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ESO Guideline on Primary Central Nervous System Angiitis (PACNS)

Rosario Pascarella, Katherina Antonenko, Grégoire Boulouis, Hubert De Boysson, Caterina Giannini, Mirjam R. Heldner, Odysseas Kargiotis, Thanh N. Nguyen, Claire M. Rice, Carlo Salvarani, Antje Schmidt-Pogoda, Daniel Strbian, Salman Hussain, Marialuisa Zedde

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None relevant for the topic

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Module Working Group Members

Pascarella Rosario
Italy

Antonenko Katherina
Ukraine

Boulouis Grégoire
France

De Boysson Hubert
France

Giannini Caterina
USA

Heldner Mirjam R.
Switzerland

Kargiotis Odysseas
Greece

Nguyen Thanh N.
USA

Rice Claire M.
UK

Salvarani Carlo
Italy

Schmidt-Pogoda Antje
Germany

Strbian Daniel
Finland

Hussain Salman
Czech Republic

Zedde Marialuisa
Italy

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Background

Definition and epidemiology

- Primary angiitis of the central nervous system (PACNS) is a subtype of vasculitis with isolated involvement of the central nervous system (CNS).
- The diagnosis may be challenging at three overlapping levels: neuropathological, neuroimaging and clinical.
- Incidence: 2.4 cases per 1000000 persons/year
- M/F ratio 1:1
- Median age at diagnosis: 50 years

Diagnostic criteria

Calabrese and Mallek 1988

(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.

Birnbaum and Hellmann 2009

- "Definite" PACNS if histopathological confirmation
- "Probable" PACNS if a high-probability angiogram (DSA) is associated with abnormal findings on MRI and CSF profile consistent with PACNS.

Limitations

- No strong data support the current diagnostic criteria
- Angiography-proven PACNS and biopsy-proven PACNS refer to large and medium-sized vessel involvement (LV-PACNS) and small vessel involvement (SV-PACNS), respectively
- The involvement of medium-sized vessels is a neglected issue
- New technologies and new differential diagnoses

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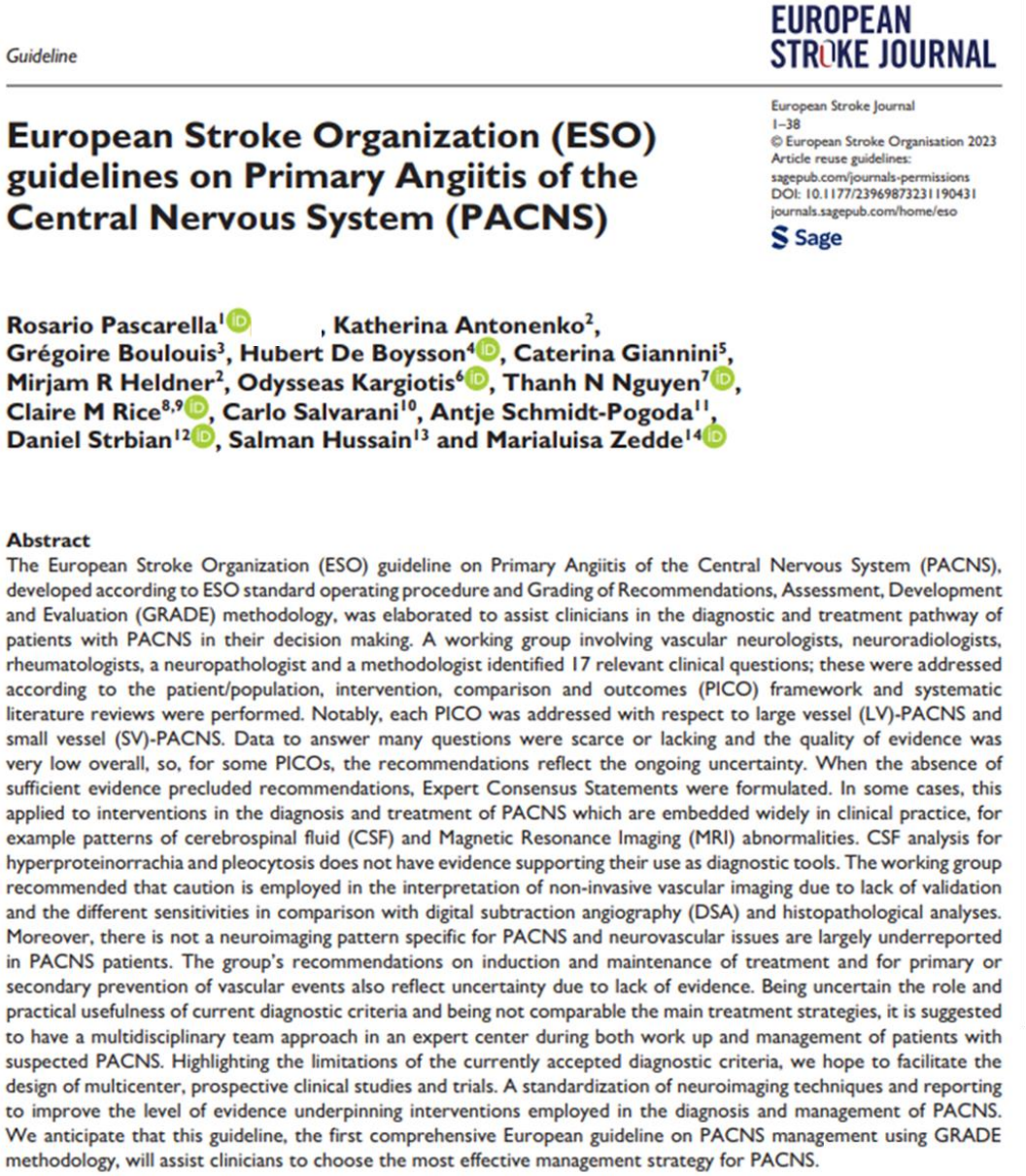
Why a guideline on PACNS?



Guideline

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

Rosario Pascarella[1], Katherina Antonenko[2], Grégoire Boulouis[3], Hubert De Boysson[4], Caterina Giannini[5], Mirjam R Heldner[2], Odysseas Kargiotis[6], Thanh N Nguyen[7], Claire M Rice[8,9], Carlo Salvarani[10], Antje Schmidt-Pogoda[11], Daniel Strbian[12], Salman Hussain[13] and Marialuisa Zedde[14]

Abstract

The European Stroke Organization (ESO) guideline on Primary Angiitis of the Central Nervous System (PACNS), developed according to ESO standard operating procedure 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 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.

Challenges in diagnosis and management

- The definite diagnosis therefore requires histopathological confirmation, but this is particularly challenging for CNS
- The risk/ benefit ratio of an invasive surgical procedure which may return a non-diagnostic or false-negative biopsy needs to be carefully considered
- The increasing development and availability of non- or minimally invasive techniques means that the historical diagnostic criteria are not always fully adhered to
- 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
- Many areas regarding the diagnosis and management of PACNS lack of standardization and clinical evidence

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

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ESO Standard Operating Procedures

- P of the PICO is ‘probable’ and ‘definite’ PACNS
- Formulation of 17 main PICO questions focusing on accuracy of diagnostic techniques, differential diagnosis of PACNS subtypes, and the efficacy of treatment regimens
- The diagnostic PICOs were divided according to the techniques suggested by the diagnostic criteria:
  - CSF
  - neuroimaging findings
  - histopathological abnormalities
- The therapeutic PICOs were divided into:
  - disease-specific treatment (acute and maintenance therapy),
  - secondary prevention
  - acute stroke
- No RCT is available, but there are only small retrospective case series covering a wide years range

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ESO Standard Operating Procedures

- The MWG focused on "**probable**" and "**definite**" PACNS as defined by the Birnbaum and Hellmann criteria, 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)

The **high probability angiographic pattern** was defined as follows *[J Rheumatol 1995; 22: 662–667]*:

- 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

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.

Remission was defined as the absence of relapse within 6months after first-line therapy.

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 definition of "**induction**" therapy was agreed as treatment in the acute phase. "**Maintenance**" therapy was defined as therapeutic interventions made after induction therapy.

Unfortunately, the timing of induction and maintenance therapy tended to be poorly defined and highly variable, so the MWG agreed to not consider these.

J Neurol 2019; 266: 1481–1489

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PICO 1: In adults with suspected PACNS, does CSF analysis for pleocytosis and hyperproteinorrhachia vs no CSF analysis improve the diagnostic accuracy?

Evidence-based Recommendation

In adults with suspected PACNS, there is uncertainty over the utility of CSF examination for pleocytosis and/or hyperproteinorrhachia as a diagnostic tool. This is due to the lack of specific comparative studies and to the heterogeneous data, regarding the diagnostic procedures and populations in the available studies.

Quality of evidence: -

Strength of recommendation: -

Expert Consensus Statement

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 and normal CSF analyses cannot, by themselves, exclude the diagnosis of PACNS.

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PICO 1: In adults with suspected PACNS, does CSF analysis for pleocytosis and hyperproteinorrhachia vs no CSF analysis improve the diagnostic accuracy?

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

PICO 1: In adults with suspected PACNS, does CSF analysis for pleocytosis and hyperproteinorrhachia vs no CSF analysis improve the diagnostic accuracy?

- 17 papers (case series and cross-sectional studies) on 763 PACNS patients
- Lumbar puncture was performed in 588/763 (77%) patients
- CSF data were provided in 508/588 (86%) of patients who underwent a lumbar puncture
- The overall rate of positive CSF findings in PACNS patients was 77.8% (395/508), distributed as pleiocytosis in 46% and hyperproteinorrhachia in 70% of patients

- Different thresholds for hyperproteinorrhachia: CSF protein > 45 mg/dl, > 50 mg/dl, > 80 mg/dl
- The diagnosis cannot be excluded or regarded as unlikely when CSF white blood cell counts are less than 5/mcl.
- 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 (95% CI 24.0 - 93.4 mg/dl; range, 14.0-148.0 mg/dl) *[Mayo Clin Proc 2023; 98: 239-251]*

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

Evidence-based Recommendation

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. This is due to underreporting and lack of specific comparative studies, as well as heterogeneity in the neuroimaging techniques employed and data reported in the available studies.

Quality of evidence: -

Strength of recommendation: -

Expert Consensus Statement

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

- 18 studies
- 660 patients
- wide time range (1987 to 2020)
- 230 ‘definite’ PACNS, predominantly SV-PACNS (226)
- 303/398 patients with ‘probable’ PACNS had LV-PACNS

- acute ICH/SAH	90/660 (13.6%)
- tumefactive pattern (t-PACNS)	27/660 (4.1%)
- multiple acute/subacute ischemic lesions	135/660 (20.45%)
- single acute/subacute ischemic lesion	42/660 (6.36%)
- SVD pattern (according to the STRIVE criteria)	58/660 (8.79%)
- parenchymal contrast enhancement	135/660 (20.45%)
- spinal cord involvement	5/660 (0.76%)

- 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
- No neuroimaging pattern (including tPACNS) was reported to be indicative of a subtype of PACNS
- Whilst pre-biopsy parenchymal enhancement was positively associated with biopsy-proven PACNS compared with DSA-diagnosed patients (60% versus 23%; P=0.001), a potential selection bias was that contrast enhancement was a criterion for biopsy.

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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?

Evidence-based Recommendation

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 Statement

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 comparable to MRA if multislices (>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 does not show compatible neuroimaging features.

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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?

- 5 papers
- 186 patients with PACNS

- 109/186 (58.6%) underwent DSA
- 122/186 (65.6%) MRA or CTA

- Direct comparison MRA (1.5T and 3T) vs DSA in 31 patients
- Among the 25/31 patients (81%) with abnormal DSA findings, all but one had changes 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)
- Detection of vessel stenosis in predefined segments of the large intracranial vessels, rather than detection of the high probability angiographic pattern

[Am J Neuroradiol. 2017 Oct;38(10):1917-1922]

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

Evidence-based Recommendation

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 ↑?

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

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.

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

- 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
- There is one study directly comparing MRA and DSA in a small sample of 31 patients from the French registry, but the comparison focused on stenosis and not on the high probability pattern and the definition of DSA and MRA findings was “abnormal” vs “normal” without further grading of the “abnormal” category
- 24/25 false negative MRA segments could be defined as “medium sized vessels” and MRA had 7 false positive segments too
- Atherosclerosis is 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
- The “high probability angiographic pattern” was originally proposed for a broader differential diagnosis, including atherosclerosis, than the one outlined by the Birnbaum and Hellmann’s criteria

AJNR 2017; 38: 1917–1922

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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 the diagnostic accuracy?

Evidence-based Recommendation

In adults with probable LV-PACNS, there are insufficient data on HRVWI-MRI to determine whether the technique improves the diagnostic accuracy of PACNS when used with DSA

Quality of evidence: -

Strength of recommendation: -

Expert Consensus Statement

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 unique neuroimaging modality supporting the diagnosis of PACNS.

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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 the diagnostic accuracy?

- 3 papers
- 73 patients with PACNS [29 (40%) with LV-PACNS], included between 2009 and 2020
- All described vessel wall enhancement (VWE) as the main finding, co-localizing with MRA/DSA arterial stenoses when present
- 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
- Selection bias (availability of HRVWI-MRI)
- 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.

PICO 9: In adults with definite PACNS, does the presence of MRI leptomeningeal enhancement (LME) vs positive biopsy findings change the diagnostic accuracy?

Evidence-based Recommendation

In adults with definite PACNS there is persistent uncertainty regarding the effect on diagnostic accuracy of the presence of MRI leptomeningeal enhancement (LME).

Quality of evidence: -

Strength of recommendation: -

Expert Consensus Statement

Although a very low quality of evidence, we suggest proceeding to biopsy where there is clinical suspicion of PACNS, LME and normal findings on DSA.
If there is no LME, we suggest that targeted biopsy of gadolinium-enhanced lesions may increase the diagnostic accuracy of the biopsy in comparison to blind biopsy

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PICO 9: In adults with definite PACNS, does the presence of MRI leptomeningeal enhancement (LME) vs positive biopsy findings change the diagnostic accuracy?

- 2 descriptive cohorts with available information regarding the neuroimaging features of biopsy-proven PACNS patients
- 203 PACNS patients were analyzed and LME was reported in 33/203 patients (16.3%)

- Two main limitations explain the low level of evidence

  - Information regarding GBCA administration is not provided in all studies.
  - In patients with LME and positive biopsy, information regarding the location of the sample, i.e. whether the biopsy was guided on a LME and whether the biopsy collected meningeal and/or brain tissue, is often lacking, precluding any precise analysis of the link between LME and the biopsy result.

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PICO 12: In adults with probable/definite PACNS, does using glucocorticoids + any further immunosuppressive drug vs glucocorticoids alone improve outcome?

Evidence-based Recommendation

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

Given the potential severity of PACNS, the relapsing course of the disease, and the well-known glucocorticoid-related toxicity, we suggest consideration of adding an immunosuppressant to glucocorticoid therapy in most patients with PACNS.
We also suggest that in milder disease phenotypes, use of glucocorticoids alone might be discussed in a multidisciplinary team with relevant expertise and/or an expert in the diagnosis and management of PACNS.

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PICO 12: In adults with probable/definite PACNS, does using glucocorticoids + any further immunosuppressive drug vs glucocorticoids alone improve outcome?

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	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)	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.

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PICO 12: In adults with probable/definite PACNS, does using glucocorticoids + any further immunosuppressive drug vs glucocorticoids alone improve outcome?

- The literature search identified no relevant RCTs
- 4 papers suitable for data extraction
- 357 PACNS patients
- 181/357 (50.7%) had definite PACNS
- 207/357 (58%) had combined therapy with glucocorticoids and immunosuppressants
- 29/357 (8.1%) had glucocorticoids alone
- The predefined outcomes were largely underreported
- 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
- There is also a possible selection bias regarding mild disease phenotypes treated with corticosteroids alone versus more aggressive presentations treated with combinations treatment

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

Evidence-based Recommendation

In adults with PACNS, there is uncertainty regarding the routine use of antiplatelets.

Quality of evidence: -

Strength of recommendation: -

Expert Consensus Statement

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.

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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.

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

- 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
- 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)
- 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 the prevalence of intracranial hemorrhage (6.5%vs 13%)
- 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

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

Evidence-based Recommendation

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

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.

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

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.

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

- The extracted data derived from two retrospective case series providing 293 PACNS patients, including 82 patients receiving maintenance therapy after induction and 211 patients without maintenance therapy after induction
- French cohort: among the 106 patients, who achieved remission, 52 (46%) received maintenance therapy with an immunosuppressant (41 pts azathioprine 2 mg/kg per day, 7 pts methotrexate 0.3–0.5 mg/kg per week, 4 pts MMF 2 g/day) and 45/52 continued glucocorticoids in addition to the maintenance therapy
- Mayo Clinic cohort: among the 185 patients, who achieved remission, 35 (19%) received maintenance therapy (19 pts azathioprine 100–200 mg/die, 8 pts MMF 2–3 g/die, 5 pts methotrexate 7.5–20 mg/kg/week, 2 pts oral CYC, 1 pt infliximab 5 mg/kg after oral)
- Observational data consistently show that long term immunosuppression improves outcomes
- The best evidence exists for azathioprine
- The available data do 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)

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Conclusion

- This is the first international multidisciplinary guideline on PACNS
- The current diagnostic criteria have several limitations and this issue was addressed in detail
- The quality of the evidence is very low
- No dedicated neurovascular approach emerges in analyzing the data
- Neuroimaging information on acquisition, findings and reporting for different techniques is rarely reported and it makes the data not comparable
- New techniques (e.g. HRVWI-MRI) are promising, but they needs to be validated and standardized
- DSA is still the gold standard for large and medium-sized vessel imaging
- The outcomes are largely underreported

Areas of future research

Primary/secondary prevention of Stroke

- Indications and benefit for antithrombotic treatment
- Role of the control of ‘classical’ vascular risk factors
- SV-PACNS vs LV-PACNS

Diagnosis

- Updated criteria according to technological improvement (but DSA remains the gold standard techniques for large and medium-sized vessels)
- Updated criteria according to a wide range of differential diagnosis
- Search for new CSF markers (diagnosis, pathogenesis, prognosis)
- Medium-sized vessel involvement as a distinct category
- Definition of an updated and standardized diagnostic pathway

Treatment

- RCTs for induction and maintenance therapy (SV-PACNS vs LV-PACNS)
- Treatment of vascular risk factors

Prognosis

- Consistent information on long-term prognosis
- Consistent information on the cerebrovascular outcome

Patients often have several diseases simultaneously and diagnostic criteria have to consider it
Rare and frequent diseases may cohabit, but also more than one rare disease may be present in the same individual

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ESO Guideline on Primary Central Nervous System Angiitis (PACNS)

Rosario Pascarella, Katherina Antonenko, Grégoire Boulouis, Hubert De Boysson, Caterina Giannini, Mirjam R. Heldner, Odysseas Kargiotis, Thanh N. Nguyen, Claire M. Rice, Carlo Salvarani, Antje Schmidt-Pogoda, Daniel Strbian, Salman Hussain, Marialuisa Zedde

Thanks for your attention