statements are summarised in Table 8.

The guideline addressed 4 major domains:

I Criteria and Diagnosis of SAP

Diagnosis of SAP is confounded by several factors, contributing to the challenges of accurate diagnosis and appropriate antibiotic stewardship.¹⁸ We examined whether the use of standardised diagnostic criteria in SAP, advanced imaging modalities (chest US or CT), and blood-based biomarkers improves diagnostic accuracy and translates into better clinical outcomes compared with non-standardised or conventional approaches. Given the

Table 8 Synoptic table of all recommendations and expert consensus statements.

Recommendation	Expert consensus statement
PICO1: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, does use of any standardised diagnostic criteria for SAP, compared to non-standardised clinician based diagnosis, improve clinical outcomes?	
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there are insufficient data to support recommendations on whether the use of standardised diagnostic criteria for SAP improves clinical outcomes. Consequently, no evidence-based recommendation can be made. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: -	In the absence of appropriately designed RCTs, and on the basis of observational studies and secondary analysis of RCTs, we suggest to use an algorithm-based approach for SAP diagnosis (for example PISCES) guided by a minimum set of agreed criteria. This may improve diagnostic accuracy and require further evaluation in research in clinical practice. Voting: 8/8
PICO 2: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, does use of chest ultrasound or computed tomography to diagnose SAP, compared to chest X-ray alone, increase diagnostic accuracy and improve clinical outcomes?	
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, uncertainty remains regarding the most accurate diagnostic approach for SAP when using chest ultrasound or computed tomography compared with chest X-ray alone. The potential benefits and risks of these procedures in relation to clinical outcomes are also unclear. Therefore, no evidence-based recommendation can currently be made. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: -	We suggest to consider a pulmonary CT scan if SAP is suspected and the diagnosis uncertain, particularly where there is a need to inform further antibiotic/ medical therapy and/or exclude other pathologies (e.g. pulmonary embolism). Voting: 8/8
PICO 3: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, does incorporation of any diagnostic (blood) biomarker, compared to not making use of diagnostic (blood) biomarkers, increase diagnostic accuracy and improve clinical outcomes?	
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is insufficient data to make an evidence-based recommendation and continued uncertainty of the role of blood inflammatory or stress biomarkers in the diagnostic approach to SAP. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: -	We suggest considering the addition of CRP to standardised diagnostic algorithms for SAP to improve diagnostic accuracy in afebrile patients, with available data indicating cut-off values between 30 and 40 mg/L. Voting: 8/8
PICO 4: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, does use of clinical prediction scores or biomarkers, compared to not using clinical prediction scores or biomarkers, identify patients who will develop SAP?	

Table 8 Continued.

Recommendation	Expert consensus statement
PICO1: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, does use of any standardised diagnostic criteria for SAP, compared to non-standardised clinician based diagnosis, improve clinical outcomes?	
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset t, there are insufficient data to support recommendations on whether the use of standardised diagnostic criteria for SAP improves clinical outcomes. Consequently, no evidence-based recommendation can be made. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: -	In the absence of appropriately designed RCTs, and on the basis of observational studies and secondary analysis of RCTs, we suggest to use an algorithm-based approach for SAP diagnosis (for example PISCES) guided by a minimum set of agreed criteria. This may improve diagnostic accuracy and require further evaluation in research in clinical practice. Voting: 8/8
PICO 2: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, does use of chest ultrasound or computed tomography to diagnose SAP, compared to chest X-ray alone, increase diagnostic accuracy and improve clinical outcomes?	
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, uncertainty remains regarding the most accurate diagnostic approach for SAP when using chest ultrasound or computed tomography compared with chest X-ray alone. The potential benefits and risks of these procedures in relation to clinical outcomes are also unclear. Therefore, no evidence-based recommendation can currently be made. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: -	We suggest to consider a pulmonary CT scan if SAP is suspected and the diagnosis uncertain, particularly where there is a need to inform further antibiotic/ medical therapy and/or exclude other pathologies (e.g. pulmonary embolism). Voting: 8/8
PICO 3: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, does incorporation of any diagnostic (blood) biomarker, compared to not making use of diagnostic (blood) biomarkers, increase diagnostic accuracy and improve clinical outcomes?	
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is insufficient data to make an evidence-based recommendation and continued uncertainty of the role of blood inflammatory or stress biomarkers in the diagnostic approach to SAP. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: -	We suggest considering the addition of CRP to standardised diagnostic algorithms for SAP to improve diagnostic accuracy in afebrile patients, with available data indicating cut-off values between 30 and 40 mg/L. Voting: 8/8
PICO 4: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, does use of clinical prediction scores or biomarkers, compared to not using clinical prediction scores or biomarkers, identify patients who will develop SAP?	

Table 8 Continued.

In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, clinical prediction scores and selected biomarkers may help identify individuals at increased risk of developing SAP, with moderate to good discriminatory performance. However, there is currently insufficient evidence to support the routine combination of biomarkers with existing clinical prediction tools for risk stratification. Continued uncertainty remains regarding the incremental clinical value of these approaches, and their implementation will ultimately depend on the availability, feasibility, and effectiveness of targeted preventive interventions. Please refer to the Expert Consensus Statement below. Quality of evidence: Very Low ⊕ Strength of recommendation: Weak for intervention †?	We suggest using validated clinical prediction scores or biomarkers to identify patients at increased risk of SAP and to better target preventive standard measures. However, their clinical utility is currently limited by only moderate to good discriminatory performance and is likely to depend on the availability of more effective preventive treatment strategies. Voting: 8/8
PICO 5: In hospitalised adults with stroke associated pneumonia (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptoms onset, does antibiotic treatment guided by clinical prediction scores or biomarkers, compared to standard clinical practice, improve clinical outcomes?	
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there are currently insufficient data to support an evidence-based recommendation regarding the routine use of clinical prediction scores or blood biomarkers to guide antibiotic treatment of SAP. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: -	Due to insufficient evidence, we advise against using clinical prediction scores or biomarkers to guide antibiotic treatment of SAP. For information on the start and duration of antibiotic therapy, the choice of antibiotic, and the role of microbiological tests, please refer to PICO questions 12 to 14. Voting: 8/8
PICO 6: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, does preventive antibiotic treatment compared to no preventive antibiotic treatment reduce SAP frequency and improve clinical outcomes?	
1. In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, we suggest not using preventive antibiotic therapy, as it has not been shown to reduce the incidence of SAP. Quality of evidence: Very low ⊕ Strength of recommendation: Weak against intervention ↓? 2. In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, we recommend not using preventive antibiotic therapy, as it has not been shown to improve clinical outcomes. Quality of evidence: Moderate ⊕⊕⊕ Strength of recommendation: Weak against intervention ↓?	

Table 8 Continued.

PICO 7: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, does usage of specific drugs (e.g. beta-blockers, statins, acid-suppressing medication) compared to no usage of these specific drugs affect SAP frequency and clinical outcomes?	
Antiemetics: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is currently insufficient evidence to make an evidence-based recommendation regarding the use of antiemetics for the prevention of SAP. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: - Beta-blockers: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is no evidence from RCTs or observational studies to determine whether starting beta-blockers after stroke prevents pneumonia. We are therefore unable to make an evidence-based recommendation. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: - Statins: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is insufficient evidence to make an evidence-based recommendation regarding the use of statins for the prevention of pneumonia. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: - Other preventive treatments: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is insufficient evidence to recommend the use/avoidance of ACEIs/ARBs, antacids, PPIs and H2 RAs, and benzodiazepines for the prevention of stroke-associated pneumonia. Please see the Expert Consensus Statement below. Quality of evidence: Very low ⊕ Strength of recommendation: -	We suggest not to administer antiemetics for the prevention of SAP hospitalized, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset outside of clinical trials, as there is insufficient evidence for this indication. However, we suggest using these drugs for the treatment of nausea and vomiting, guided by local guidelines and clinical judgement. A large phase 3 randomised controlled trial investigating metoclopramide for preventing SAP in the first two weeks after stroke is currently ongoing. Voting: 8/8 Beta Blockers: In hospitalised, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset, we suggest not to initiate beta-blockers for the prevention of SAP. However, if patients are taking beta-blockers for other reasons after the stroke, these should be continued, as there is no reason to stop them and weak evidence for a reduction in mortality. Voting: 8/8 Statins: In hospitalised, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset, we suggest not to initiate statins for the purpose of preventing SAP. Where statins have been started for other indications, they should be continued. Voting: 8/8 Other preventive treatments: In hospitalised, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset, concomitant medications prescribed for other indications may influence the risk of SAP. Acid-suppressive therapy may increase SAP risk, whereas treatment with ACEIs or ARBs in patients with intracerebral haemorrhage may be associated with reduced pneumonia and mortality risk. Given the limited evidence, we suggest considering these potential effects and using these medications strictly according to their primary indications, i.e. PPIs/H2 antagonists for the prevention and treatment of peptic ulceration, and ACEIs or ARBs for the management of hypertension. Voting: 8/8

Table 8 Continued.

PICO 8: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset who require nasogastric feeding, does intermittent feeding via the nasogastric tube, compared to continuous feeding via the nasogastric tube, reduce SAP frequency and improve clinical outcomes?	
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset who require nasogastric feeding, there is continued uncertainty regarding the balance of benefits and risks of intermittent feeding compared with continuous enteral feed delivery. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: -	Given the limited evidence for intermittent versus continuous nasogastric feeding, with no clear evidence favoring either approach, we suggest to use the feeding mode with which clinicians and their teams are most familiar. Voting: 8/8
PICO 9: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, do physical treatments to improve lung function, compared to no physical treatments to improve lung function, reduce SAP frequency and improve clinical outcomes?	
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, there is currently insufficient evidence to support an evidence-based recommendation regarding the use of physical treatments to improve lung function for the prevention of SAP or improvement of outcome. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: -	In hospitalised, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset, we suggest respiratory physiotherapy as part of an early post-stroke rehabilitation programme to prevent SAP. This is based on evidence suggesting improvements in respiratory function and reductions in respiratory complications when delivered over several weeks—primarily during the rehabilitation phase and often in combination with other interventions—as well as a trend towards reduced SAP and mortality in a meta-analysis of two small studies. Voting: 8/8
PICO 10: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset, do early physical treatments to address mobility, compared to no early physical treatments to address mobility, reduce SAP frequency and improve clinical outcomes?	
In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset, we suggest that physical interventions to promote mobilization, either within bed or out of bed, should be initiated early (within 48 hours) to prevent SAP. Please see the Expert Consensus Statement below. Quality of evidence: Very low ⊕ Strength of recommendation: Weak for intervention †?	In hospitalised, non-ventilated adults with acute ischaemic or haemorrhagic stroke within 7 days of symptom onset, we therefore suggest to mobilise within the 48 hour window for the prevention of SAP. However, based on the results of the AVERT study very early (within less than 24 h of onset) and prolonged mobilisation out of bed should be avoided in patients with severe strokes, as it is associated with worse outcomes in that group. Voting: 8/8
PICO 11: In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptoms onset who have reduced level of consciousness, does positioning in the recovery position, compared to no specific positioning, reduce SAP frequency and improve clinical outcomes?	

Table 8 Continued.

In hospitalised adults with acute ischaemic or haemorrhagic stroke (non-ventilated) within 7 days of stroke symptom onset and a reduced level of consciousness, there is currently no clinical trial evidence to support recommendations on the use of the recovery position for preventing SAP. Please refer to the expert consensus statement below. Quality of evidence: - Strength of recommendation: -	Based on the results of a single small study (turn-mob) we suggest that patients, including those with reduced level of consciousness, should be turned from supine to the left and right lateral recumbent position every 2 hours during the day and mobilized passively in bed to prevent SAP, if they are unable to change position independently. In line with clinical practice and guidance for enteral feeding, we suggest that during and after enteral feeds patients should be nursed in the 30-45 degree head-up position to avoid aspiration. Guided by the results of the HeadPost study, we suggest that alert patients with mild strokes and without enteral tubes in place should maintain any position they find comfortable. Voting: 8/8
PICO 12: In hospitalised adults with stroke associated pneumonia (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptoms onset, does longer duration of antibiotic treatment (>7d), compared to standard duration of antibiotic treatment (≤7d), improve clinical outcomes?	
In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, uncertainty remains regarding the effect of antibiotic treatment duration on clinical outcomes following acute stroke. Consequently, no evidence-based recommendations can currently be made. Please refer to the expert consensus statement below. Quality of evidence: - Strength of recommendation: -	There is consensus in the group that the duration of the antibiotic treatment should depend on the clinical response and should generally be at least five days. Voting: 8/8
PICO 13: In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptoms onset, does using broad spectrum antibiotics, compared to narrow spectrum antibiotics in pneumonia treatment (including choice of specific subclasses), improve clinical outcomes?	

Table 8 Continued.

In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, there is currently no clinical trial evidence to support recommendations on the use of broad-spectrum versus narrow-spectrum antibiotics to improve clinical outcomes. Please refer to the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: -	In patients with SAP, we suggest initiating empirical antibiotic therapy in accordance with local or regional protocols, with primary reference to recommendations for aspiration pneumonia, targeting aerobic Gram-negative bacilli and Gram-positive cocci. Even in the presence of dysphagia or confirmed aspiration, extended antimicrobial treatment is not justified. Where relevant risk factors exist, empirical therapy should include coverage for <i>Pseudomonas</i> spp. For pneumonia developing more than 7 days after stroke onset, the group suggests following local or regional HAP protocols. Voting: 8/8
PICO 14: In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptoms onset, does antibiotic treatment guided by identification of microbiologic aetiology, compared to empirical antibiotic treatment, improve clinical outcomes?	
In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, there is currently no clinical trial evidence to support recommendations on the use of pathogen-directed antibiotic therapy guided by microbiological identification compared with empirical antibiotic treatment. Please refer to the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: -	In patients with SAP, we suggest initiating empiric antibiotic therapy as early as possible, ideally within a few hours of clinical diagnosis. Where feasible, the group also suggests performing routine microbiological diagnostics (e.g., sputum cultures) prior to starting antibiotic treatment to enable subsequent targeted antibiotic therapy based on pathogen identification. Voting: 8/8
PICO 15: In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptoms onset, does use of adjuncts (e.g. cough assisted device, breathing therapy), compared to treatment without adjuncts, improve clinical outcomes?	
In hospitalised adults with SAP (ischaemic or haemorrhagic stroke; non-ventilated) within 7 days of stroke symptom onset, uncertainty remains regarding whether the use of adjunctive therapies improves clinical outcomes. Consequently, no evidence-based recommendation can currently be made. Please see the Expert Consensus Statement below. Quality of evidence: - Strength of recommendation: -	In patients with SAP, we suggest that adjunctive measures, such as cough-assist devices or breathing therapies, may be considered on an individual basis within an interdisciplinary stroke unit setting, although they are not part of standard treatment. These interventions may be particularly beneficial in patients with relevant comorbidities, such as COPD. Voting: 8/8

heterogeneity of diagnostic criteria across studies, this domain aimed to clarify whether diagnostic standardisation improves patient-level outcomes beyond improving diagnostic precision.

While the use of standardised, algorithm-based criteria is recommended for the diagnosis of SAP in this guideline, there remains no high-quality evidence to define definitive diagnostic criteria or biomarker thresholds in clinical stroke research or practice. However, available data suggest that CRP may be considered as an adjunct within diagnostic algorithms, particularly in afebrile patients, with proposed cut-off values between 30 and 40 mg/L. In a prospective, multicentre observational study of 342 patients with moderate-to-severe ischemic stroke, only pneumonia defined according to the PISCES-modified CDC (mCDC) criteria was associated with worse outcomes. Antibiotic initiation was driven primarily by clinical signs—particularly fever—rather than adherence to formal criteria. The authors concluded that applying mCDC criteria may help reduce unnecessary antibiotic use without compromising clinical outcomes.¹⁹³

Chest radiography has limited diagnostic accuracy and is often difficult to perform with adequate image quality in patients with severe stroke. The 2025 American Thoracic Society guidelines recommend lung ultrasonography by a trained clinician as a first-line alternative, particularly in patients with acute respiratory failure in whom high-quality chest X-ray imaging is challenging.¹⁷⁰ However, data in stroke populations are limited and do not support a specific recommendation; the diagnostic accuracy and clinical utility of lung ultrasonography in this setting remain uncertain.

A key limitation is the absence of a universally accepted gold standard for SAP diagnosis. Although pulmonary CT offers higher sensitivity and specificity than chest radiography and may serve as a reference standard, it has not been validated against an independent gold standard. This broader diagnostic uncertainty may affect estimates of diagnostic accuracy.

The PISCES group proposed a pragmatic, algorithm-based approach to the diagnosis of SAP, based on modified CDC criteria. SAP is classified as probable when CDC criteria are met in the absence of typical chest X-ray findings, and as definite when CDC criteria are met in conjunction with typical radiographic findings. Given the limited sensitivity of chest X-ray, particularly in the early stages of SAP, the PISCES group recommended initiating empirical antibiotic therapy promptly in both probable and definite cases. Figure 25 illustrates an algorithm-based diagnostic pathway for SAP.

Prospective studies to validate clinical diagnostic criteria, adjunctive blood (or breath) biomarkers and additional chest imaging techniques are a priority—primarily to guide appropriate use of antibiotics when SAP is suspected in clinical care, but also to improve design of subsequent clinical trials of SAP prediction, prevention and treatment.

II Prediction and Guidance of SAP

Recognising the need for early risk stratification, we evaluated whether clinical prediction scores or biomarkers can reliably identify patients at risk of developing SAP and whether biomarker- or score-guided antibiotic strategies improve outcomes compared with standard clinical judgement. This reflects the growing emphasis on personalised and risk-adapted care in acute stroke.

Several well-validated clinical prediction scores—including A2DS2, ISAN and AIS-APS—demonstrate moderate to good discriminatory performance for SAP (pooled AUC 0.78–0.88), and blood biomarkers such as CRP, NLR and IL-6 show comparable

performance individually (see above PICO 4). Combining biomarkers with prediction scores may modestly improve discrimination, though the additive value is small and external validation is lacking. The fundamental challenge is that identifying patients at risk is only clinically meaningful if an effective preventive intervention exists to deploy in response; until that threshold is met, prediction tools are most useful for clinical trial enrichment rather than routine bedside practice.

Machine learning approaches for the prediction of SAP are increasingly being applied and have gained considerable attention in recent years. However, at the time of data analysis for the present guideline, such approaches were not yet widely established and were therefore not considered. Similar to the clinical risk scores evaluated in this guideline, ML models primarily rely on routinely available clinical data at hospital admission, such as age, sex, stroke severity and comorbidities, but may additionally incorporate early monitoring data from the first 1–2 days (eg, heart rate variability derived from ECG recordings)¹⁹⁴ and, in some cases, imaging-derived features. A systematic review and meta-analysis of 27 studies (~155,000 patients) evaluated machine learning models for predicting SAP. Most models were based on routinely available clinical data at hospital admission (eg, age, stroke severity, dysphagia, comorbidities and laboratory markers), with some incorporating imaging-derived radiomic features. Overall performance was good, with a pooled AUC of ~0.84 and an accuracy of ~80%. The models showed high specificity (0.85) but only moderate sensitivity (0.73), indicating they are better at ruling out SAP than detecting all true cases.¹⁹⁵ In practical terms, among 100 stroke patients (~19% SAP prevalence), about 14 of 19 SAP cases are correctly identified while ~5 are missed, and 69 of 81 non-SAP patients are correctly classified while ~12 are false positives. Overall, these models are useful for early risk stratification—particularly for identifying low-risk patients—but they cannot replace clinical judgement and require further external validation before routine clinical use.

Early chest CT studies suggest that SAP may develop within hours of stroke onset,¹⁹⁶ consistent with experimental data.¹¹⁰ In a prospective cohort, approximately 15% of patients showed radiological signs of infection within this early time window, which were associated with an increased risk of subsequent pneumonia and early mortality.¹⁹⁶ These findings support the potential role of early imaging for risk stratification and targeted intervention, while also indicating that conventional preventive strategies may be initiated too late.

The only RCT addressing biomarker-guided treatment, the STRAWINSKI trial, found that high sensitive PCT-guided antibiotic therapy did not improve 3-month functional outcomes and was associated with increased antibiotic use.⁹⁹ This underscores the diagnostic uncertainty surrounding SAP and the risk of overtreatment when general sepsis biomarker strategies are applied in stroke, highlighting the need for SAP-specific diagnostic frameworks before biomarker-guided approaches can be reliably implemented.

III Prevention of SAP

Given the substantial morbidity associated with SAP, prevention was considered a high-priority area. In a large national registry study including over 400,000 stroke patients from England and Wales, substantial variation in SAP incidence across stroke units was observed, which was only minimally explained by patient-level characteristics. These findings suggest that

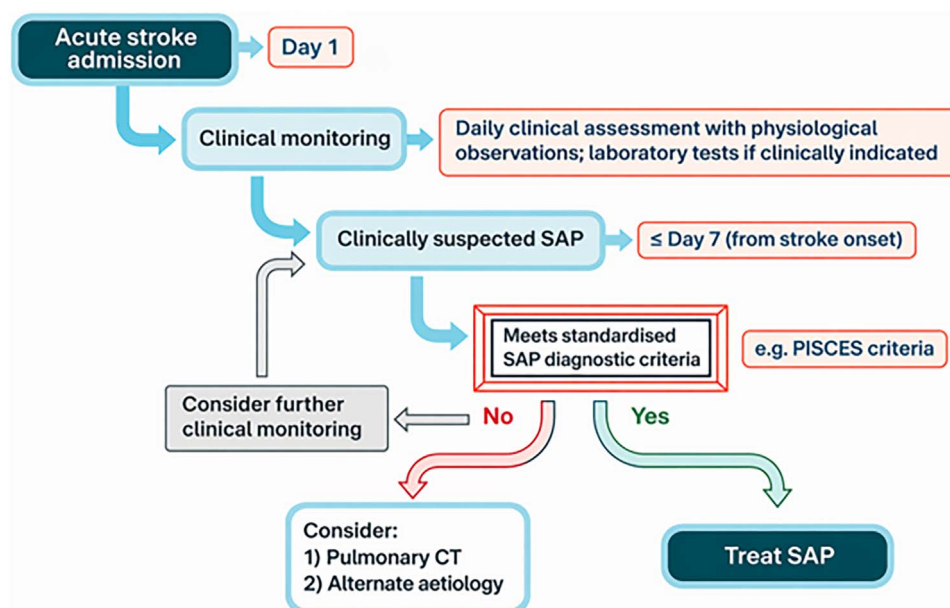


Figure 25 Proposed algorithm for SAP diagnosis and treatment decision-making.

differences in acute stroke care and management practices play a major role in determining SAP risk.⁴ Accordingly, prevention strategies represent a key opportunity to improve outcomes, as SAP prevention may, for example, reduce in-hospital mortality by up to 43%.¹⁹² The guideline examined preventive strategies including pharmacological approaches (eg, preventive antibiotics and commonly used stroke-related medications), nutritional management (eg, nasogastric feeding regimens), respiratory and physical interventions, early mobilisation and positioning strategies in patients with reduced consciousness, with a focus on whether reductions in SAP incidence translated into meaningful clinical outcomes. Preventive antibiotic therapy is not supported and should not be used, as it neither reduces pneumonia incidence nor improves outcomes. Prevention should primarily focus on optimising supportive care, including structured positioning, mobilisation of dependent patients and head-up positioning during enteral feeding. Early mobilisation may be beneficial, although caution is warranted within the first 24 hours in patients with severe stroke. Nutritional strategies may be tailored to local expertise and patient needs. Other pharmacological approaches (eg, antiemetics, beta-blockers, statins or acid-suppressive therapy) are not recommended for SAP prevention.

Although SAP typically becomes clinically apparent several days after stroke onset (around day 3),¹⁰³ early chest CT findings showing signs of pulmonary infection in approximately 15% of patients at admission suggest that infection may already be present within hours,¹⁹⁶ indicating that the window for preventive interventions is uncertain but likely favours earlier treatment.

Preventive antibiotic therapy (PAT) is not recommended. Across 6 Phase II and III RCT including nearly 6000 participants, PAT did not reduce the incidence of SAP, mortality or improve functional outcome at 90 days, although overall infection rates were consistently reduced. The guideline group agreed that, in the context of responsible antibiotic stewardship, routine PAT is not justified.

Three large phase III trials (PASS, STROKE-INF, PRECIOUS) investigating PAT in 4850 patients were central to the evidence appraisal. PASS demonstrated no improvement in 3-month functional outcome with preventive ceftriaxone in unselected

acute stroke patients.¹⁰⁹ STROKE-INF, conducted in a higher-risk population with post-stroke dysphagia using co-amoxiclav and clarithromycin based regimens, found no reduction in SAP frequency, irrespective of whether assessed algorithmically or by physician diagnosis.¹⁰⁷ PRECIOUS similarly found no benefit of preventive ceftriaxone on 90-day functional outcome in older patients with moderately severe to severe stroke.¹⁰⁴ Notably, these neutral findings contrast with the use of the same antibiotics in the treatment of established SAP.

From a clinical perspective, these large trials might be expected to provide strong evidence against prophylaxis, as key patient-relevant outcomes—SAP, functional recovery and mortality—were not improved. However, under GRADE, large trials alone do not guarantee high-certainty evidence. Certainty depends on how likely it is that any potential new evidence may influence the outcome of interest, and this is influenced by the risk of bias of individual studies, inconsistency, indirectness, imprecision, publication bias or effect size. Within the current guideline, the overall certainty remains insufficient to support a high-certainty recommendation against routine PAT after acute stroke (only moderate for mRS 0-2 that allows to do a strong recommendation). Given the remaining uncertainty in the evidence base and the clinical importance of SAP, further research on PAT strategies, particularly in the context of SAP-predictive scores and biomarkers, is justified.

For other pharmacological strategies including antiemetics, statins, beta-blockers and acid-suppressive agents, evidence remains insufficient to support practice-changing recommendations, though acid-suppressive therapy may paradoxically increase pneumonia risk and should not be prescribed without clear clinical indication.

Dysphagia screening and management is established as an important and effective method of pneumonia prevention and is already an integral part of stroke management guidelines.¹⁷ In addition to this, we identified only early mobilisation in bed and/or out of bed within 48 hours of stroke as sufficiently evidence-based to recommend, with a caveat to avoid very early intensive mobilisation out of bed within the first 24 hours in patients with

severe strokes. Our meta-analysis of 4 studies demonstrated an approximately 60% reduction in pneumonia incidence with early mobilisation.

While respiratory physiotherapy to improve ventilation of the lungs and encourage coughing seems a physiologically justifiable intervention to prevent pneumonia, there are only 2 small RCTs, which provide insufficient evidence to support an evidence-based recommendation. Conversely, our data provide no reason to avoid this intervention either. Overall, the expert group recommended that respiratory physiotherapy may be considered as part of an early post-stroke rehabilitation program.

How and when feeds are administered in patients with acute stroke could potentially have a significant impact on bowel function, pneumonia and rehabilitation. Current practice is based on local traditions rather than evidence, and varies in between countries and services, and pending new evidence, the committee recommends that clinicians use the feeding pattern they are most comfortable with.

Positioning of stroke patients is likely to have an impact on aspiration in those who are unable to swallow safely. Use of the recovery position for patients with a reduced level of consciousness is a key aspect of first aid. While this also applies to stroke patients, other priorities, such as the need to protect pressure areas, patient comfort and ease of care provision need to be considered. Based on the evidence from a single small trial conducted in Mexico¹⁵⁶ and current clinical practice in the European context the expert committee recommends turning the patient from the supine to the left and right lateral recumbent position every 2 hours, where possible, together with regular passive mobilisation of all joints. In the original study mobilisation was conducted by family members, trained by nursing staff. This may challenge governance and safety policies in a European context but could be provided by hospital staff.

One aspect not specifically addressed in this guideline is oral hygiene. Current evidence remains limited. The CHOSEN feasibility trial demonstrated that structured oral health care interventions in patients with acute dysphagic stroke are feasible, safe and achieve high adherence when supported by staff training. However, exploratory analyses showed no differences in pneumonia, survival or functional outcomes, highlighting the need for a definitive phase III trial to assess efficacy and cost-effectiveness.¹⁹⁷

The overriding conclusion from the review of methods to prevent pneumonia is that although it is a very important aspect of acute stroke care, there is very little reliable evidence. The breadth of the potential interventions highlights the need for the whole multidisciplinary team and, possibly even the family, to be involved in prevention and further research into preventative strategies.

IV Treatment of SAP

For patients who develop SAP, we addressed clinically pragmatic treatment questions: optimal duration of antibiotic therapy, spectrum of antimicrobial coverage, microbiology-guided versus empirical treatment strategies, and the role of adjunctive supportive therapies.

In the absence of robust evidence from randomised or uncontrolled studies addressing key aspects of SAP treatment, the expert consensus statements in this section are informed by existing guideline recommendations for aspiration pneumonia, CAP, HAP,^{170,173,175} and most importantly by the work of the PISCES group, which has extensively addressed the diagnosis,

microbiology and treatment of SAP.^{18–20} Since the publication of the PISCES work, the evidence base relevant to SAP treatment has not materially changed. No clinical trials have directly compared antibiotic durations, spectra or treatment strategies specifically in SAP. Therefore, guidance was extrapolated from evidence in CAP, HAP and aspiration pneumonia.

However, the guideline group departs from PISCES in one key aspect. While PISCES considered SAP, particularly occurring within the first 3 days after stroke onset, as microbiologically comparable to CAP,²⁰ the guideline group classifies SAP primarily as aspiration pneumonia, based on its underlying pathophysiology, with dysphagia as the main risk factor, and consistent with available microbiological data. The predominant pathogens—mainly aerobic Gram-negative bacilli and Gram-positive cocci—more closely resemble those seen in hospital-acquired or aspiration pneumonia than CAP, even in the early post-stroke period.^{19,198} Accordingly, empirical antibiotic selection should reflect this and follow local protocols targeting aspiration-associated organisms. Microbiological samples should be obtained prior to treatment initiation wherever feasible to enable subsequent de-escalation. Treatment duration should be guided by clinical response and be at least 5 days, with extension reserved for complicated infections or delayed recovery. Excessive antibiotic exposure has been associated with increased in-hospital mortality in ICH, underscoring the importance of antimicrobial stewardship. For pneumonia with onset later than 7 days after stroke, recommendations remain consistent with PISCES, and management should follow HAP guidelines.

This guideline does not address aspiration pneumonitis. It is typically distinguished from aspiration pneumonia based on clinical history, usually involving the aspiration of a large volume of sterile, acidic gastric contents. Clinically overt cases appear to be rare in acute stroke, although robust epidemiological data are lacking. A standardised diagnostic approach to SAP based on CDC criteria (eg, PISCES) may help support this distinction in clinical practice and avoid unnecessary antibiotic treatment.

Antibiotic selection should primarily be guided by anti-infective considerations. However, potential effects on the injured brain should also be taken into account, as antibiotics may exert both harmful and beneficial (eg, neuroprotective or immunomodulatory) effects. A retrospective analysis of 2708 patients with ischaemic stroke from the VISTA-Acute registry suggested that macrolide use was independently associated with improved 3-month functional outcomes, both in overall SAI and specifically in SAP.¹⁷⁴ In contrast, treatment with carbapenems, cephalosporins or monobactams, beta-lactam/beta-lactamase inhibitor combinations, and aminoglycosides was associated with less favourable recovery. While these findings have no immediate implications for clinical practice, they underscore the urgent need for prospective RCTs evaluating antibiotic strategies in SAP.

Although systemic corticosteroids are recommended for severe CAP,¹⁷⁰ their routine use in patients with acute stroke is not advised.¹⁹⁹ Available evidence has not consistently shown a benefit of corticosteroids on stroke outcomes, and their use may be associated with an increased risk of adverse effects such as hyperglycaemia, infections and gastrointestinal complications. In the absence of stroke-specific evidence supporting benefit, corticosteroids should only be used if there are compelling clinical indications.²⁰⁰

Adjunctive interventions, such as cough-assist devices and respiratory physiotherapy, are not routinely recommended for SAP

but may be considered in selected patients, particularly those with relevant respiratory comorbidities. Routine oxygen supplementation is not indicated in non-hypoxic patients, as demonstrated in the large Stroke Oxygen Trial (>8000 patients).¹⁸⁶ However, continuous SpO₂ monitoring in the early phase is essential to ensure prompt detection and management of hypoxia.

Fever management represents an important aspect in the context of SAP, as elevated body-temperature is a well-recognised negative prognostic factor for neurological outcomes after stroke.^{201,202} However, as this guideline primarily focuses on the diagnosis, prevention and treatment of SAP, fever management was not systematically addressed. Notably, the PRECIOUS trial also evaluated paracetamol as an antipyretic strategy based on the hypothesis that reducing fever may improve outcomes.¹⁰⁴ However, no benefit was observed with respect to pneumonia, mortality or functional recovery, consistent with previous evidence.^{203–206} An unexpected interaction between paracetamol and ceftriaxone associated with worse outcomes was reported in PRECIOUS, although the underlying mechanism remains unclear.¹⁰⁴ Similarly, the large INTREPID trial demonstrated that preventive normothermia using automated temperature management significantly reduced fever burden in critically ill stroke patients but did not improve functional outcomes at 3 months compared with standard care.²⁰⁷ Together, these findings indicate that while fever is associated with poor prognosis, active fever prevention alone does not translate into clinical benefit.

Further direction of research

Given that only 6 of the 15 clinically relevant questions identified by the guideline group could be answered with available evidence—and that this evidence was predominantly of low quality—there is a clear and substantial need for further research in the field of SAP. Key research priorities should build on a deeper understanding of SAP pathophysiology, particularly the central roles of dysphagia-driven aspiration and stroke-induced immunodepression, and translate these mechanisms into clinically relevant advances in diagnosis, risk prediction, prevention and treatment (Table 9).¹

Accurate individual risk prediction is fundamental to enabling targeted and effective prevention. This requires the further development of predictive scores and biomarkers to identify high-risk populations for future intervention trials. In addition to optimising pragmatic preventive strategies (eg, aspiration prevention), immunomodulatory approaches—supported by emerging experimental data—should be explored.^{1,11} In parallel, optimisation of antibiotic therapy requires a more precise definition of the pathogen spectrum and a better understanding of how different antibiotics influence both pulmonary infection and neuroinflammation in the injured brain. Addressing these questions will require well-designed prospective RCTs and appropriate funding. Finally, health services research should address the impact of decision-making in advanced disease stages, including end-of-life considerations, where SAP may play a central role and thereby influence observed outcomes. This is essential to better define the true effect of SAP on survival and long-term neurological function.

Conclusion

This guideline represents a structured synthesis of the best available outcome-focused evidence addressing key clinical

Table 9 Key research priorities for SAP.

Domain	Key Gaps	Relation to PICO	Research Needs
Pathophysiology	Incomplete translation of mechanisms (dysphagia, immunodepression) into clinical practice	all	Mechanistic studies linking pathobiology to diagnosis, prevention, and therapy
Diagnosis	Lack of validated, standardised criteria	1 to 3	Development and validation of a robust diagnostic framework
Risk prediction	Limited ability to identify high-risk patients	4 and 5	Highly predictive biomarker (patterns) and risk scores for treatment guidance
Prevention	Unclear effectiveness of targeted strategies	6 to 11	Trials focusing on high-risk populations and mechanism driven approaches
Immunomodulation	Experimental evidence but no clinical translation	7	Clinical trials testing immunomodulatory approaches
Microbiology	Incomplete understanding of pathogen spectrum	13 and 14	Contemporary studies defining pathogens in SAP, including systematic research into anaerobic bacteria
Antibiotic therapy	Uncertainty regarding optimal agents and timing	12 to 14	RCTs evaluating antibiotic strategies targeting pulmonary infection and long-term outcomes, including their potential effects on neuroinflammation
Healthcare research	Influence of end-of-life decisions on outcomes unclear		Research on decision-making, care pathways, and outcome interpretation

questions in the diagnosis, prediction, prevention and treatment of SAP in non-ventilated acute stroke patients. By integrating these domains within a unified framework, we aim to provide pragmatic, evidence-informed guidance for clinical practice while identifying important gaps in the current evidence base. It should be acknowledged that most recommendations are supported by low- or very low-quality evidence and are therefore accompanied by expert consensus statements rather than formal evidence-based recommendations. This highlights the urgent need for well-designed RCTs to address the remaining uncertainties and strengthen the evidence base for SAP management in acute stroke care.

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Supplementary material

Supplementary material is available at *European Stroke Journal* online.

Conflicts of interest

All authors have completed a declaration of competing interests and details are available in [Table S1](#).

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