Guideline

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European Stroke Organisation (ESO) guidelines on Primary Angiitis of the Central Nervous System (PACNS)

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Abstract

The European Stroke Organisation (ESO) guideline on Primary Angiitis of the Central Nervous System (PACNS), developed according to ESO standard operating procedures (SOP) and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology, was elaborated to assist clinicians in the diagnostic and treatment pathway of patients with PACNS in their decision making. A working group involving vascular neurologists, neuroradiologists, rheumatologists, a neuropathologist and a methodologist identified 17 relevant clinical questions; these were addressed according to the patient/population, intervention, comparison and outcomes (PICO) framework and systematic literature reviews were performed. Notably, each PICO was addressed with respect to large vessel (LV)-PACNS and small vessel (SV)-PACNS. Data to answer many questions were scarce or lacking and the quality of evidence was very low overall, so, for some PICOs, the recommendations reflect the ongoing uncertainty. When the absence of sufficient evidence precluded recommendations, Expert Consensus Statements were formulated. In some cases, this applied to interventions in the diagnosis and treatment of PACNS which are embedded widely in clinical practice, for example patterns of cerebrospinal fluid (CSF) and Magnetic Resonance Imaging (MRI) abnormalities. CSF analysis for hyperproteinorrachia and pleocytosis does not have evidence supporting their use as diagnostic tools. The working group recommended that caution is employed in the interpretation of non-invasive vascular imaging due to lack of validation and the different sensitivities in comparison with digital subtraction angiography (DSA) and histopathological analyses. Moreover, there is not a neuroimaging pattern specific for PACNS and neurovascular issues are largely underreported in PACNS patients. The group's recommendations on induction and maintenance of treatment and for primary or secondary prevention of vascular events also reflect uncertainty due to lack of evidence. Being uncertain the role and practical usefulness of current diagnostic criteria and being not comparable the main treatment strategies, it is suggested

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to have a multidisciplinary team approach in an expert center during both work up and management of patients with suspected PACNS. Highlighting the limitations of the currently accepted diagnostic criteria, we hope to facilitate the design of multicenter, prospective clinical studies and trials. A standardization of neuroimaging techniques and reporting to improve the level of evidence underpinning interventions employed in the diagnosis and management of PACNS. We anticipate that this guideline, the first comprehensive European guideline on PACNS management using GRADE methodology, will assist clinicians to choose the most effective management strategy for PACNS.

Keywords
Vasculitis, PACNS, angiitis, stroke, cerebrovascular, large arteries, magnetic resonance imaging, angiography, HRVWI, immunosuppression, steroid

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Introduction

Primary angiitis of the central nervous system (PACNS) is a subtype of vasculitis with isolated involvement of the central nervous system (CNS), including brain and spinal cord. In the Chapel Hill classification of vasculitides,[1] PACNS is unique in being the only single organ-specific vasculitis. The diagnosis may be challenging, but features can be recognized on several, potentially overlapping, levels: (1) neuropathological, which is the gold standard; (2) neuroimaging, which is currently the most widely used diagnostic tool, and (3) clinical, which also includes the integration of radiological and pathological diagnostic information into management strategies.

Definition and diagnostic criteria

As reported by Birnbaum and Hellmann,[2] PACNS is a rare form of vasculitis of unknown cause involving the arteries (less frequently the veins too) of the brain, spinal cord and leptomeninges[3] and occurring in the absence of systemic vasculitis. In order to accomplish this definition several diseases should be considered in the differential diagnosis, including secondary (e.g. post-infectious) vasculitis. In PACNS, pathological findings can affect both small vessels (SV) and large vessels (LV) of the CNS.[4] The terms "vasculitis" and "angiitis" refer to the same disease and are used interchangeably in the paper.

Clinical and epidemiological features

Typically, PACNS has a long prodromal period (mean time from onset to diagnosis 170 days), with some patients presenting acutely.[5] It may affect any part of the CNS, causing highly variable and non-specific clinical manifestations including, but not limited to, headache, psychosis and stroke. Notably, the latter may occur as multiple events unrestricted to a single vascular territory.

The estimated incidence of PACNS is 2.4 cases per 1,000,000 persons/year with a male-to-female ratio 1:1, according to a single center case series.[6] The median age at diagnosis is 50 years,[7] but it can occur at any age of life.

Challenges in diagnosis and management

The hallmark of vasculitis is the presence of inflammatory cells which is not limited to a peri-adventitial inflammatory infiltrate but rather affects the full thickness of the vessels. The gold standard for diagnosis therefore requires histopathological confirmation, but this is particularly challenging in the context of CNS disease given that the threshold for brain biopsy is, appropriately, relatively high; the risk/benefit ratio of an invasive surgical procedure which may return a non-diagnostic or false-negative biopsy needs to be carefully considered.[8–10] In addition, the increasing development and availability of non- or minimally invasive techniques being employed to establish the diagnosis of vasculitis means that the historical diagnostic criteria are not always fully adhered to. However, given the lack of specificity of both the presenting symptoms and non-invasive investigations, confirmation of the diagnosis remains challenging and, even once the diagnosis is confirmed, the evidence base for therapeutic interventions is poor. Indeed, there are still many areas regarding the investigation and management of PACNS where improved standardization of diagnostic techniques and a higher grade of clinical evidence to support management strategies are required.

Thus, the main purpose of these guidelines is to provide answers to predefined, clinically important questions regarding diagnosis and treatment for patients with probable or definite PACNS, including both induction phase therapy and maintenance therapy.

Methods

Composition and approval of the Module Working Group

These guidelines were initiated by ESO. One chairperson (MZ) was identified by the ESO Guidelines Board to assemble and coordinate the Guideline Module Working Group (MWG). The final MWG contained 13 experts (KA, GB, HdB, CG, MH, TN, OK, RP, CR, ASP, CS, DS, MZ) and was supported by a methodologist (SH). The MWG included eight neurologists (among them one is also a

neurointerventionalist), two neuroradiologists, two rheumatologists, one neuropathologist; all clinicians have a special interest in PACNS and neurologists and neuroradiologists are experts in cerebrovascular diseases. Of the 13 MWG members, 12 were European and one based in USA. The ESO Guideline Board and Executive Committee reviewed the intellectual and financial disclosures of all MWG members and approved the composition of the group. All participants were asked to disclose any conflict of interest that could influence their participation. The group communicated using e-mail and virtual conferences. The full details of all MWG members and their disclosures are included in Supplemental Materials.

Development and approval of clinical questions

This guideline was prepared according to the ESO standard operating procedures (SOP),[11] which are based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.[12] The MWG developed a list of topics and corresponding questions of greatest clinical interest. Questions were formatted using the PICO approach (Population, Intervention, Comparator and Outcome), and reviewed by two 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. The final decision on outcomes used a Delphi approach. Results of the outcomes rating for each PICO question are included in the Supplemental Materials. Both efficacy and safety issues were considered for defining the outcomes, in particular for the PICOs about treatment, including first or recurrent stroke (ischemic or hemorrhagic) and disability from any cause. Moderate to severe disability was defined by a modified Rankin Scale (mRS) score 3–5. The selected outcomes were rated as important or critical for making a decision, according to the GRADE method.[12]

Definitions and diagnostic criteria

Literature for review was selected with the prerequisite that the diagnosis of PACNS was made according to the criteria proposed by Calabrese and Mallek[3] and updated by Birnbaum and Hellmann.[2] The two sets of criteria have only minor practical differences; both aimed to distinguish between PACNS and mimics according to understanding of the disease and the technology available at the time. In 1988, the diagnostic criteria of Calabrese and Mallek[3] were stated as follows:

(1) history of clinical findings of an acquired, otherwise unexplained neurologic deficit,
(2) presence of classic angiographic or histopathologic features of angiitis within the CNS, and
(3) no evidence of systemic vasculitis or of any other disorder that could cause or mimic the angiographic or pathologic features.

In 2009, Birnbaum and Hellmann[2] suggested revision of the criteria with the aim of differentiating PACNS from reversible cerebral vasoconstriction syndrome (RCVS), subdividing the level of certainty of diagnosis into "definite" and "probable." A "definite" diagnosis of PACNS requires histopathological confirmation of vasculitis on cerebral biopsy or autopsy. A "probable" diagnosis requires a high-probability angiogram with abnormal findings on magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) profile consistent with PACNS. In the original version of the criteria, patients with high-probability angiogram but normal CSF may have either RCVS or PACNS.

Here, we refer to "definite" and "probable" PACNS according to the Birnbaum and Hellmann criteria.[2]

The high probability angiographic pattern was defined as follows[13]:

- alternating areas of smooth-wall segmental narrowing and dilatation of cerebral arteries
- arterial occlusions affecting many cerebral vessels
- absence of proximal vessel atherosclerosis or other recognized abnormalities

Angiography-proven PACNS represents the involvement of the arteries now called large and medium sized vessels, but previously labeled as LV-PACNS. Biopsy-proven PACNS underlines mainly the involvement of small vessels, substantially under the resolution of catheter angiography, but there is not a perfect correspondence, being theoretically possible a medium vessel involvement and a positive biopsy. The definition of the size of intracranial vessels is outside the topic of this guideline and the medium vessel category has been detailed only recently and for the purposes of acute stroke diagnosis and treatment. We will refer in the text to LV-PACNS as PACNS affecting large and medium vessels and SV-PACNS as PACNS affecting small vessels. According with the current diagnostic criteria,[2] only LV-PACNS can be diagnosed as probable PACNS according with the diagnostic criteria. Instead, SV-PACNS is only defined as biopsy or autopsy proven and therefore definite PACNS. Therefore, although the histopathological diagnosis is the gold standard, it is practically difficult to apply it to LV-PACNS, so the two categories of diagnostic probability (probable and definite PACNS) apply to two different subtypes of disease with two different diagnostic gold standards, that is, histopathology for SV-PACNS and DSA for LV-PACNS.

In order to evaluate the outcomes in the PICOs addressing treatment, the MWG members agreed a definition of "relapse" and "remission" prospectively. Relapse was defined as:

(1) the reoccurrence or worsening of neurological symptoms attributable to active PACNS, or
(2) worsening of existing and/or evidence of new abnormal neuroimaging findings on MRI consistent with PACNS activity, necessitating treatment change or escalation.[14]

Clinically silent neuroimaging changes (e.g. new diffusion weighted imaging [DWI] findings, contrast-enhanced lesions or progressive intracranial stenosis) were considered as relapses, if reported as such in the selected manuscripts. The same asymptomatic ischemic or hemorrhagic lesions in neuroimaging studies were included in the outcome definition for treatment PICOs.

The definition of "induction" therapy was agreed as treatment in the acute phase. "Maintenance" therapy was defined as therapeutic interventions made after induction therapy, generally steroid-sparing agents prescribed over a more enduring time-frame. Unfortunately, the timing of induction and maintenance therapy tended to be poorly defined and highly variable, so the MWG agreed to not consider these.

Selection of population, intervention, comparator, and outcome (PICO)

The MWG formulated 17 main PICO questions and subquestions relevant to the investigation and management of PACNS, focusing on accuracy of diagnostic techniques, differential diagnosis of PACNS subtypes, and the efficacy of treatment regimens.

Outcomes were adjusted for diagnostic and therapeutic PICOs with only slightly different subpopulations, as relevant to each PICO. These proposals were reviewed and refined following comments from the ESO Executive Committee, ESO Guidelines Board and dedicated reviewers prior to the approval of ESO Executive Committee and ESO Guidelines Board. One methodological mentor within the ESO Guidelines Board members was assigned to the MWG.

Two main areas – diagnostic and therapeutic – were covered in the formulation of PICOs. The diagnostic PICOs were divided according to the techniques suggested by the diagnostic criteria[2] and aimed to describe the sensitivity and specificity of the following: CSF (hyperproteinorrachia, pleocytosis), multimodal neuroimaging findings (both for brain parenchymal lesions and vessel abnormalities), and histopathological abnormalities. The therapeutic PICOs were divided into: disease-specific treatment (induction and maintenance therapy), treatment of acute stroke and secondary prevention of cerebrovascular events.

The MWG focused on "probable" and "definite" PACNS as defined by the Birnbaum and Hellmann criteria,[2] with additional interpretation of the available evidence retrieved for each PICO according to the subtyping of PACNS according to vessel caliber (SV-PACNS and LV-PACNS). In order to facilitate the readability of this guideline by non-experts on PACNS, the wording of PICOs, where possible, considered the clinical suspicion of PACNS, using the available data on "probable" and "definite" PACNS to guide the clinician toward a better definition of this diagnostic hypothesis.

The final PICOs and the corresponding outcomes are listed in Table 1.

Literature search

For each PICO question, search terms were developed by the MWG and guideline methodologist. Where a validated search strategy was available, this was used or adapted. Where there was a recent relevant, robust systematic review on the question of interest, the corresponding search strategy and results were used and updated as necessary. Search strings are included in the Supplemental Material.

Searches were performed by the ESO Guideline methodologist (SH). Bibliographic databases – Medline, and Embase (using the OVID platform) – were searched from inception until 10th October 2022. Reference lists of relevant review articles, the author's personal reference libraries, and previous guidelines were also searched for additional relevant records. Searches were restricted to human studies and those with adult patients (>18 years age), published as a full-text in English/French/German language. Studies published as case reports and case series with fewer than five patients were excluded, as were studies with a primary focus on systemic vasculitis with CNS involvement and secondary vasculitis (e.g. VZV, Treponema, HIV, etc.). All angiographic techniques (digital subtraction, magnetic resonance, and computed tomography angiography) were eligible for inclusion.

Search results were imported into the Covidence platform (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) for assessment by the MWG members. Articles were independently reviewed for inclusion based on title and abstract screening at the first screening level, followed by full-text screening at the second level by two or more MWG members. All disagreements were resolved by discussion between the two reviewers or by a third MWG member at both levels of screening. We prioritized randomized controlled trials (RCTs) but, where evidence from RCTs was limited, registry-based studies and observational studies were also considered. Studies were considered eligible for inclusion if they meet the predefined inclusion criteria by answering the PICO questions.

If multiple studies from the same patient cohort/database were found, then the study reporting detailed or recent data with a larger cohort size was included. When different outcomes were reported in the studies, all were included.

We identified four reviews[15–18] pertinent to this Guideline; these differed in their precise focus and none aligned with our inclusion criteria so, although we considered these manuscripts, we did not incorporate their synthesis of results.

Data extraction and analysis

Data extraction and analysis were performed by the ESO methodologist. Where relevant data were not reported in an

Table 1. Summary of the final PICOs.

Diagnosis		Outcomes
CSF study		
PICO 1	In adults with suspected PACNS, does CSF analysis for pleocytosis and hyperproteinorrachia vs no CSF analysis improves the diagnostic accuracy?	Sensitivity, specificity, PPV, NPV
Neuroimaging of brain parenchyma		
PICO 2	In adults with suspected PACNS, does assessing for predefined pattern of parenchymal abnormalities on brain MRI vs not searching them improve diagnostic accuracy?	Sensitivity, specificity, PPV, NPV
PICO 3	In adults with suspected PACNS, does the presence of MRI leptomeningeal enhancement vs no MRI leptomeningeal enhancement improve diagnostic accuracy?	Sensitivity, specificity, PPV, NPV
Neuroimaging of brain vessels		
PICO 4	In adults with suspected PACNS, does cerebral computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) with high probability angiographic pattern vs digital subtraction angiography (DSA) with high probability pattern improve diagnostic accuracy?	Sensitivity, specificity, PPV, NPV
PICO 5	In adults with suspected PACNS and normal MRA, does performing a DSA vs not performing a DSA improve diagnostic accuracy?	Sensitivity, specificity, PPV, NPV
PICO 6	In adults with probable LV-PACNS, does performing high resolution vessel wall imaging-MRI (HRVWI-MRI) vs performing a digital subtraction angiography (DSA) increase diagnostic accuracy?	Sensitivity, specificity, PPV, NPV
PICO 7	In adults with suspected PACNS, does performing high resolution vessel wall imaging-MRI (HRVWI-MRI) vs not performing HRVWI-MRI improve diagnostic accuracy?	Sensitivity, specificity, PPV, NPV
Neuropathology		
PICO 8	In adults with definite PACNS, does the presence of high probability angiographic pattern with any technique (DSA/CTA/MRA) vs biopsy change diagnostic accuracy?	Sensitivity, specificity, PPV, NPV
PICO 9	In adults with definite PACNS does the presence of MRI leptomeningeal enhancement (LME) vs positive biopsy findings increase the diagnostic accuracy?	Sensitivity, specificity, PPV, NPV
PICO 10	In adults with definite PACNS, does autopsy increase the diagnostic accuracy vs biopsy alone?	Sensitivity, specificity, PPV, NPV
PICO 11	In adults with definite PACNS, does the presence of a lymphocytic histological pattern vs a granulomatous/necrotizing histological pattern is associated to an improved outcome?	O1: death at 3 months O2: death at 12 months O3: mRS 0–2 at 3 months O4: mRS 0–2 at 12 months O5: first or recurrent ischemic and hemorrhagic stroke (defined as new neurological symptoms occurrence with neuroimaging confirmation of a new cerebral lesion)

(Continued)

Table 1. (Continued)

Diagnosis		Outcomes
Treatment		
Induction		
PICO 12	In adults with probable/definite PACNS, does using glucocorticoids in addition to any further immunosuppressive drug vs glucocorticoids alone improve outcome?	O1: death at 3 months O2: death at 12 months O3: mRS 0–2 at 3 months O4: mRS 0–2 at 12 months O5: first or recurrent ischemic and hemorrhagic stroke (defined as new neurological symptoms occurrence with neuroimaging confirmation of a new cerebral lesion) O6: side effect which lead to stopping or changing therapy
PICO 13	In adults with probable/definite PACNS, is the combination of mycophenolate mofetil (MMF) and glucocorticoids vs cyclophosphamyde (CYC) and glucocorticoids associated with different outcomes	O1: death at 3 months O2: death at 12 months O3: mRS 0–2 at 3 months O4: mRS 0–2 at 12 months O5: first or recurrent ischemic and hemorrhagic stroke (defined as new neurological symptoms occurrence with neuroimaging confirmation of a new cerebral lesion) O6: side effect which lead to stopping or changing therapy
Secondary prevention		
PICO 14	In adults with probable/definite PACNS, do antiplatelets vs no antiplatelets improve outcome?	O1: death at 3 months O2: death at 12 months O3: mRS 0–2 at 3 months O4: mRS 0–2 at 12 months O5: first or recurrent ischemic and hemorrhagic stroke (defined as new neurological symptoms occurrence with neuroimaging confirmation of a new cerebral lesion)
Maintenance		
PICO 15	In adults with probable/definite PACNS, does long-term immunosuppression vs no long-term immunosuppression improve outcome?	O1: death at 24 months O2: mRS 0–2 at 24 months O3: recurrent ischemic and hemorrhagic stroke at 12–24 months O4: PACNS remission O5: PACNS relapses/progression
Acute ischemic stroke treatment		
PICO 16	In adults with probable/definite PACNS and acute ischemic stroke, does intravenous thrombolysis (IVT) vs no IVT improve outcome?	O1: death at 3 months O2: mRS 0–2 at 3 months O3: any hemorrhagic event within 24 h from IVT O4: sICH
PICO 17	In adults with probable/definite PACNS and acute ischemic stroke, does endovascular thrombectomy (EVT) vs no EVT improve outcome?	O1: death at 3 months O2: mRS 0–2 at 3 months O3: any hemorrhagic event within 24 h from IVT O4: sICH

sICH: symptomatic intracerebral hemorrhage; IVT: intravenous thrombolysis; EVT: endovascular thrombectomy; mRS: modified Rankin Scale; MMF: mycophenolate; CYC: cyclophosphamide.

eligible study, we contacted the corresponding author and, in case of no response, the co-authors of the study. If no answer was received, data were considered missing. In some cases, the authors were members of the MWG, so missing data were checked.

If needed for the PICO, and appropriate to the data, we planned summary estimates based on random-effects meta-analyses using RevMan software version 5.4.1 (Cochrane). We decided not to proceed with a meta-analysis due to the inconsistencies of the definitions, and outcomes across studies. For PICOs concluded with a recommendation, based on observational studies, study conduct, subject selection, assessment, and statistical confounding were assessed using the Scottish Intercollegiate

Guidelines Network (SIGN) checklist (https://www.sign.ac.uk/what-we-do/methodology/checklists/).

Evaluation of the quality of evidence and formulation of 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[12] and the ESO-SOP.[11]

Expert Consensus Statements were proposed whenever the MWG members assigned to the particular PICO 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 (Supplemental Material, Appendix 4).

Drafting of the document, revision and approval

Each PICO question was addressed in distinct sections, according to the ESO SOP.[11] First, "Analysis of current evidence" summarized the findings of the selected papers focusing on the most relevant data to answer the PICO question. Second, "Additional information" was added when more detail on the studies referred to in the first section was needed or to provide information from studies which did not meet eligibility criteria but were considered to provide important clinical guidance on the topic. Third, an "Expert consensus statement" paragraph was added when the MWG considered that insufficient evidence was available to provide evidence-based recommendations but where practical guidance was needed.

The Guideline document was reviewed several times by all MWG members. Recommendations and expert consensus statement wording were modified using a Delphi approach until an agreement was reached. The final submitted document was peer-reviewed by two external reviewers, two members of the ESO Guideline Board, and one member of the Executive Committee. All recommendations and expert consensus statements are summarized in Table 2.

Results

PICO questions

Diagnosis

CSF study

PICO 1: In adults with suspected PACNS, does CSF analysis for pleocytosis and hyperproteinorrachia versus no CSF analysis improves the diagnostic accuracy?

Analysis of current evidence. The literature search identified no RCTs and no comparative studies specifically evaluating the clinical effectiveness of diagnostic strategies based on CSF assessment versus no CSF assessment. We identified 17 papers (case series and cross-sectional studies) collecting data on 763 PACNS patients, but lumbar puncture was performed in 588/763 (77%) patients and CSF data were provided (often as "positive" ore "negative") in 508/763 (67%) of the whole group and in 508/588 (86%) of patients who underwent a lumbar puncture. The details of the selected papers are summarized in Table 3.

CSF analysis was not included in the initial diagnostic criteria proposed by Calabrese and Mallek,[3] but they reported abnormal CSF results in 41 of 46 (81%) patients, yielding a sensitivity for pleocytosis or hyperproteinorrachia of 68%. In the Mayo Clinic series,[19] abnormal CSF was found in 81.1% (91.4% and 74.4% in biopsy proven and angiography proven cases, respectively). In the French registry,[20] the comparison of LV-PACNS versus SV-PACNS found a statistically significant higher rate of CSF abnormalities in SV-PACNS (91%) than in LV-PACNS (62%).

The overall rate of positive CSF findings in PACNS patients was 77.8% (395/508), distributed as pleiocytosis in 46% and hyperproteinorrachia in 70% of patients.

By extracting data from the eligible studies we calculated the sensitivity (77.7%), specificity (68.3%), positive predictive value (PPV: 86.6%), negative predictive value (NPV: 53.6%) and diagnostic accuracy (75.1%) of abnormal CSF analysis in patients with PACNS. In addition, we found rates of CSF pleiocytosis (defined as >5 cells/ml) and hyperproteinorrachia (defined as protein >45 mg/dl) of 47% and 71%, respectively.

Additional information. Two systematic reviews[15,16] analyzed data on CSF results in patients with PACNS, most of whom had a diagnosis based on the Calabrese and Mallek criteria.[3] Abnormal test results were reported in 74.4% and 75% of patients, respectively. In addition, the systematic review and meta-analysis by Beuker et al.[17] reported CSF data on 581/911 patients with abnormalities reported in 75% samples.

Most of the studies summarized in Table 3 defined hyperproteinorrachia as CSF protein >45 mg/dl, but three studies[20,25,29] used a threshold of 50 mg/dl and one used 80 mg/dl.[31] A recent study evaluating total CSF protein levels in a community-based population of 633 participants (mean age 70.9 ± 11.6 years), documented mean CSF protein 52.2 ± 18.4 mg/dl, with 95% confidence interval of 24.0–93.4 mg/dl (range, 14.0–148.0 mg/dl).[33] Age, male sex and diabetes were independently associated with higher CSF protein levels. Moreover, CSF analysis was repeated in 66 individuals within 2.5 years and the coefficient of repeatability was 26.1 mg/dl, with 11 cases showing a difference of >20 mg/dl between serial measurements. Therefore, CSF protein levels may show considerable variation and may exceed the 45 or 50 mg/dl threshold even in healthy individuals.

Table 2. Summary of PICOs and recommendations.

Recommendation	Expert consensus statement
PICO 1 **In adults with suspected PACNS, does CSF analysis for pleocytosis and hyperproteinorrachia vs no CSF analysis improves the diagnostic accuracy?**	
In adults with suspected PACNS, there is uncertainty over the utility of CSF examination for pleocytosis and/or hyperproteinorrachia as a diagnostic tool. Quality of evidence: - Strength of recommendation: -	For adults with a clinical suspicion of PACNS, we suggest CSF examination during the diagnostic workup to gain diagnostic information relevant for other differential diagnosis (e.g. post-infectious vasculitis). For adults with a clinical suspicion of PACNS, we suggest CSF examination during the diagnostic workup to provide information relevant to the exclusion of conditions to be considered in the differential diagnosis (e.g. post-infectious vasculitis). CSF analyses should not be limited to determination of cell count and protein concentration. Normal CSF analyses cannot, by themselves, exclude the diagnosis of PACNS.
PICO 2 **In adults with suspected PACNS, does assessing for predefined pattern of parenchymal abnormalities on brain MRI vs not searching them improve diagnostic accuracy?**	
In adults with suspected PACNS there is uncertainty regarding the clinical utility of identifying predefined patterns of parenchymal signal change to improve the diagnostic accuracy of PACNS and for differentiating SV-PACNS from LV-PACNS. Quality of evidence: - Strength of recommendation: -	In adults with definite or probable PACNS, we suggest reporting neuroimaging findings in a standardized way, according to the described patterns of parenchymal involvement and contrast enhancement on MRI to collect relevant data prospectively. Given potential selection bias in those undergoing biopsy (i.e. those with tumefactive or contrast enhancing lesions), we suggest to be cautious in attributing some patterns (e.g. tumefactive patterns) to SV-PACNS or LV-PACNS.
PICO 3 **In adults with suspected PACNS, does the presence of MRI leptomeningeal enhancement vs no MRI leptomeningeal enhancement improve diagnostic accuracy?**	
In adults with suspected PACNS, the presence of leptomeningeal enhancement on MRI is not a specific neuroimaging sign and its role in increasing confidence in the diagnosis of PACNS and in differentiating between SV-PACNS and LV-PACNS is uncertain. Quality of evidence: - Strength of recommendation: -	
PICO 4 **In adults with suspected PACNS, does cerebral computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) with high probability angiographic pattern vs digital subtraction angiography (DSA) with high probability pattern improve diagnostic accuracy?**	
In adults with suspected PACNS, we do not recommend using MRA routinely in place of DSA. No recommendations can be drawn for CTA. Quality of evidence: **Very low** ⊕ Strength of recommendation: **Strong against intervention** ↓↓	1. The clinical utility of CTA in PACNS has not been formally compared to MRA and DSA although it is widely used in the assessment of cerebrovascular disorders. We suggest that it could be non inferior to MRA if multislice (>128) technique is employed 2. DSA has a higher sensitivity and specificity in detection of medium-sized vessel involvement in PACNS and it is less invasive than brain biopsy. It is suggested that DSA is considered in patients with clinical suspicion of PACNS, when the MRA/CTA are not diagnostic for a high probability pattern.
PICO 5 **In adults with suspected PACNS and normal MRA, does performing DSA vs not performing a DSA improve diagnostic accuracy?**	
In adults with suspected PACNS, a single study suggests that concordance of MRA and DSA in medium vessel involvement is globally low, so we suggest considering performing a DSA if the MRA is normal. Quality of evidence: **Very low** ⊕ Strength of recommendation: **Weak for intervention** ↑?	

(Continued)

Table 2. (Continued)

Recommendation	Expert consensus statement
PICO 6 **In adults with probable LV-PACNS, does performing high-resolution vessel wall imaging-MRI (HRVWI-MRI) vs performing a digital subtraction angiography (DSA) increase diagnostic accuracy?** PICO 7 **In adults with suspected PACNS, does performing high-resolution vessel wall imaging-MRI (HRVWI-MRI) vs not performing HRVWI-MRI improve diagnostic accuracy?**	
In adults with probable LV-PACNS, there are uncertainty insufficient data on diagnostic improvement of diagnosis by using HRVWI-MRI to determine whether the technique improves the diagnostic accuracy of PACNS when used with vs DSA. Quality of evidence: - Strength of recommendation: - In adults with suspected PACNS, there is uncertainty insufficient data on change in diagnostic accuracy of performing vs not performing HRVWI-MRI to assess the changes in diagnostic accuracy of performing vs not performing HRVWI-MRI. Quality of evidence: - Strength of recommendation: -	HRVWI-MRI is a promising but not yet validated technique. We suggest that it should be investigated and validated in prospective multi-center trials. In the meantime, we suggest that use of HRVWI-MRI should be limited to expert centers and the interpretation of a positive finding should not be the sole neuroimaging modality supporting the diagnosis of PACNS.
PICO 8 **In adults with definite PACNS, does the presence of high probability angiographic pattern with any technique (DSA/CTA/MRA) vs biopsy change diagnostic accuracy?**	
In adults with definite PACNS there is uncertainty on the diagnostic utility for comparing the presence of high probability angiographic pattern with any technique (DSA/CTA/MRA) compared with biopsy with biopsy for the diagnostic accuracy. Quality of evidence: - Strength of recommendation: -	Although the interpretation of data is biased since patients with angiographic demonstration of vascular stenosis are less likely addressed for CNS biopsy, we suggest to propose CNS biopsy in patients with suspicion of SV-PACNS, i.e. with normal angiogram. We suggest that the possibility of medium vessel involvement is addressed using DSA, even in patients with normal MRA or CTA, before brain biopsy, unless biopsy is considered to have additional clinical utility in the exclusion of differential diagnoses. In patients with vascular abnormalities on DSA, CTA or MRA, we suggest that the possibility of a CNS biopsy should be individually discussed in a multidisciplinary team with relevant expertise and/or an expert in the diagnosis and management of PACNS.
PICO 9 **In adults with definite PACNS does the presence of MRI leptomeningeal enhancement (LME) vs positive biopsy findings change increase the diagnostic accuracy?**	
In adults with definite PACNS there is persistent uncertainty regarding the improvement of effect on diagnostic accuracy of the presence of MRI leptomeningeal enhancement (LME) vs biopsy. Quality of evidence: - Strength of recommendation: -	We suggest proceeding to biopsy where there is clinical suspicion of PACNS, LME leptomeningeal enhancement and normal findings on DSA. If there is no leptomeningeal enhancement, we suggest that targeted biopsy of gadolinium-enhanced lesions may increase the diagnostic accuracy of the biopsy in comparison to blind biopsy.
PICO 10 **In adults with definite PACNS, does autopsy increase the diagnostic accuracy vs biopsy alone?**	
In adults with definite PACNS there is uncertainty regarding the diagnostic accuracy of biopsy when compared with autopsy findings. Quality of evidence: - Strength of recommendation: -	We suggest proposing autopsy in patients who have had a fatal outcome in the context of a high suspicion of PACNS and inconclusive investigations in life e.g. a non-diagnostic brain biopsy. Review of these cases may yield new knowledge to improve future management of the condition.
PICO 11 **In adults with definite PACNS, is the presence of a lymphocytic histological pattern vs a granulomatous/necrotizing histological pattern associated with a better outcome?**	
In adults with definite PACNS, there is uncertainty regarding the prognostic significance of the lymphocytic histological pattern vs a granulomatous/necrotizing histological pattern Quality of evidence: - Strength of recommendation: -	Acknowledging the low quality of evidence, we suggest that lymphocytic vasculitis seems to be a relatively more benign condition characterized by lower disability and mortality when compared with necrotizing and granulomatous vasculitis. Moreover, we suggest that the histological pattern should not be used to guide treatment decisions.

(Continued)

Table 2. (Continued)

Recommendation	Expert consensus statement
PICO 12 **In adults with probable/definite PACNS, does using glucocorticoids in addition to any further immunosuppressive drug vs glucocorticoids alone improve outcome?**	
In adults with probable/definite PACNS there is uncertainty regarding the clinical benefit associated with use of immunosuppressive drugs in addition to glucocorticoids Quality of evidence: - Strength of recommendation: -	Given the potential severity of PACNS, the relapsing course of the disease, and the well-known glucocorticoid-related toxicity side effects in a long-term administration, we suggest consideration of adding an immunosuppressant to glucocorticoid therapy in most patients with PACNS. We also suggest that the treatment protocol in milder disease phenotypes, use of glucocorticoids alone might should be discussed in a multidisciplinary team with relevant expertise and/or an expert in the diagnosis and management of PACNS. In this context, the use of glucocorticoids alone might be considered, in particular in milder disease phenotypes.
PICO 13 **In adults with probable/definite PACNS, is the combination of mycophenolate mofetil (MMF) and glucocorticoids vs cyclophosphamide (CYC) and glucocorticoids associated with altered outcome?**	
In adults with PACNS, there is uncertainty regarding the optimal induction therapy (CYC or MMF) to be used in conjunction with glucocorticoids. Quality of evidence: - Strength of recommendation: -	In all patients with PACNS, we suggest commencing therapy with either CYC (orally or intravenously delivered) or MMF when an immunosuppressant agent is considered in the induction phase in conjunction with glucocorticoids. We suggest that the decision to start with CYC and glucocorticoids or MMF and glucocorticoids for initial therapy should be made based on the physician's experience, the severity of the disease and the patient's preferences. MMF should be considered for maintenance therapy to reduce the toxicity of long-term treatment with CYC.
PICO 14 **In adults with probable/definite PACNS, do antiplatelet vs no antiplatelet improve outcome?**	
In adults with PACNS, there is uncertainty regarding the routine use of antiplatelets. Quality of evidence: - Strength of recommendation: -	Aspirin may have a beneficial effect in PACNS due to a combined antithrombotic and anti-inflammatory effect and its possible complementary action with glucocorticoid therapy. In patients with large/medium vessel involvement, we suggest including aspirin therapy.
PICO 15 **In adults with probable/definite PACNS, does long-term immunosuppression vs no long-term immunosuppression improve outcome?**	
In adults with probable/definite PACNS there is uncertainty regarding the use of long-term immunosuppression. Quality of evidence: - Strength of recommendation: -	We suggest initiating maintenance therapy when no recurrence has been registered after the induction therapy. We suggest continuing maintenance therapy for at least 2 years before considering cessation in patients without recurrences.
PICO 16 **In adults with probable/definite PACNS and acute ischemic stroke, does intravenous thrombolysis (IVT) vs no IVT improve outcome?**	
In adults with probable/definite PACNS and acute ischemic stroke, there is uncertainty regarding the use of IVT. Quality of evidence: - Strength of recommendation: -	IVT has been proven a powerful and safe treatment for acute ischemic stroke, and in the absence of absolute contraindications, we suggest considering IVT even in patients with a history of PACNS presenting with symptoms of acute ischemic stroke. In the absence of relevant data, we suggest adherence to the inclusion and exclusion criteria for IVT as per acute ischemic stroke.
PICO 17 **In adults with probable/definite PACNS and acute ischemic stroke, does endovascular thrombectomy (EVT) vs no EVT improve outcome?**	
In adults with probable/definite PACNS and acute ischemic stroke, there is uncertainty regarding the use of EVT. Quality of evidence: - Strength of recommendation: -	Since large vessel occlusion is typically associated with devastating strokes and that in the hyperacute phase, a different cause for the LVO-related stroke cannot be excluded, even in patients with known PACNS, we suggest that EVT is reasonable in patients with a history of PACNS presenting within the early or extended (by using advanced imaging) time windows for EVT.

Table 3. PICO 1 summary of data. CSF analysis.

Study	Study design	Number of PACNS patients	Study duration	Age (mean or median)	Women (N)	Population with available CSF results (N)	PACNS with positive CSF (N)¨	CSF pleiocytosis (>5 cells/mL) (N)	CSF hyperproteinorrhachia (>45 mg/dl) (N)	PACNS with negative CSF (N)	Angiography proven with negative CSF (N)	Angiography proven with positive CSF (N)	Biopsy proven with negative CSF (N)	Biopsy proven with positive CSF (N)	Non-PACNS with positive CSF (N)	Non-PACNS with negative CSF (N)
Salvarani et al., 2020[19]	Retrospective	191	1983–2017	49 (17–85)	92	148	120	63	96	28	23	67	5	53	NR	NR
de Boysson et al., 2017[20,£]	Retrospective	102	2010–2017	46 (18–80)	48	94	65	NR	NR	29	27	44	NR	NR	NR	NR
Agarwal, et al., 2022[21]	Retrospective and prospective	82	2010–2019	34 (27.8–42)	14	48	42	17	32	6	NR	NR	NR	NR	NR	NR
Schuster et al., 2017[22]	Retrospective	31	2008–2014	44.5 (range 14.7–84) for LV-PACNS; 47 (31.1–63.9) for SV-PACNS	18	31	29	11	19	2	NR	NR	NR	NR	NR	NR
Sundaram and Sylaja, 2022[23]	Retrospective	20	2016–2019	42.55 (±9.48)	6	20	14	3	14	6	NR	NR	NR	NR	NR	NR
Wang et al, 2019[24]	Retrospective	18	2015–201	30 (10–47	8	18	8	NR	NR	10	NR	NR	NR	NR	NR	NR
Abu-Shakra et al., 1994[25,£]	Retrospective	16	1984–1993	36.5 (26–53)	8	12	5	1	4	7	NR	NR	NR	NR	NR	NR
Amin et al., 2021[26,§]	Retrospective	36	2012–2021	NA	30	36	NR	24	24	NR	NR	NR	NR	NR	NR	NR
Raghavan et al., 2019[27,*]	Retrospective	128	2005–2016	49.8 (±15.9)	78	113	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Becker et al., 2017[28,°]	Case-control	23	2013–2014	NA	NA	23	16	NR	NR	7	NR	NR	NR	NR	NR	NR
Torres et al., 2016[9,**]	Retrospective	9	2005–2013	49 (35–70)	9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stoecklein et al., 2021[10,***]	Retrospective	7 biopsy-proven	2010–2017	67 ± 10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Karaman et al., 2021[29,£]	Retrospective	13	2018–2020	40 (12–58)	12	15	10	6	10	0	NR	NR	NR	NR	5	0
Vera-Lastra et al., 2015[30,§§]	Retrospective	12	2004–2010	32 ± 13.19	27	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Duna and Calabrese., 1995[13]	Prospective	7	NR	NR	NR	NR	7	NR	NR	0	NR	NR	NR	NR	12	20
Singhal et al., 2016[31,∞]	Retrospective	47	1998–2015	51 ± 15	127	42	31	NR	NR	11	NR	NR	NR	NR	13	98
Kraemer et al., 2011[32]	Retrospective	21	2003–2008	43 (11–65)	13	21	19	13	8	2	4	8	2	3	NR	NR

N: number of patients; NR: not reported/retrievable; RCVS: reversible cerebral vasoconstriction syndrome; SCNSV: secondary central nervous system vasculitis.
¨Positive CSF: either >5 cells/mL or protein >45 mg/dl.
£These studies defined increased CSF protein when >50 mg/dl.
∞Defined increased CSF protein when >80 mg/dl.
§Pleiocytosis and mean protein levels were significantly higher in PACNS patients.
*CSF pleiocytosis was the only diagnostic test associated with biopsy proven vasculitis.
°Non-PACNS cohort included patients with secondary CNS vasculitides and inflammatory CNS diseases.
**Non-significant differences in CSF protein levels ($p = 0.31$) and leukocytes ($p = 0.39$) between 9 biopsy-confirmed PACNS samples and 70 patients without CNS vasculitis.
***No significant differences in median CSF cell counts and median CSF protein levels were detected between biopsy positive and biopsy negative patients. Median CSF protein levels were higher in the histologically versus angiography confirmed cases.
§§Significantly elevated CSF cell counts ($p = 0.009$) and protein levels ($p = 0.0426$) in the samples from PACNS patients compared to those from the secondary vasculitis cases.

Given the lower rates of CSF pleocytosis in patients diagnosed with PACNS, the diagnosis cannot be excluded or regarded as unlikely when CSF white blood cell counts are less than 5/μl.

Since total CSF protein levels may frequently exceed 45 mg/dl in healthy individuals or patients with non-inflammatory CNS conditions, caution should be taken when interpreting CSF protein levels that exceed the 45 mg/dl threshold but are close to it, especially when CSF pleocytosis is absent. Moreover, the available data do not allow discussing about differential diagnosis between SV-PACNS and LV-PACNS.

Finally, there are even scarcer data in the literature about the role of other CSF analysis, including oligoclonal bands and flow cytometry, and no data is available on antineuronal antibodies, being autoimmune encephalitis a growing and unexplored field of differential diagnosis. Similarly, there is not a standardization for the differential diagnosis of post-infectious vasculitides, for example, VZV arteriopathy.

The lack of specific comparative studies and the heterogeneity of data about the diagnostic procedures and the populations in the available studies is the main conclusion of the analysis and prevent to derive a recommendation.

Evidence-based Recommendation (PICO 1)
In adults with suspected PACNS, there is uncertainty over the utility of CSF examination for pleocytosis and/or hyperproteinorrachia as a diagnostic tool.
Quality of evidence: -
Strength of recommendation: -

Expert consensus statements (PICO 1)
For adults with a clinical suspicion of PACNS, we suggest CSF examination during the diagnostic workup to gain diagnostic information relevant for other differential diagnosis (e.g. post-infectious vasculitis). CSF analyses should not be limited to determination of cell count and protein concentration. Normal CSF analyses cannot exclude the diagnosis of PACNS.

Neuroimaging of brain parenchyma

PICO 2: In adults with suspected PACNS, does assessing for predefined patterns of parenchymal abnormalities on brain MRI versus not assessing improve the diagnostic accuracy?

Analysis of current evidence. This PICO refers to review of neuroimaging acquired in patients with PACNS with specific reference to predefined patterns of signal abnormality with the aim of providing additional diagnostic accuracy, including differentiating SV-PACNS from LV-PACNS.[2,3] The following neuroimaging patterns were predefined within the MWG: acute intracerebral hemorrhage (ICH)/subarachnoid hemorrhage (SAH); tumefactive (or pseudotumoral) pattern (t-PACNS); multiple acute/subacute ischemic lesions; single acute/subacute ischemic lesion; small vessel disease (SVD) pattern (according to the STRIVE criteria)[34]; presence of lesional parenchymal contrast enhancement; spinal cord involvement.

The literature search identified no RCT and no comparative studies specifically evaluating the effectiveness of MRI assessment versus no assessment. The 18 studies selected for data extraction (Table 4) yielded a total amount of 660 patients over a wide time range (1987–2020). Three studies[19,27,35] reported data from the greatest number of patients (393/660, 59.5%). There were 230 patients reported to have "definite" PACNS, predominantly SV-PACNS (226). Of the 398 patients with "probable" PACNS, 303 had LV-PACNS. For 32 patients, information on subtype was not available. MRI data were available for 615 patients but were not consistently reported in terms of pattern of parenchymal involvement, availability of post-contrast sequences, and detailed findings.

An ICH/SAH pattern was reported in 90/660 (13.6%) patients, but in several studies this information was missing and it may therefore be underreported. A pseudotumoral pattern was reported in a minority of patients (27/660 or 4.1%). This pattern was also likely to be underreported, but, in single institution case series, it was rare. The presence of an acute/subacute ischemic pattern was not consistently rated as either single or multiple lesions; single ischemic lesion pattern was reported in 42/660 (6.4%) patients and multiple ischemic lesions in 123/660 (18.6%). Parenchymal contrast enhancement was reported in 135/660 (20.4%). The SVD pattern was also likely to be largely underreported and it was described in only 58/660 (8.8%) patients. Spinal cord involvement was even more rarely reported [5/660 (0.8%)] and only a single case was not reported to have co-existent brain involvement.

Additional information. The available data were heterogeneous and reporting of many of the key features was incomplete. This largely reflects the retrospective design of studies and the lack of a preplanned, standardized diagnostic work-up. There was an overlap in the reported patterns of neuroimaging findings; for example, the coexistence of several patterns (e.g. ICH with SVD pattern or single/multiple ischemic lesions) in the same patient was not reported. The description of the SVD pattern was not detailed in the majority of manuscripts and, where information was provided, recommendations for standardization of SVD reporting were not used.[34] In all cases with spinal involvement, the diagnosis was made on histopathological analyses as definite PACNS,[2] but information on the exclusion of differential diagnoses was not available. A systematic study of the entire neuraxis was not routinely performed in the included case-series or, indeed, consistently in clinical

Table 4. PICO 2 summary of data. Neuroimaging of brain parenchyma.

Reference	Study design	Study duration	Mean age (years)	PACNS patients/ women (N)	Definite PACNS (N)	Probable PACNS (N)	SV	LV	MRI performed (N)	MRI available	MRI abnormal	ICH/ SAH	Pseudotumoral pattern	Single acute/ subacute lesion	Multiple acute/ subacute lesion	Parenchymal lesion with CE	SVD pattern (Yes/ No)	Spinal cord	Sensitivity	Specificity	PPV	NPV
Becker et al., 2017[28]	Case-control	2013–2014	NR	25/NR	18	7	18	7	25	25	25	2	10	NR	NR	14	NR	3	NR	NR	NR	NR
Abu-shakra et al., 1994[25]	Retrospective	1984–1993	Median age: 36.5 (range: 26–53)	16/8	16	0	16	0	9	9	7	NR	NR	NR	NR	NR	2	NR	NR	NR	NR	NR
Schuster et al., 2017[22]	Retrospective	2008–2014	45.6	31/18	17	14	17	14	31	31	31	21	NR	NR	NR	17	NR	NR	NR	NR	NR	NR
Cloft et al., 1999[36]	Retrospective	1990–1995	Median age: 51 (range: 17–80)	9/7	0	9	0	9	9	9	8	2	0	3	3	2	NR	NR	NR	NR	NR	NR
Destrebecq et al., 2020[37]	Retrospective	2016–2018	59 ± 13	20/9	0	20	0	16	20	20	20	2	0	15	NR	NR	NR	NR	NR	NR	NR	NR
Kuker et al., 2008[38]	Retrospective	1998–2006	27	27/17	3	24	3	24	27	27	27	NR	NR	NR	NR	2	NR	NR	NR	NR	NR	NR
Salvarani et al., 2016[6]	Retrospective	1987–2011	NR	163/NR	53	96	58	105	149	149	143 (96%)	13	NR	9	72	34	NR	2	NR	NR	NR	NR
Shimoyama et al., 2022[39]	Retrospective	2012–2019	40.2 ± 11.6	9/5	5	4	5	4	9	9	NR	NR	NR	NR	NR	NR	No	No	NR	NR	NR	NR
Stoecklein et al., 2021[10]	Retrospective	2010–2017	67 ± 10.4	7/4	7	0	7	0	7	7	NR	2	NR	5	NR	3	No	No	NR	NR	NR	NR
Torres et al., 2016[9]	Retrospective	2005–2013	Median age: 35–70	9/4	9	0	9	0	NR	NR	NR	NR	NR	4	NR	NR	NR	NR	NR	NR	NR	NR
Vera-Lastra et al., 2015[30]	Retrospective	2004–2010	32.9 ± 13.9	12/11	NR	NR	NR	NR	11	11	12	NR	NR	4	NR	NR	NR	NR	NR	NR	NR	NR
Geri et al., 2014[40]	Retrospective	1990–2009	Median age: 45 (37–54)	18/9	18	0	18	0	18	18	18	NR	NR	0	18	NR	NR	NR	NR	NR	NR	NR
Raghavan et al., 2019[27]	Retrospective	2005–2016	49.8	128/78	34	94	34	94	125	NR	112	NR	NR	NR	NR	NR	NR	NR	94%	12%	29%	85%
Kraemer and Berlit 2011[32]	Retrospective	2003–2008	42.48 (median 43, range 11–65)	21/13	6	13	6	13	21	21	21	NR	NR	0	16	8	14	NR	NR	NR	NR	NR
de Boysson et al., 2017[20]	Retrospective	2010–2017	median 46 (18–80)	102/48	26	76	26	76	91	91	NR	34 (33%)	12 (12%)	NR	NR	35/85 (41%)	NR	NR	NR	NR	NR	NR
Thaler et al., 2019[41]	Retrospective	2009–2014	43 [± 15.3]	33/17	16	13	8	25	33	33	33	11	5	NR	NR	19	NR	NR	NR	NR	NR	NR
Sundaram and Sylaja, 2022[23]	Retrospective	2016–2019	42.55 (9.48)	20/6	1	19	1	19	20	20	20	0	0	2	14	1	13	NR	NR	NR	NR	NR
Karaman, 2021 [2]	Retrospective	2018–2020	median age 40 (range 12–58)	10/NR	1	9	0	10	10	10	10	3	NR	NR	NR	NR	9	NR	NR	NR	NR	NR

NR: not reported/retrievable; SVD: small vessel disease.

practice. Previous reports suggested that 5%–29% of PACNS can present with "masslike" or "tumefactive" lesion, mimicking a neoplasm, so tumors are an important differential diagnosis and these patients usually undergo brain biopsy. However, in most cases it was not possible to retrieve information about the biopsy execution and findings, so it was not possible to speculate regarding the caliber of vessel affected. In the French cohort,[35] there was no significant difference in neuroimaging patterns between the two subgroups of PACNS. The largest case series of t-PACNS so far published is a retrospective review[42] of 10 histopathologically proven cases, which excluded patients with histopathology findings of amyloid-beta-related angiitis (ABRA), cerebral amyloid angiopathy-related inflammation (CAA-ri) and vasculitis occurring in the context of infection.[42] The exclusion of ABRA and/or CAA-ri patients may constitute a pitfall in the application of these data in clinical practice, missing SV-PACNS presenting with a tumefactive pattern.

Unfortunately, most reports or case series did not define precisely the pattern of contrast enhancement accordingly to standardized descriptions (e.g. miliary or punctate and curvilinear gadolinium enhancement).[43,44]

Finally, no neuroimaging pattern (including tPACNS) was reported to be indicative of a subtype of PACNS. In the absence of data from prospective studies, this does not support considering individual neuroimaging patterns for the diagnosis and subtyping of PACNS. Whilst pre-biopsy parenchymal enhancement was positively associated with biopsy-proven PACNS compared with DSA-diagnosed patients (60%vs 23%; $p = 0.001$),[20] a potential selection bias was that contrast enhancement was a criterion for biopsy.

The underreporting of neuroimaging issues and the lack of specific comparative studies, as well as the heterogeneity in the employed neuroimaging techniques and reported data prevent to derive a recommendation.

Evidence-based Recommendation (PICO 2)
In adults with suspected PACNS there is uncertainty regarding the clinical utility of identifying predefined patterns of parenchymal signal change to improve the diagnostic accuracy of PACNS and for differentiating SV-PACNS from LV-PACNS.
Quality of evidence: -
Strength of recommendation: -

Expert consensus statements (PICO 2)
In adults with definite or probable PACNS, we suggest reporting neuroimaging findings in a standardized way, according to the described patterns of parenchymal involvement and contrast enhancement on MRI to collect relevant data prospectively.
Given potential selection bias in those undergoing biopsy (i.e. those with tumefactive or contrast enhancing lesions), we suggest to be cautious in attributing some patterns (e.g. tumefactive patterns) to SV-PACNS or LV-PACNS.

PICO 3: In adults with suspected PACNS, does the presence of MRI leptomeningeal enhancement versus no MRI leptomeningeal enhancement improve diagnostic accuracy?

Analysis of the current evidence. This PICO assessed the benefit of leptomeningeal enhancement (LME) after gadolinium-based contrast agent (GBCA) administration to improve the diagnostic accuracy of PACNS including refinement of the diagnosis according to vessel caliber.

Four papers were considered suitable for data extraction (Table 5).[19,20,23,29]

All studies were retrospective case series, including a total amount of 323 patients, of whom 297 (91.9%) underwent MRI, although the proportion of patients undergoing GBCA was not reported in most studies. 98/323 (30.3%) patients had a diagnosis of "definite" SV-PACNS, and 225/398 (56.5%) had LV-PACNS; 9 patients had a positive biopsy and angiography.[19] A total amount of 73 patients had LME (22.6% of the total and 24.6% of MRI studied patients). According to the SV-PACNS and LV-PACNS subcategories 14/26 patients with LME had SV-PACNS and 10/59 had LV-PACNS (53.8% and 16.9%, respectively) in the French cohort[20] and 29/71 had SV-PACNS versus 8/120 with LV-PACNS (40.8% and 6.7%, respectively) in the Mayo Clinic case series.[19]

Within the Mayo Clinic series,[4] a small subset of eight patients had prominent leptomeningeal enhancement which was noted to be diffuse, multilobar and often biemispheric, as well as involving the posterior cranial fossa.

Additional information. Leptomeningeal enhancement not associated with PACNS has not been explored here. Several diseases are well recognized to be associated with leptomeningeal enhancement, ranging from neoplastic or infectious processes to neuroinflammatory diseases as neurosarcoidosis and multiple sclerosis.[45] Among cerebrovascular diseases, leptomeningeal enhancement is associated with hyperacute injury markers (HARM) both in ischemic stroke and TIA.[46,47] Moreover, leptomeningeal enhancement probably reflects the breakdown of the blood–leptomeningeal barrier in vessels traversing the subarachnoid space and is a nonspecific imaging sign.[48]

There are no manuscripts supporting the diagnostic utility of leptomeningeal enhancement to discriminate between PACNS and other diseases. Moreover, perivascular and non-transmural inflammatory infiltrates are histopathological features of CAA-ri and Amyloid-related Imaging Abnormalities or ARIA, whose clinical and neuroimaging findings, including leptomeningeal enhancement, may be indistinguishable from SV-PACNS.[49–52]

Finally, although it seems that the presence of leptomeningeal enhancement is more frequent in SV-PACNS, it is uncertain if it is useful for differentiating between SV-PACNS and LV-PACNS with high accuracy.

Table 5. PICO 3 summary of data. Neuroimaging of brain parenchyma.

Reference	Study design	Study duration	Mean Age	PACNS patients/ Women (N)	MRI performed (N)	Definite PACNS (N)	Probable PACNS (N)	SV PACNS	LV PACNS	MRI LE	True positive	False positive	False Negative	True Negative	Sensitivity	Specificity	PPV	NPV
de Boysson et al., 2017[20]	Retrospective	2010–2017	median 46 (18–80), SV-PACNS 41.5 (18–61), LV-PACNS 48.5 (19–80)	102/48 (12 SV + 36 LV)	91	26	76	26	76	24/85 (14/26 SV + 10/59 LV)	NR	NR	NR	NR	NR	NR	NR	NR
Salvarani, 2020[19]	Retrospective	1983–2017	49 (17–85); biopsy 58 (17–84) and angiopgraphy 48 (17–85)	191/92 (W 30 biopsy and 72 angiographic)	176	71	120 (+9 with positive DSA and positive biopsy)	71	120	37 (29 SV and 8 LV)	NR	NR	NR	NR	NR	NR	NR	NR
Sundaram and Sylaja, 2022[23]	Retrospective	2016–2019	42.55 (9.48)	20/6	20	1	19	1	19	10	10	0	10	0	NR	NR	NR	NR
Karaman 2021[29]	Retrospective	December 2018–March 2020	median age of 40 (range 12–58	10/NR	10	0/9	10	0	10	2/10	2	0	8	13	NR	NR	NR	NR

NR: not reported/retrievable.

Evidence-based recommendation (PICO 3)
In adults with suspected PACNS, the presence of leptomeningeal enhancement on MRI is not a specific neuroimaging sign and its role in increasing confidence in the diagnosis of PACNS and in differentiating between SV-PACNS and LV-PACNS is uncertain.
Quality of evidence: -
Strength of recommendation: -

Neuroimaging of brain vessels

PICO 4: In adults with suspected PACNS does cerebral computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) with high probability angiographic pattern versus digital subtraction angiography (DSA) with high probability pattern improve diagnostic accuracy?

Analysis of the current evidence. This PICO compares the diagnostic accuracy of noninvasive vascular imaging techniques (MRA, CTA) with DSA in probable/definite PACNS patients. This topic has become increasingly important due to the ongoing reduction in use of DSA as there is a simultaneous increase in the use of non-invasive vascular techniques (CTA, MRA). For the purposes of the PICO, MRA means intracranial 3D-time of flight (TOF)-MRA; no data are available for other techniques.

The literature search identified 64 manuscripts but, after full text examination, only five[20,28,40,41,53] were suitable for data extraction and they are summarized in Table 6. Table 6bis summarizes the risk of bias.

The selected literature retrieved 186 patients with PACNS, among whom 109/186 (58.6%) underwent DSA and 122/186 (65.6%) MRA or CTA; data about the remaining patients were not available or sufficiently detailed.

Cosottini et al.[53] selected eight patients with LV-PACNS diagnosed by DSA to make a direct comparison between 1.5T MRA and 3T MRA. The study has several limitations including, in particular, the different time frames in which the diagnostic techniques were performed. However, the authors reported that in PACNS patients, DSA identified 827 intracranial stenoses with a corresponding sensitivity for vessel stenosis of 47% for 3 T3D-TOF MRA and 14% for 1.5 T TOF. In the French Registry cohort[20,54–56] a subset of 31 patients[55] provided data for direct comparison of MRA and DSA (but not for CTA) regarding the diagnostic concordance of vessel imaging. They underwent, at baseline, both intracranial 3D-TOF-MRA (20 imaged with a 1.5T MR unit and 11 with a 3T MR unit) and DSA in an interval $\leqslant$2 weeks and prior to initiation of treatment. Of the 25/31 patients (81%) with abnormal DSA findings, all but one had changes on 3D-TOF-MRA. The six patients with normal DSA were also reported to have no abnormalities on 3D-TOF-MRA. In a per-segment analysis, the concordance between 1.5T 3D-TOF-MRA and DSA was 0.82 (95% CI, 0.75–0.93), and between 3T 3D-TOF-MRA and DSA, it was 0.87 (95% CI, 0.78–0.91).

Additional information. The definition of the "angiographic pattern with high probability for PACNS diagnosis" was proposed by Duna and Calabrese[13] using DSA and was originally referred to as "classic angiographic features of angiitis within the CNS." Although MRA is widely used for the non-invasive evaluation of patients with PACNS as an alternative to DSA, the use of different neuroimaging modalities such as MRA has not been validated and CTA in particular has been under researched. The different modalities have different potential applications, particularly with respect to vessel caliber but all reported findings are non-specific. Direct comparison of MRA and DSA is lacking and conclusions about diagnostic accuracy are based on a single retrospective study, which includes 31 patients and has several limitations, such that its conclusions are not generalizable.[55] Weaknesses of the study include the small sample size and restriction of the comparison to vessels of the first and second order branches of the Willis circle; MRA does not reliably identify involved vessels in the $>$M3-A3-P3 segments and the involvement of most medium size vessels would therefore remain undetected. In light of this, the degree of concordance between DSA and MRA was evaluated only for the detection of vessel stenosis in predefined segments of the intracranial vessels, rather than for detection of the high probability angiographic pattern. The main differential diagnosis for LV-PACNS is atherosclerosis and the proposal of the high probability angiographic pattern by Duna and Calabrese[13] considered mainly this issues. Nevertheless, intermediate and low probability angiographic pattern have been described too and some studies[13] considered ad LV-PACNS patients with

Table 6. Bis. Risk of bias evaluation.

Reference	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias
Becker et al., 2017[28]	Case-control	Very serious	Not serious	Very serious	Very serious	Not serious
Cosottini et al., 2013[53]	Retrospective case-series	Very serious	Very serious	Very serious	Very serious	Not serious
Geri et al., 2014[40]	Retrospective	Very serious	Very serious	Very serious	Very serious	Not serious
de Boysson et al., 2017[20]	Retrospective	Very serious	Not serious	Not serious	Very serious	Not serious
Thaler et al., 2019[41]	Retrospective	Very serious	Not serious	Not serious	Very serious	Not serious

high and intermediate probability angiographic pattern. This issue has not been formally addressed by techniques different from DSA.

Finally, the diagnostic accuracy of MRA versus DSA has been assessed in a single retrospective study with good concordance between MRA and DSA in large vessel stenosis (only slightly higher for 3 T scanners vs 1.5T scanners) and low in medium vessel involvement, so MRA seems to have a lower diagnostic accuracy than DSA. On the contrary, we have no data for CTA.

Evidence-based recommendation (PICO 4)
In adults with suspected PACNS, we do not recommend using MRA routinely in place of DSA.
No recommendations can be drawn for CTA
Quality of evidence: Very low ⊕
Strength of recommendation: **Strong against intervention** ↓↓

Expert consensus statements (PICO 4)

1. The clinical utility of CTA in PACNS has not been formally compared to MRA and DSA although it is widely used in the assessment of cerebrovascular disorders. We suggest that it could be non inferior to MRA if multislice (>128) technique is employed
2. DSA has a higher sensitivity and specificity in detection of medium-sized vessel involvement in PACNS and it is less invasive than brain biopsy. It is suggested that DSA is considered in patients with clinical suspicion of PACNS, when the MRA/CTA are not diagnostic for a high probability pattern.

PICO 5: In adults with suspected PACNS and normal MRA does performing a DSA versus not performing a DSA improve the diagnostic accuracy?

Analysis of the current evidence. The topic of the PICO is the clinical utility of a normal MRA in large and medium vessel PACNS versus DSA. The available evidence is the same as for PICO 4 and summarized in Table 7. There is one study directly comparing MRA and DSA in a small sample of 31 patients from the French registry,[55] but the comparison focused on stenosis and not on the high probability pattern.

Additional information. The main limitation of MRA is in the evaluation of medium size vessels and DSA is known to have the greatest spatial resolution. CTA has not been evaluated in this setting but the known limitation of CTA (without CT perfusion) in identifying medium vessel occlusion in acute stroke would contribute to lack of confidence in the technique as a substitute for DSA when MRA is normal and the clinical suspicion of PACNS persists.[57,58] Another issue in the previously mentioned study[55] is that the definition of DSA and MRA findings were abnormal versus normal but without further grading of the "abnormal" category. Moreover, an abnormal brain biopsy was reported in 8/16 (50%) of the 31 patients, so the overlapping medium vessel involvement category may be present and affect the global reliability of the PACNS diagnosis between the two techniques. Indeed, the 25 false negative segments observed only on DSA but not on 3D TOF-MRA were reported as "small-sized vessels" in 16 cases, "medium sized vessels" in 8 cases, and "large-sized vessels" in 1 case. The actual consensus on the caliber of intracranial vessels is not the topic of this paper, but the caliber of small vessels means that they are not always seen even with DSA and 24/25 false negative MRA segments could be defined as "medium sized vessels." About the 7 false-positive vascular segments involved in MRA but not on DSA (medium-sized vessels in 4 cases and small-sized vessels in 3) a similar reasoning can be proposed with the potential artifactual finding on MRA due to the low sensitivity/specificity for medium size vessels. The issue of the impact of the strength of magnetic field (e.g. 1.5T vs 3T) on the MRA sensitivity, in particular for medium size arteries, had been recently addressed by Shi et al.,[59] but not directly in PACNS and without comparison with DSA.

It should be taken into account that atherosclerosis remains the main differential diagnosis in patients with multifocal involvement of large and medium-sized vessels and DSA has the higher accuracy for evaluating the burden and pattern of involvement. Another issue is that atherosclerosis is a widespread disease and the simultaneous presence of PACNS and atherosclerosis should be considered in some cases. The "high probability angiographic pattern"[13] was originally proposed for a broader differential diagnosis, including atherosclerosis, than the one outlined by the Birnbaum and Hellmann's criteria.[2]

Evidence-based recommendation (PICO 5)
In adults with suspected PACNS, we suggest performing a DSA if the MRA is normal.
Quality of evidence: Very low ⊕
Strength of recommendation: **Weak for intervention** ↑?

PICO 6: In adults with probable LV-PACNS does performing High Resolution Vessel Wall Imaging-MRI (HRVWI-MRI) versus performing a digital subtraction angiography (DSA) increase the diagnostic accuracy?

PICO 7: In adults with suspected PACNS does performing HRVWI-MRI versus not performing HRVWI-MRI improve the diagnostic accuracy?

Analysis of the current evidence. The topic of PICOs 6 and 7 refers to the clinical value of high-resolution vessel wall magnetic resonance imaging (HRVWI-MRI) in addition to DSA to improve the diagnostic accuracy of PACNS, in adult patients meeting criteria for probable/definite PACNS.

After literature screening, three papers were suitable for data extraction and they are summarized in Table 8.[23,29,41]

Table 7. PICO 4 and PICO 5 summary of data. Neuroimaging of brain vessels.

Reference	Study design	Study duration	Mean Age (years)	PACNS pts/W (N)	Test performed (N)	Definite PACNS (N)	Probable PACNS (N)	MRA high probability (N)	CTA high probability (N)	DSA high probability (N)	MRA Positive	MRA Negative	True positive	False positive	False Negative	True Negative	Sensitivity	Specificity	PPV	NPV
Becker et al. 2017[28]	Case-control	2013–2014	NR	25/NR	14 DSA, 18 MRA or CTA	18/22 biopsies	10	10/18	NR	10/14	10/18	8/18	NR	NR	NR	NR	NR	NR	NR	NR
Cosottini et al. 2013[53]	Retrospective case-series	NR	49.13 ± 6.22	8/6	8 DSA 6 MRA	0	8	4 (1.5T); 6 (3T) for proximal vessels	NR	8	8	0	8	NR (Reported in number of stenoses)	NR	NR	NR	NR	NR	NR
Geri et al. 2014[40]	Retrospective	1990–2009	Median age: 45 (37–54)	18/9	10 DSA, 7 MRA	1	17	5	NR but all abnormal	8	5	2	NR	NR	NR	NR	NR	NR	NR	NR
de Boysson et al., 2017[20]	Retrospective	2010–2017	median 46 (18–80), SV-PACNS 41.5 (18–61), LV-PACNS 48.5 (19–80)	102	91 MRA, 87 DSA	26	76	57/91 (62%), SV 0/23, LV 57/68 (84%)	NR	67/87 in the whole group (0/19 in SV and 67/68 in LV)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Thaler et al., 2019[41]	Retrospective	2009–2014	43 [±15.3]	33	33	17 (8 were defined as SV)	11 (25 were defined as LV)	17	NR	11	25	3	NR	NR	NR	NR	NR	NR	NR	NR

NR: not reported/retrievable.

Table 8. PICO 6 and PICO 7 summary of data. Neuroimaging of brain vessels.

Reference	Study design	Study duration	Mean Age	PACNS patients/ Women (N)	Definite PACNS (N)	Probable PACNS (N)	SV PACNS	LV PACNS	MRA/ CTA/DSA stenosis (N)	MRA/ CTA/DSA negative (N)	HRVWI (number)	HRVWI positive	HRVWI negative	True positive	False positive	False Negative	True Negative	Sensitivity	Specificity	PPV
Thaler et al., 2019[41]	Retrospective	2009–2014	43 [±15.3]	33/17	17	11	8	25	25	8	29	14/29, but 13/14 of patients with stenosis	15/29, but 9/23 of patients with stenosis	14	0	9	6	NR	NR	NR
Sundaram and Sylaja 2022[23]	Retrospective	2016–2019	42.55 (9.48)	27/6	1	19	1	19	19	1	20	20	0	NR	NR	0	NR	NR	NR	NR
Karaman et al., 2021[29]	Retrospective	December 2018 – March 2020	median age of 40 (range 12–58	10/NR	10	0	10	0	0	10	10	0	10	13	NR	NR	NR	NR	NR	NR

NR: not reported/retrievable.

The selected studies provided data on 73 patients with PACNS [29 (40%) with LV-PACNS], included between 2009 and 2020.[23,29,41] All described vessel wall enhancement (VWE) as the preeminent finding, co-localizing with MRA/DSA arterial stenoses when present and frequently identified in other non-stenotic segments. Thaler et al.,[41] reported that all patients with VWE also had arterial stenosis on TOF-MRA or DSA, co-localizing with VWE in 38% of patients. In Sundaram and Sylaja.,[23] 19/20 (95%) with VWE showed DSA abnormalities.

In studies specifying the enhancement pattern,[23,29] concentric VWE was more common than eccentric VWE (85%−95%) There were insufficient data to assess for other HRVWI-MRI derived biomarkers, including pre-contrast thickening, and spontaneous T2 signal of the vessel wall.

Additional information. HRVWI-MRI is an emerging MRI-based neuroimaging technique that can display the vessel walls, including those of intracranial arteries, with sufficient signal to noise ratio to appreciate intramural gadolinium uptake (VWE) following peripheral intravenous contrast injection. In inflammatory processes of the intracranial arteries, including PACNS, HRVWI-MRI can demonstrate vessel wall thickening, and VWE at sites of, or independent from arterial stenoses identified on MRA or DSA.[60] There is growing research and clinical interest in VWE as it may have potential to inform regarding pathological processes within the vessel wall that are not well visualized using luminal-based imaging techniques (CTA, MRA, DSA).

A study by Ferlini et al.,[61] included patients with PACNS and secondary CNS vasculitis, and they presented limited data on PACNS subgroup. However, all patients with CNS vasculitis diagnosed by DSA had corresponding VWE.

In three studies,[23,41,61] patients with a diagnosis of PACNS were selected for inclusion based on availability of HRVWI-MRI, thus the change in PACNS diagnostic accuracy due to HRVWI-MRI remains unknown. No study provided adequate information regarding the change in diagnostic accuracy provided by HRVWI-MRI when compared with DSA. Additionally, all were biased toward LV-PACNS because HRVWI-MRI is commonly used in patients with previously demonstrated intracranial stenosis. Indeed, Karaman et al. [29] included 23 patients with new-onset ischemic events and significant intracranial large vessel stenosis on DSA or MRA. According to features of concentric thickening and VWE, the authors reported the sensitivity and specificity of distinguishing PACNS and other vasculopathies to be 95.2%, 75% and 95.2%, 68.8%, respectively. Unfortunately, there were no specific data on the diagnostic performance of HRVWI-MRI for the subgroup of 10 patients with a diagnosis of "probable" PACNS, nor a comparison between DSA and HRVWI-MRI. One of the relevant mimicker of vessel wall enhancement with a vasculitic pattern is the endovascular treatment, in particular when a stentriever has been employed. This issue is treated in the discussion of PICO 17.

Altogether, the available data do not provide a sufficient basis to answer the PICOs. Additional limitations to the interpretation of data include variability in MRI hardware, "black blood" techniques field strengths and the sequence parameters employed. Finally, there is no standardized way to assess VWE, nor homogeneity on the timing of HRVWI-MRI following or preceding diagnosis, and administration of treatments.

The available literature does not provide sufficient data to answer the question and derive a recommendation.

Evidence-based recommendations (PICO 6 and 7)
In adults with probable LV-PACNS, there are uncertainty on diagnostic improvement of diagnosis by using HRVWI-MRI versus DSA
Quality of evidence: -
Strength of recommendation: -

In adults with suspected PACNS, there is uncertainty on change in diagnostic accuracy of performing versus not performing HRVWI-MRI

Quality of evidence: -
Strength of recommendation: -

Expert Consensus Statement (PICO 6 and 7)
HRVWI-MRI is a promising but not yet validated technique. We suggest that it should be investigated and validated in prospective multi-center trials.
In the meantime, we suggest that use of HRVWI-MRI should be limited to expert centers and the interpretation of a positive finding should not be the sole neuroimaging modality supporting the diagnosis of PACNS.

Neuropathology

PICO 8: In adults with definite PACNS does the presence of a high probability angiographic pattern with any technique (DSA/CTA/MRA) versus biopsy change the diagnostic accuracy?

Analysis of the current evidence. In current practice, cerebral biopsy is less often undertaken in patients with angiographic demonstration of vascular stenoses. Conversely, in patients with normal neurovascular imaging and clinical suspicion of PACNS, biopsy may be proposed. The threshold for biopsy is also likely to be lower in cases with t-PACNS where the main differential diagnosis is likely to be malignancy. The literature search identified limited data regarding results of both cerebro-meningeal biopsy and angiography. Four manuscripts were selected and the extracted data were summarized in Table 9.[19,20,29,62] The manuscripts included information on 437 PACNS patients (146 definite PACNS and 304 probable PACNS); only nine patients had PACNS confirmed on both angiography and histopathology.

Table 9. PICO 8 Summary of data. Neuropathology.

Reference	Study design	Study duration	Mean Age (years)	PACNS patients/ Women (N)	Definite PACNS (N)	Probable PACNS	LV-PACNS	SV-PACNS	DSA/CTA/ MRA done	High probability angiographyc pattern (N)	Angio positive and biopsy positive	Angio positive and biopsy negative	Angio negative and biopsy positive	Angio negative and biopsy negative	Sensitivity (TP/ TP+FN)	Specificity (TN/ TN+FP)	PPV (TP/ TP+FP)	NPV (TN/ TN+FN)	Notes
de Boysson et al., 2017[20]	Retrospective	2010–2016	Median age: 46 (18–80)	102/48	49	76	76	26	DSA (*n*) = 87; MRA (n) =91	Stenosis DSA (n) =67 Stenosis MRA (n) =57	NR	NR	26	NR	NR	NR	NR	NR	
Kadkhodayan et al., 2004[62]	Retrospective	1992–2000	55 years (range: 29–88 years)	16/NR	2	14	14	0	DSA= 14	14	0	14	2	NR	0%	60%	NR	NR	,*
Raghavan et al., 2019[27]	Retrospective	2005–2016	49.8 years	128/78	34	94	34	94	Angiography (*n*) = 93; MRI/ MRA (n) =12; DSA (n)= 23	94	5	46	18	24	22%	34%	10%	57%	
Salvarani et al., 2020[19]	Retrospective	1982–2017	49 (17–85); biopsy 58 (17–84) and angiography 48 (17–85)	191/92 (W 30 biopsy and 72 angiographic)	71	120 (+9 with positive DSA and positive biopsy)	71	120	DSA in 130 patients but data available in 120 patients	129	9	NR	3	NR	NR	NR	NR	NR	

NR: not reported/retrievable.
*Primary angiitis of the CNS was found at biopsy in two of the remaining 24 patients (0% sensitivity).

Additional information. PACNS subgroups are defined according to the size of the affected vessels. The absence of abnormalities in large vessels will usually lead to the recommendation for a cerebral biopsy if PACNS is suspected. Unfortunately, the absence of a high probability angiographic pattern was reported in the literature irrespective of the angiographic technique performed (DSA, MRA, CTA) and the lack of data comparing the sensitivity of neuroimaging modalities has been alluded to previously. Furthermore, the presence of stenosis rather than the specific angiographic pattern has been reported. Noting these limitations in the published studies, SV-PACNS was not associated with angiographic abnormalities and these patients were more likely to have a diagnostic biopsy. They were also more frequently seen to have gadolinium-enhanced lesions on MRI and less acute cerebral infarctions than patients with LV-PACNS. On the other hand, patients with angiographic demonstration of vascular stenosis, more frequently had acute ischemic lesions, less gadolinium-enhanced lesions and were less likely to undergo histopathological analysis.[20,62,63] In the cohort from the Mayo Clinic,[19] the 71 (37%) patients with a biopsy-proven diagnosis had fewer acute infarctions (30%vs 68%), fewer angiographic abnormalities (50%vs 67%) but more gadolinium-enhanced lesions (73%vs 21%) than the 120 (63%) with an angiographic diagnosis. In 34 patients who underwent both angiogram and biopsy, the procedures were positive and negative in 9 and 25 patients, respectively.[19]

In the French registry,[20] 34 patients with a positive biopsy were compared to 17 with a negative result. In patients with positive biopsy, DSA or MRA was abnormal in 26% and 19%, respectively, of patients who underwent vascular imaging. Conversely, it was positive (DSA or MRA) in 94% and 82%, respectively, in patients with negative biopsies who underwent DSA or MRA.[56] The main limitation is that the remaining 6% and 18% of patients respectively did not probably fulfill the diagnostic criteria for definite nor for probable PACNS.

In another cohort,[29] 23 patients with biopsy-proven PACNS underwent a DSA that was positive in only 5 (22%) patients. On the contrary, in 70 patients with negative biopsy who all underwent an angiogram, vascular stenoses were observed in 46 (66%) of them. As previously outlined, the presence of abnormalities on DSA and MRA is not rated according to the 'high probability angiographic pattern', but it is often referred to isolated and nonspecific arterial changes.

The definition of risk/benefit ratio of biopsy is outside the aim of this specific PICO and of this paper. However, the data available in the literature are fragmented and heterogeneous, merging open and close biopsies, targeted and blind biopsies and referring more often to cohorts of patients who underwent brain biopsy for any reason than patients with a clinical suspicion of PACNS as reason to propose biopsy. Moreover, no information exists about the reasons for not performing biopsies in the published cohorts.

The available literature does not provide sufficient data to answer the question and derive a recommendation.

Evidence-based recommendation (PICO 8)
In adults with definite PACNS there is uncertainty on the diagnostic utility of high probability angiographic pattern with any technique (DSA/CTA/MRA) compared with biopsy
Quality of evidence: -
Strength of recommendation: -

Expert consensus statement (PICO 8)
Although the interpretation of data is biased since patients with angiographic demonstration of vascular stenoses are less likely addressed for CNS biopsy, we suggest to propose CNS biopsy in patients with suspicion of SV-PACNS, that is, with normal angiogram.
We suggest that the possibility of medium vessel involvement is addressed using DSA, even in patients with normal MRA or CTA, before brain biopsy, unless biopsy is considered to have additional clinical utility in the exclusion of differential diagnoses.
In patients with vascular abnormalities on DSA, CTA or MRA, we suggest that the possibility of a CNS biopsy should be individually discussed in a multidisciplinary team with relevant expertise and/or an expert in the diagnosis and management of PACNS.

PICO 9: In adults with definite PACNS does the presence of MRI leptomeningeal enhancement (LME) versus biopsy increase the diagnostic accuracy?

Analysis of the current evidence. The literature review of the question retrieved only two descriptive cohorts with available information regarding the neuroimaging features of biopsy-proven PACNS patients. Two main limitations explain the low level of evidence. First, information regarding contrast administration is not provided in all studies. Second, in patients with leptomeningeal enhancement and positive biopsy, information regarding the location of the sample, that is, whether the biopsy was guided on a leptomeningeal enhancement and whether the biopsy collected meningeal and/or brain tissue, is often lacking, precluding any precise analysis of the link between leptomeningeal enhancement and the biopsy result.

The data extraction was performed on the papers describing two cohorts[19,20] and they are summarized in Table 10. A total amount of 203 PACNS patients were analyzed and leptomeningeal enhancement was reported in 33/203 patients (16.3%).

Additional information. Considering the significant aforementioned limitation about the uncertain rate of contrast administration and reporting of enhancement in the available

Table 10. PICO 9 Summary of data. Neuropathology.

Study author, year	Study design	Study duration	Mean Age (years)	PACNS/ Women (N)	Definite PACNS (N): Biopsy proven	LV-PACNS	SV-PACNS	MRI done	Presence of leptomenigeal enhancement	LM enhancement positive and biopsy positive	LM enhancement positive and biopsy negative	LM enhancement negative and biopsy positive	LM enhancement negative and biopsy negative	Sensitivity	Specificity	PPV	NPV
De Boysson et al., 2017[20]	Retrospective	2010–2016	Median age: 46 (18–80) years	102/48 (12 SV + 36 LV)	26	76	26	85	24/85 (14/26 SV + 10/59 LV)	14	NR	NR	NR	NR	NR	NR	NR
Salvarani, 2007[4]	Retrospective	1983–2003	46 (25–84); biopsy 49 (26–84), Angiography 43 (25–57)	101/46	29/46 performed biopsies	72	29 (17 granulomatous, 8 lymphocitic and 4 necrotyzing)	41	9	8	1	17	16	NR	NR	NR	NR

NR: not reported/retrievable.

studies, patients with positive biopsy might be more likely to have leptomeningeal enhancement on MRI when compared to patients with angiography-proven PACNS. In the Mayo Clinic cohort,[19] 44% of patients with biopsy-proven PACNS had meningeal enhancement (not specifically defined as leptomeningeal) versus 7% in the other patients. In the French cohort,[20,56] 77% of patients with a positive biopsy had gadolinium-enhancing lesions (including meningeal and parenchymal) versus 20% in patients with negative biopsy. Similarly, the German cohort[22] found more parenchymal and meningeal enhancement in patients with positive biopsy in comparison with patients diagnosed on imaging (77%vs 29%).

In studies analyzing the precise site of the biopsy, the yield increased when the sample included leptomeninges, and/or when the biopsy was performed on a lesioned area.[8,56]

The available literature does not provide sufficient data to answer the question and derive a recommendation.

Evidence-based recommendation (PICO 9)
In adults with definite PACNS there is persistent uncertainty regarding the improvement of diagnostic accuracy of the presence of MRI leptomeningeal enhancement (LME) versus biopsy.
Quality of evidence: -
Strength of recommendation: -

Expert consensus statement (PICO 9)
We suggest proceeding to biopsy where there is clinical suspicion of PACNS, leptomeningeal enhancement and normal findings on DSA.
If there is no leptomeningeal enhancement, we suggest that targeted biopsy of gadolinium-enhanced lesions may increase the diagnostic accuracy of the biopsy in comparison to blind biopsy.

PICO 10: In adults with definite PACNS, does autopsy increase the diagnostic accuracy versus biopsy alone?

Analysis of the current evidence. The topic of the PICO was not systematically addressed by the literature in recent decades and the practice of autopsy has progressively declined. Only one manuscript suitable for data extraction was identified and the findings are summarized in Table 11.[64]

Additional information. There are very few data comparing biopsy and autopsy in people with definite PCNSV. In a case series published in 1988,[64] 4 patients (1 woman, 3 men) were reported to have CNS vasculitis detected by autopsy. One patient had Hodgkin's lymphoma, one had herpes zoster, one had neurosarcoidosis and one had no concomitant disease, suggesting that the secondary CNS vasculitis was caused by systemic disease rather than

Table 11. PICO 10 Summary of data. Neuropathology.

Study author, year	Study design	Population	Reference group	Study duration	Mean Age	Total number of patients (PACNS)	Women (N)	Number of Biopsies	Definite PACNS (N): Biopsy proven	Number of Autopsies	Autopsy definite PACNS (number)	LV-PACNS	SV-PACNS	Autopsy positive and biopsy positive	Autopsy positive and biopsy negative	Autopsy negative and biopsy positive	Autopsy negative and biopsy negative	Sensitivity	Specificity	PPV	NPV
Younger et al., 1988[64]	Case-series	Granumolatous angiitis patients	Autopsy	NR	NR	4	1	NR	NR	4	4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

NR: not reported/retrievable.

PACNS in at least a significant proportion of the reported cases. In all cases, the diagnosis was made by post-mortem examination. CNS vasculitis was confined to the brain in all four patients and involved large arteries, small arteries and veins or both large and small vessels. Inflammation of the vessels was associated with variable severity of vessel destruction and irregularities, brain lesions and disease. The authors concluded that the diagnosis of CNS vasculitis could not be made without histological confirmation and that a definitive diagnosis could be established in living patients only by histopathological analysis.

In a consecutive case series,[56] 9 out of 79 biopsies (11%) had pathological findings diagnostic of PACNS. Nevertheless, there are few data about autopsy findings in patients with negative biopsy results.[56]

The available literature does not provide sufficient data to answer the question and derive a recommendation.

Evidence-based recommendation (PICO 10)
In adults with definite PACNS, there is a persistent uncertainty to assess the diagnostic accuracy of biopsy versus autopsy.
Quality of evidence: -
Strength of recommendation: -

Expert Consensus Statement (PICO 10)
In order to increase the diagnostic yield of brain biopsy in PACNS, we suggest proposing autopsy in patients with high suspicion of PACNS, a non-conclusive diagnostic pathway before death (e.g. a negative biopsy) and a fatal outcome.

PICO 11: In adults with definite PACNS is the presence of a lymphocytic histological pattern versus a granulomatous/necrotizing histological pattern associated with a better outcome?

Analysis of the current evidence. The topic of the PICO refers to the differential outcomes of two histopathological subtypes of PACNS, that is, lymphocytic pattern and granulomatous/necrotizing pattern. As with the previous PICOs on neuropathology, the retrieved data were scarce and of low quality, often without precise and reliable information about the natural history of the patients and the treatment. Table 12 summarized the two manuscripts considered suitable for data extraction.[14,19] A total amount of 235 patients with PACNS were analyzed and among them 96/235 (40.8%) had a "definite" diagnosis. 25/96 (26%) of those with "definite" PACNS had a lymphocytic pattern and 61/96 (63.5%) had a granulomatous or necrotizing pattern. The predefined outcomes are largely underreported.

Additional information. Two cohorts were assessed – one from Germany[14] and one from the USA.[19] The German cohort[14] had eight patients with a lymphocytic pattern and six patients with granulomatous and necrotizing pattern but none of the predefined outcomes were reported in these

Table 12. PICO 11 summary of data. Neuropathology.

Study author, year	Study design	Study duration	Mean Age	PACNS/ Women (N)	Women (N)	Number of Biopsies	Biopsy definite PACNS (number)	Lymphocitic pattern (number)	Granulomatose-necrotizing pattern (number)	Follow-up duration (mean-range)	Outcomes				
											Death at 3 months	Death at 12 months	mRS 0–2 at 3 months	mRS 0–2 at 12 months	First or recurrent ischemic and hemorrhagic stroke
Schuster et al., 2019[14]	Retrospective	2008–2017	43.5 (Range: 14–83 years)	44/26 (25 biopsy-proven PACNS; 19 imaging-based PACNS)	NR	25	25	8	6 (4 patients granulomatous PACNS; 2 patients necrotizing vasculitis)	5.1 years	NR	NR	NR	33	NR
Slavarani, 2020[19]	Retrospective	1983–2017	49 (17–85); biopsy 58 (17–84) and angiography 48 (17–85)	191	92 (30 biopsy and 72 angiographic)	96	71	17	44 + 10	19 months (range: 0–28.1 years)	0 vs 15 + 1	0 vs 15 + 1	NR	mRS 4–6 at the lastest FU 8 vs 18 + 6	NR

NR: not reported/retrievable.

patients. The Mayo Clinic cohort[19] consisted of 17 patients with a lymphocytic pattern, 44 with a granulomatous pattern and 10 with a necrotizing pattern. Mortality was reported and rated as 0 for patients with lymphocytic pattern and 16 for patients with granulomatous and necrotizing pattern, but without precise details regarding the duration of follow-up. No information was provided for the remaining outcomes. Considering all 191 patients, univariate Cox proportional hazards modeling showed an increased mortality rate in those with increasing age (hazard ratio, HR, 1.4), cerebral infarction on initial MRI (HR 2.95), and angiographic large vessel involvement (HR 3.2), while mortality rate was lower in those with gadolinium–enhancing lesions on MRI (HR 0.3), mRS > 4 was reported in one patient with tumor-like presentation. Relapses were 7 in lymphocytic pattern group versus 19 in the other patterns respectively; similarly, long term remission was 0 versus 11 in lymphocytic and other patterns groups respectively. Severe relapses were reported in the group with lymphocytic pattern versus 19 in the other patterns; similarly, long term remission was respectively 0 versus 11 in lymphocytic and other patterns groups. The selected cohorts showed several differences, for example in the duration of follow-up, respectively of 5.1 years[14] and 19 months.[19] In this last cohort a quarter of patients had a follow-up ⩾ 8 years.

The available literature does not provide sufficient data to answer the question and derive a recommendation.

Evidence-based recommendation (PICO 11)
In adults with definite PACNS, there is uncertainty regarding the prognostic significance of the lymphocytic histological pattern versus a granulomatous/necrotizing histological pattern.
Quality of evidence: -
Strength of recommendation: -

Expert consensus statement (PICO 11)
Acknowledging the low quality of evidence, lymphocytic vasculitis seems to be a relatively less severe condition than necrotizing and granulomatous vasculitis, being associated with lower disability and mortality.
Despite this, we suggest that histological pattern should not be used to guide treatment decisions.

Treatment

Induction

PICO 12: In adults with probable/definite PACNS, does using glucocorticoids in addition to any further immunosuppressive drug versus glucocorticoids alone improve outcome?

Analysis of current evidence. The literature search identified no relevant RCTs. The four manuscripts suitable for data extraction are summarized in TABLE13Table 13.[14,19,20,23] A total amount of 357 PACNS patients were analyzed and among them 181/357 (50.7%) had definite PACNS; 207/357 (58%) had combined therapy with glucocorticoids and immunosuppressants and 29/357 (8.1%) had glucocorticoids alone. The predefined outcomes were largely underreported.

Additional information. Important differences exist in the therapeutic strategies used in published retrospective studies.

In PACNS, few retrospective studies described data on outcomes relating to therapeutic management, especially regarding the use of immunosuppressants.

The literature search identified four studies providing details about treatments and outcomes.[14,19,23,54] However, definitions of outcomes, especially regarding long-term remission, differed across the studies and outcome data were available in only two of the studies. In patients treated with glucocorticoids alone from the Mayo Clinic[19] and French[20] cohorts, 24/87 (28%) remained in prolonged remission, that is, without any relapse at last follow-up. A quarter (18/72) of patients treated with glucocorticoids alone in the Mayo Clinic cohort[19] died at any time point of their natural history (the median duration of the follow-up was 19 months).

Glucocorticoids were given in association with an immunosuppressant in 258 (70%) patients. A lack of homogeneity in the four studies regarding the chosen agent, the therapeutic schedules and the neurologic presentations of the patients who received combined therapy precluded meaningful pooled analysis. In the French cohort,[20] among the 95 patients who received both glucocorticoids and an immunosuppressant (45 for induction only, 45 for induction and maintenance, and 5 for maintenance only), 56 (59%) remained in prolonged remission. Of note, the initial clinical presentation was not different in patients treated with glucocorticoids alone. The choice of therapy is probably affected by the more severe involvement in patients treated by combination therapy from the induction phase. Indeed, the patients diagnosed by angiogram were significantly more frequently treated with CYC compared to those diagnosed by biopsy (66/120, 55% vs 26/71, 37%, $p = 0.02$). Among the 90 patients who received glucocorticoids with CYC, 23 (26%) remained in prolonged remission.

The use of an immunosuppressant for maintenance was associated with a better rate of prolonged remission in the French cohort[20] (82%vs <71% in other group without maintenance) but not in the Mayo Clinic cohort[19] (23% and 25% of prolonged remission with and without maintenance respectively). Of note, the use of maintenance therapy differed in three studies with available data: Nineteen percent in the Mayo Clinic cohort,[19] 45% in the French cohort[20] and 82% in the German cohort,[14]

Table 13. Summary of the extracted data for PICO 12, Therapy: induction phase.

Reference	Study design	Study duration	Follow-up period	Mean Age (years)	PACNS/ Women (N)	Definite PACNS	Probable PACNS	Treatment type	Treatment				Outcomes					
									Glucocorticoids + any immunosuppressant drug	Glucocorticiods alone	Cyclophosphamide + Gulcocorticoids	MMF + Glucocorticoids	Death at 3 months (number/hazard ratio)	Death at 12 months (number/ hazard ratio)	mRS 0–2 at 3 months (number)	mRS 0–2 at 12 months (number)	Stroke (first or recurrence)	Serious adverse events
De Boysson et al., 2017[20]	Retrospective	2010–2017	median months 52.5 (0–198),*	median 46 (18–80)**	102/48 (12 SV + 36 LV)	26	76	Induction	84, (SV 21, LV 63)	16			4 (biopsy proven)	4 during a relapse	NR	NR***	32 (31%) patients§	NR
Salvarani 2020[19]	Retrospective	1983–2017	Median 19 months (range: 0–28.1 years)	49 (17–85); biopsy 58 (17–84) and angiography 48 (17–85)	191(NR)	129 (9 with positive angiogram and positive biopsy)	112	Induction§§	72	NR			18 PDN, 20 PDN + any immunosuppressive drug	NR	NR	NR	NR	NR
Sundaram and Sylaja 2022[23]	Retrospective	2016–2019	409 days, range (118-1240)	42.55 (9.48)	20/6	1	19	Induction	12	8	NR	NR	NR	NR	NR	15	NR	NR
Schuster et al. 2019[14]	Retrospective	2008–2017	5.1 years (median)	median age 43.5 (range 14–83)	44/26	25	19	Induction	39	5	33	0	NR	NR	NR	NR	NR	NR

NR: not reported/retrievable.
*SV 67 (1–198) LV 47.5 (0–188).
**SV-PACNS 41.5 (18–61), LV-PACNS 48.5 (19–80).
***At last FU 58 (57%), SV 13 (50%) and LV 45 (59%).
§16 (5–145) months after diagnosis, mainly in patients with isolated SV PACNS [14 (54%) with isolated SV PACNS vs 18 (24%) with demonstration of large/medium vessel involvement; $p = 0.004$.
§§In 86, IV pulse methylprednisolone therapy (from 3 to 42 pulses, median: 5 pulses, mostly 1 g/pulse), preceded the beginning of oral prednisone (PDN) therapy.

In systemic vasculitis, especially antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, therapeutic management includes two main steps. The first, "induction" phase, aims to achieve vasculitis remission, often using a combination of glucocorticoids and an immunosuppressant (mainly cyclophosphamide (administered either orally or intravenously) or rituximab). The second "maintenance" phase, aims to maintain remission without relapse, and relies on the prolonged use of an immunosuppressant with a tapering schedule of glucocorticoids. The combination of glucocorticoids and immunosuppressant is thus commonplace in ANCA-associated vasculitis. Another important issue when interpreting these data is the variable presentations of the disease, in particular in LV-PACNS versus SV-PACNS. In addition, the diagnostic approach differs in the both subsets since more patients with SV-PACNS have a definite biopsy-proven diagnosis, whereas LV-PACNS are often diagnosed on the basis of a combination of stenosis on vascular imaging and the non-standardized exclusion of PACNS mimics. The diagnosis in this latter group remains "probable" and, in the reported literature, inclusion of other conditions such as intracranial atheroma or RCVS is not always excluded, especially in patients diagnosed prior to 2007. Outcomes varied according to the size of affected vessels in the published cohorts. In the Mayo Clinic cohort,[19] a trend to a significant higher relapse rate was observed in patients with LV-PACNS ($p=0.059$) whereas the French cohort[20] identified more relapses in patients with SV- PACNS, independent of treatment prescribed.

Due to heterogeneity in patients and clinical practice, definitive conclusions are not possible regarding the beneficial effect of adding an immunosuppressant to glucocorticoids in the treatment of PACNS. Based on the available data, the rate of prolonged remission without relapse seemed to be lower in patients treated with glucocorticoids alone in comparison with those who received glucocorticoids combined with an immunosuppressant. However, the number of patients treated with glucocorticoids alone is small and data about outcomes (relapse, functional status and death) are limited. No tolerability data were presented in published cohorts. There is also a possible selection bias regarding mild disease phenotypes treated with corticosteroids alone versus more aggressive presentations treated with combinations treatment.

Important questions remain unanswered: use of an immunosuppressant for induction and/or maintenance, for all PACNS patients or for PACNS subsets, which agent, duration of therapy, which glucocorticoid tapering schedule?

The available literature does not provide sufficient data to answer the question and derive a recommendation.

Evidence-based recommendation (PICO 12)
In adults with probable/definite PACNS there is uncertainty regarding the clinical benefit associated with use of immunosuppressive drugs in addition to glucocorticoids.
Quality of evidence: -
Strength of recommendation: -

Expert consensus statement (PICO 12)
Given the potential severity of PACNS, the relapsing course of the disease, and the well-known glucocorticoid-related side effects in a long-term administration, we suggest consideration of adding an immunosuppressant to glucocorticoid therapy in most patients with PACNS. We also suggest that the treatment protocol should be discussed in a multidisciplinary team with relevant expertise and/or an expert in the diagnosis and management of PACNS. In this context, the use of glucocorticoids alone might be considered, in particular in milder disease phenotypes.

PICO 13: in adults with probable/definite PACNS is the combination of mycophenolate mofetil (MMF) and glucocorticoids versus cyclophosphamyde (CYC) and glucocorticoids associated to different outcomes?

Analysis of the current evidence. No relevant RCTs were identified. The main data of relevance are those discussed for PICO 12 and two cohorts were selected for data extraction (Table 14).[19,20] A total amount of 293 PACNS patients were analyzed, but the predefined outcomes were largely underreported and, in the French cohort,[20] no patient was treated with MMF in the induction phase.

Additional information. However, although they represent the two largest reported series of cases in adult PACNS, there are few data for comparing the efficacy and safety of these two traditional immunosuppressants. CYC with glucocorticoids was used as initial treatment in 82% of patients in the French series[20] compared with 47% in the Mayo Clinic series.[19] MMF was used only as maintenance therapy in four cases in the French series,[20] while 26 patients received MMF in addition to glucocorticoids in the Mayo Clinic series.[19] In 13 patients MMF was the initial treatment, while in the other 13 it was introduced for a relapse of vasculitis or as maintaining/sparing glucocorticoid therapy. Therefore, it is possible to compare the efficacy of CYC and MMF for inducing remission only in the Mayo Clinic series.[19] Compared to the patients initially treated with CYC and prednisone, the 13 patients initially treated with MMF had better response to treatment (100%vs 81%,

Table 14. PICO 13 summary of data. Therapy: induction phase.

Reference	Study design	Study duration	Follow-up period	Mean Age (years)	PACNS/ Women (N)	Definite PACNS	Probable PACNS	Treatment type	Treatment				Outcomes						Notes
									Glucocorticoids + any immunosuppressant drug	Glucocorticoids alone	Cyclophosphamide + Gulcocorticoids	MMF + Glucocorticoids	Death at 3 months (number/ hazard ratio)	Death at 12 months (number/ hazard ratio)	mRS 0–2 at 3 months (number)	mRS 0–2 at 12 months (number)	Stroke (first or recurrence)	Serious adverse events	
De Boysson, et al., 2017[20]	Retrospective	2010–2017	median months 52.5 (0–198)	median 46 (18–80)	102/48 (12 SV + 36 LV)	26	76	Induction	84, SV 21, LV 63		84, SV 21, LV 63	0	4 (biopsy proven)	4 during a relapse	not provided	at last FU 58 (57%), SV 13 (50%) and LV 45 (59%)	32 (31%) patients, 16 (5–145) months after diagnosis	NR	
Salvarani, 2020[19]	Retrospective	1983–2017	Median 19 months (range: 0–28.1 years)	49 (17–85); biopsy 58 (17–84) and angiography 48 (17–85)	191/NR	129 (9 with positive angiogram and positive biopsy)	112	Induction	72	85	12	NR	19/90 vs 1/13 at the altest available FU	NR	NR	NR	NR	NR	

NR: not reported/retrievable.

$p=0.0001$), more patients off therapy (62%vs 32%, $p=0.06$) and less severe disability scores (Rankin 4–6: 8% vs 37%, $p=0.050$) at last follow-up. No significant differences in mortality and frequency of flares were observed between the two treatments. No data comparing the safety of CYC and MMF associated to glucocorticoids in PACNS were reported. No conclusion can be drawn on the administration route of CYC (oral vs intravenous). The quality of evidence was very low and the preselected outcomes were largely underreported.

The available literature does not provide sufficient data to answer the question and derive a recommendation.

Evidence-based Recommendation (PICO 13)
In adults with PACNS, there is uncertainty regarding the optimal induction therapy (CYC or MMF) to be used in conjunction with glucocorticoids.
Quality of evidence: -
Strength of recommendation: -

Expert consensus statement (PICO 13)
In all patients with PACNS, we suggest commencing therapy with either CYC (orally or intravenously delivered) or MMF when an immunosuppressant agent is considered in the induction phase in conjunction with glucocorticoids.
We suggest that the decision to start with CYC and glucocorticoids or MMF and glucocorticoids for initial therapy should be made based on the physician's experience, the severity of the disease and the patient's preferences.
MMF should be considered for maintenance therapy to reduce the toxicity of long-term treatment with CYC.

Secondary prevention

PICO 14: In adults with probable/definite PACNS do antiplatelets versus no antiplatelets improve outcomes?

Analysis of the current evidence. No relevant RCTs were found. Three cohorts were suitable for data extraction and they are summarized in Table 15.[19,20,32] A total amount of 314 PACNS patients were analyzed, including 92 patients taking aspirin and 222 not taking any antiplatelet agent. The predefined outcomes were largely underreported.

Additional information. Three retrospective studies investigated the use of antiplatelet agents in patients with PACNS which was either biopsy- or angiography-proven. The therapy was initiated or continued in 25% to 57.1% of patients at diagnosis, mainly in LV-PACNS.[19,20,32] The efficacy and safety of aspirin were assessed in only one retrospective study at a single center over a 29- to 35-year period (1983–2017).[19] Aspirin was not significantly associated with severe disability (mRS 4–6: 36% vs vs 30%) or mortality (23%vs 23%). There was also no significant difference in

Table 15. PICO 14 summary of data. Therapy: secondary prevention.

Study author, year	Study design	Study duration	Follow-up period	Mean Age	PACNS/ Women (N)	Definite PACNS	Probable PACNS	Treatment type	Treatment		Outcomes						Notes
									ASA + Other antiplatelets	No antiplatelets	Death at 3 months (number/ hazard ratio)	Death at 12 months (number/ hazard ratio)	mRS 0–2 at 3 months (number)	mRS 0–2 at 12 months (number)	Stroke (first or recurrence)	Serious adverse events	
De Boysson et al., 2017[20]	Retrospective	2010–2017	median months 52.5 (0–198)	median 46 (18–80)	102/48 (12 SV + 36 LV)	26	76	Secondary prevention	39 (all LV PACNS)	63	NR	NR	NR	NR	NR	NR	no separate outcomes were provided
Salvarani, 2020[19]	Retrospective	1983–2017	Median 19 months (range: 0–28.1 years)	49 (17–85); biopsy 58 (17–84) and angiography 48 (17–85	191	71	129 (9 with positive angiogram and positive biopsy)	Secondary prevention	41	134	11/47 vs 33/144	not provided; mRS 4-6 17/47 vs 43/144	NR	NR	NR	NR	
Kraemer and Berlit, 2011[32]	Retrospective cohort	2003–2008	NR	42.48 years (median 43, range 11–65 years).	21/13 (6 biopsy positive, 13 angiography positive and 2 angiography negative)	6	13	Secondary prevension	12	9	NR	NR	NR	NR	NR	NR	no separate outcomes were provided

NR: not reported/retrievable.

the prevalence of intracranial hemorrhage depending on aspirin therapy (6.5%vs 13%). Patients taking antiplatelet therapy at diagnosis were more often in long-term remission at last follow-up (34%vs 17%, $p=0.023$). After adjustment for age, aspirin therapy was found to be positively associated with long-term remission (OR 2.59, 95% CI 1.21–5.52, $p=0.013$). The quality of evidence for all reported outcomes was low.

The available literature does not provide sufficient data to answer the question and derive a recommendation.

Evidence based recommendation (PICO 14)
In adults with PACNS, there is uncertainty regarding the routine use of antiplatelets.
Quality of evidence: -
Strength of recommendation: -

Expert consensus statement (PICO 14)
Aspirin may have a beneficial effect in PACNS, which may be due to a combined antithrombotic and anti-inflammatory effect and its possible complementary action with glucocorticoid therapy. In patients with large/medium vessel involvement we suggest including aspirin therapy.

Maintenance

PICO 15: In adults with probable/definite PACNS does long-term immunosuppression versus no long-term immunosuppression improve the outcomes?

Analysis of the current evidence. The literature search identified no relevant RCTs. The extracted data derived from two retrospective case series and they are summarized in Table 16.[19,20] A total amount of 293 PACNS patients was analyzed, including 82 patients receiving maintenance therapy after induction and 211 patients without maintenance therapy after induction.

Additional information. Given the absence of RCTs, we analyzed data from the French Registry[20] and the Mayo Clinic cohort.[19]

De Boysson et al.[20] analyzed clinical outcomes of 112 patients from the French PACNS Registry, who were followed-up > 12 months or who relapsed or died before 12 months. Among the 106 patients, who achieved remission, 52 (46%) received maintenance therapy with an immunosuppressant. As maintenance therapy, 41 patients received azathioprine (2 mg/kg per day), 7 patients received methotrexate (0.3–0.5 mg/kg per week), and 4 patients received MMF (2 g/day). Notably, 45 of these 52 patients continued glucocorticoids in addition to the maintenance therapy. Maintenance therapy was initiated after a median of 4 (3–18) months from glucocorticoid initiation, and 4 and 6 weeks after the last pulses of cyclophosphamide in 2 patients who did not receive glucocorticoids, respectively. The median duration of the immunosuppressive maintenance therapy was 24 (6 –72) months. Maintenance therapy was associated with a significantly better functional status at last follow-up (OR 8.09 (3.24–22.38); $p<0.0001$) and with prolonged remission (odds ratio (OR) 4.32 (1.67–12.19); $p=0.002$).

Salvarani et al.[19] analyzed data from a cohort of 191 consecutive patients with PACNS seen at Mayo Clinic, Rochester, MN, over 35 years with long-term follow-up. Among the 185 patients, who achieved remission, 35 patients (19%) received maintenance therapy; 19 patients received azathioprine (100–200 mg per day), 8 MMF (2–3 g per day) and 5 methotrexate (7.5–20 mg/kg per week). Two patients started oral CYC 50 and 125 mg/day for 18 and 4 months, respectively) and a third patient started infliximab (5 mg/kg for 8 months) after oral cyclophosphamide for 91 months. Maintenance therapy was initiated after a median time of 6 months (range 3–91 months) and continued for a median duration of 17 months (range 4–141 months). Maintenance therapy was associated with a reduced frequency of high disability scores (mRS 4–6) and death (11%vs 37%, $p=0.003$% and 6% vs 27%, $p=0.006$, respectively). The rate of patients achieving long-term remission did not significantly differ between patients with and without maintenance therapy. Relapses were more frequently seen in patients receiving maintenance drugs (46%vs 19%, $p=0.003$), but a possible selection bias for maintenance therapy is present, being patients perceived as more severely affected more frequently treated with maintenance therapy.

Thus, observational data consistently show that long-term immunosuppression improves outcomes. From the available data, the best evidence exists for azathioprine. The available data does not allow an evidence-based recommendation regarding the duration of the maintenance treatment. In the cohorts under investigation, the median duration of maintenance therapies was 24 and 17 months, respectively.

The available literature does not provide sufficient data to answer the question and derive a recommendation.

Evidence-based recommendation (PICO 15)
In adults with probable/definite PACNS there is uncertainty regarding the use of long-term immunosuppression.
Quality of evidence: -
Strength of recommendation: -

Expert consensus statement (PICO 15)
We suggest initiating maintenance therapy when no recurrence has been registered after the induction therapy. We suggest continuing maintenance therapy for at least 2 years before considering cessation in patients without recurrencies.

Table 16. PICO 15 Summary of data. Therapy: maintenance phase.

Study author, year	Study design	Study duration	Follow-up period	Mean Age	PACNS/ Women (N)	Definite PACNS	Probable PACNS	Treatment type [Acute treatment: Induction phase; Secondary prevention; Immunosuppressive Treatment (maintenance phase)]	Treatment		Outcomes						Notes
									Long term immunosuppressive treatment	No treatment	Death at 3 months (number/ hazard ratio)	Death at 12 months (number/ hazard ratio)	mRS 0–2 at 3 months (number)		Stroke (first or recurrence)	Serious adverse events which lead to stopping or changing therapy (adverse event name and number)	
De Boysson et al., 2017[20]	Retrospective	2010–2017	median months 52.5 (0–198); SV 67 (1–198) LV 47.5 (0–188)	median 46 (18–80), SV-PACNS 41.5 (18–61), LV-PACNS 48.5 (19–80)	102/48 (12 SV + 36 LV)	26	76	Maintenance phase	After induction, 48 (47%) patients received maintenance therapy (AZA, MTX and MMF in 38, 6 and 4 cases, respectively)	NR	NR	NR	NR	NR	NR	NR	no separate outcome was provided
Salvarani, 2020[19]	Retrospective	1983–2017	Median 19 months (range: 0–28.1 years)		191/NR	71	129 (9 with positive angiogram and positive biopsy)	Maintenance phase	34	124	2/35 vs 35/131 atthe latest available FU	mRS 4–6 4/35 vs 48/131	not provided	8/35 vs 33/131	16/34 vs 24/125	NR	

NR: not reported/retrievable.

Acute ischemic stroke treatment

PICO 16: In adults with probable/definite PACNS and acute ischemic stroke does intravenous thrombolysis (IVT) versus no IVT improve outcomes?

Analysis of the current evidence. No relevant papers were found.

Additional information. In the absence of an absolute contraindication, intravenous thrombolysis (IVT) with alteplase is the standard of treatment for acute ischemic stroke presenting within 4.5 h of symptom onset and between 4.5 and 9 h after known onset or on awakening from sleep/unknown onset with the use of advanced imaging.[65] Our systematic review identified only two case reports. Ganesalingam et al. administrated IVT to a 63-year-old woman presenting within 105 min of acute onset of right sided weakness.[66] Initial National Institutes of Health Stroke Scale (NIHSS) score was 5 and 24-h NIHSS score was 2. No complications were reported. The patient was subsequently diagnosed with probable cerebral vasculitis with coexisting antiphospholipid syndrome due to the detection of lupus anticoagulant, anticardiolipin and beta-2 glycoprotein antibodies. Dziadkowiak et al.[67] published the case report of an 89-year-old woman presenting with left middle cerebral artery (MCA) occlusion and a NIHSS score of 14, and who received combined treatment with IVT and endovascular thrombectomy (EVT). No significant clinical improvement or complication were reported. Based on subsequent MRI demonstrating homogenous. intense enhancement of the thickened arterial wall on T1-weighted images, the authors made a diagnosis of probable PACNS.

Most CNS complications in cerebral vasculitis, including acute ischemic stroke, arise from endothelial damage, hypercoagulability, and inflammation, therefore IVT, at least theoretically, may augment resolution of the hyperthrombotic state.[68]

The available literature does not provide sufficient data to answer the question and derive a recommendation. Therefore, the ESO/ESMINT guideline framework[65,69,70] is reasonable in this situation too.

Evidence-based recommendation (PICO 16)
In adults with probable/definite PACNS and acute ischemic stroke there is uncertainty regarding the use of IVT.
Quality of evidence: -
Strength of recommendation: -

Expert consensus statement (PICO 16)
IVT has been proven to be a powerful and safe treatment for acute ischemic stroke, and in the absence of absolute contraindications, we suggest considering IVT even in patients with a history of PACNS presenting with symptoms of acute ischemic stroke.,
In the absence of relevant data, we suggest adherence to the inclusion and exclusion criteria for IVT as per acute ischemic stroke.

PICO 17: In adults with probable/definite PACNS and acute ischemic stroke does endovascular thrombectomy (EVT) versus no EVT improve the outcomes?

Analysis of the current evidence. No relevant papers were identified.

Additional information. Our systematic review identified only one case report. This case was treated with combination of IVT and endovascular thrombectomy (EVT) without clinical improvement nor complications, as was described in the IVT section.[67] Therefore, we decided to broaden our search to other types of vasculitis potentially affecting CNS. Regarding giant cell arteritis, we found case reports and systematic literature reviews which all referred to non-acute treatment of intracranial stenoses with percutaneous transluminal angioplasty as feasible but often requiring repeated intervention over time.[71,72] Mangiardi et al.[73] reported the case of a male patient with acute stroke due to a right T occlusion treated by IVT and EVT (thromboaspiration of the MCA and anterior cerebral artery occlusions, and stenting of the internal carotid artery (ICA)) with early ICA reocclusion. The final diagnosis was Takayasu arteritis.

However, caution should be taken when using HRVWI-MRI to investigate intracranial arteries after EVT, because smooth concentric arterial wall thickening and enhancement at the occlusion site have been reported, in particular after stent-retriever devices, up to 11 of 14 patients (79%) within 3 months from EVT.[74]

The available literature does not provide sufficient data to answer the question and derive a recommendation. Therefore, the ESO/ESMINT guideline framework is reasonable in this situation too.[65,69,70]

Evidence-based recommendation (PICO 17)
In adults with probable/definite PACNS and acute ischemic stroke there is uncertainty regarding the use of EVT.
Quality of evidence: -
Strength of recommendation: -

Expert consensus statement (PICO 17)
Since large vessel occlusion is typically associated with devastating strokes and that in the hyperacute phase, a different cause for the LVO-related stroke cannot be excluded, even in patients with known PACNS, we suggest that EVT is reasonable in patients with a history of PACNS presenting within the early or extended (by using advanced imaging) time windows for EVT.

Discussion

PACNS is a rare disease whose diagnosis is particularly challenging due to the lack of biological, clinical, and neuroradiological signs with adequate specificity. The definition of

PACNS implies the availability of neuropathological confirmation for the transmural inflammatory infiltrate in the cerebral, spinal or leptomeningeal vessels, but, in practice, this is relatively infrequently available for diseases of the CNS. Indeed, the current diagnostic criteria have several limitations, starting from the lack of validation available at the time when they were proposed. Indeed, Birnbaum and Hellmann[2] proposed in 2009 a narrative update of the original criteria from Calabrese and Mallek published in 1988[3] aiming to improve the differential diagnosis with RCVS. Moreover, the original diagnostic criteria were derived in a historical era in which diagnostics were based on much more limited technologies than the currently.[3] The few cases (8 new cases and 40 cases derived from already published papers) described by the authors[3] had brain CT as the main tool for neuroimaging diagnosis. Birnbaum and Hellmann[2] did not provide evidence that can substantially modify the previous criteria but added MRI as standard diagnostic technique. The introduction of MRI was driven by the technological evolution but was not associated with a definition and standardization of technological features, description of imaging patterns and analysis of diagnostic performance of different combinations of techniques. Vascular imaging has since undergone great technological improvements in general, mainly for the application in other more frequent diseases, as stroke, inflammatory neurological disease, epilepsy, and brain tumors, but not specifically for PACNS. Finally, the diagnostic criteria currently in use derive from a diagnostic era in which the existence of different subtypes of PACNS was not anticipated. More recently, progress in neuroimaging techniques has made it possible to define with greater precision the two main PACNS subtypes (SV and LV-PACNS) overlapping to some degree with the categories of biopsy-proven and angiography-proven PACNS, respectively. These two subtypes are not necessarily mutually exclusive; rather they are probably two extremes of a spectrum. The simultaneous and concurrent development of cerebrovascular diagnostics oriented toward the endovascular treatment of acute stroke has also allowed for greater attention and standardization on the angiographic side (DSA) with special attention given to medium-sized vessels.[57,75] This has also led to a better definition of medium size vessels than of small vessels. Therefore, those that until just over 10 years ago, even in the main case series, as the French registry[20] and the Mayo Clinic cohort,[19] were called small vessels are actually medium size vessels. It is likely that, ultimately, this evolution may lead to improved subtyping of PACNS with implications for patient management. At present however, there are no studies specifically addressing the application and diagnostic performance of MRA or CTA in PACNS patients in comparison with DSA, which remains the gold standard technique. The lack of validation of MRA versus DSA in PACNS and the total lack of information about CTA in PACNS patients should suggest caution in using any reported findings to underpin critical clinical decisions. The diagnosis of SV-PACNS does not include a probability or possibility criterion using non-invasive or minimally invasive techniques, but requires histopathology. This limitation probably leads to an underdiagnoses of this subtype and, in clinical practice, to the use of immunosuppressive therapy in patients without histopathological diagnosis but on the basis of the clinical and neuroimaging picture, which remain nonspecific not only in the distinction between SV- and LV-PACNS, but in particular in differentiating the many cerebrovascular diseases that affect the small vessels. Although the development of HRVWI-MRI is promising, it is not validated and has not been formally compared to other diagnostic techniques in patients with PACNS. Notably, it does not have a histopathological validation, and it does not differentiate between primary and secondary vasculitis and may have difficulty reliably identifying vasculitis from atherosclerosis which is, of course, extremely common. Indeed, the classic patterns of wall enhancement for single disease (eccentric, concentric or mixed) are present a variable percentage of cases (7% of patients with vasculitis have an eccentric pattern).[76] From the technical point of view, it is complex to compare the sensitivity of different machines and settings in different periods and these details, except in rare cases, are not reported.

The diagnostic criteria of Birnbaum and Hellmann[2] associated CSF abnormalities with probable PACNS (i.e. LV-PACNS), but CSF changes are now recognized to be nonspecific and normal ranges may vary according to age, gender and comorbidities. However, CSF analysis, may be critical in the consideration of other conditions included in the differential diagnosis, but this aspect has not been standardized in an accepted management pathway.

Surprisingly for a disease affecting the cerebral vessels, stroke and stroke patterns are largely underreported. Even when the differentiation between single and multiple ischemic lesions has been reported, one of the potential pitfalls is the lack of consideration of the presence of multiple infarcts in a single vascular territory with proximal vessel stenosis (or wall enhancement) versus multiple lesions in multiple vascular territories. This issue may go some way to explaining the apparently conflicting data in the literature, in particular in differentiating SV-PACNS and LV-PACNS according to neuroimaging features.

The need emerges for an evaluation by an expert multidisciplinary team with a specific background on the disease and its management, starting from the diagnosis and the differential diagnosis and concluding the path with the therapeutic choices. The treatment approach is also substantially devoid of evidence of sufficient strength and quality and it is based on the application to patients with PACNS of the same treatment strategies with the same drugs and similar timing that are currently used for the treatment of systemic vasculitis. However, it follows that the therapeutic choices, both in the induction and in the maintenance phase, are widely variable, so much so that they are not comparable between studies, not even allowing defining in an evidence-based manner

the superiority of immunosuppressive therapy associated with glucocorticoids compared with glucocorticoids alone. The most obvious bias is that the therapeutic choices made individually are affected by factors that are not clearly identifiable, both on the part of the patient and that of the treating physician. A relevant issue is the timing of therapy, both for the induction and for the maintenance phase and a shared and common timeframe is not provided in most papers.

It is surprising to find that the outcomes relating to the level of independence and the occurrence of vascular events in the follow-up are largely underreported in the available literature. Equally scarce is information on the role of classic vascular risk factors in patients with PACNS, how they vary with time and how to optimize secondary prevention for cerebrovascular events, including antiplatelet therapy.

In conclusion, PACNS is a rare disease whose diagnostic criteria are commonly used but poorly validated with knock-on effects on how the diagnosis is reached and the therapeutic choices made in clinical practice. SV-PACNS and LV-PACNS are probably the two extremes of a range including also an overlapping category, which may be provisionally identified in the isolated involvement of medium size vessels. The two subtypes may have different diagnostic findings, in particular in neuroimaging techniques, and different natural history and response to treatment. Accurate diagnosis is crucial to define the population requiring longer term immunosuppressive treatment, taking into account the potential benefit and side effects (both immediate and longer-term toxicity) of each agent. Overall, there is a glaring lack of fundamental information that would only be provided by international studies and trials undertaken with meticulous planning and standardized application of patient descriptors, disease definition and classification, implementation of diagnostic tools, therapeutic interventions and reporting of outcomes and follow up. Until these can be completed, patients and clinicians should be supported in complex management decisions with input from a multidisciplinary team with relevant expertise and /or an expert in the diagnosis and management of PACNS.

Lay summary

Primary Angiitis of the Central Nervous System (PACNS) is a rare disease affecting intracranial vessels of different size, from large to small arteries. The hallmark of the disease is the inflammation disrupting the vessel wall. Unfortunately, this can be ascertained only by examining a piece of brain through a biopsy, but it is not a procedure that can be offered to all patients. Without this information, it is possible to define a probability of the diagnosis using other investigations, as stated in the current diagnostic criteria. These criteria were proposed several years ago, when bot the knowledge of the diseases and the diagnostic performance were different and hopefully lower than nowadays. When we made a diagnosis of probable PACNS, it means that an angiographic study of the brain vessels demonstrated the involvement of several arteries of large and medium in a pattern highly suggestive for PACNS. The gold standard technique for the study of these vessels is catheter angiography or Digital Subtraction Angiography (known as DSA). When we made a diagnosis of definite PACNS, it means that the examination of the brain sampled by biopsy showed the inflammation of the vessels. The diagnosis is challenging because several diseases may affect the brain and the brain arteries and their clinical presentation and findings on investigations are similar. In these situations, the hypothesis of PACNS is often considered, but its diagnosis has a strong impact on treatment choices. The diagnostic pathway should be coordinated by a physician with a dedicated background on the disease and a multidisciplinary team evaluation is suggested to improve the consistency of diagnosing PACNS and differentiating other diseases. The treatment is based on glucocorticoids, often associated to immunosuppressant drugs, starting from the induction therapy, but a continuous uncertainty exists about the efficacy of different strategies. Several information is lacking on the course for the disease with different therapies. These guidelines aimed to review and summarize the existing evidence in order to help clinician in the routine management of patients with PACNS.

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Supplemental material

Supplemental material for this article is available online.

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