

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa.

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Dr. Archer was employed by Northwestern University while she was involved in this project but resigned from the project in March 2020, when she took a position at Janssen, her current employer. Janssen had no financial or other interest in this project and had no input in the design, content, data collection, or analysis, and had no role in the writing or approval of this article, with all opinions and conclusions expressed herein those of the authors.

8 2021 08 7 2021 73 8 494426 1384 1393 01 08 2025 05 08 2025 05 08 2025 06 08 2025 This file is available for text mining. It may also be used consistent with the principles of fair use under the copyright law. **OBJECTIVE:** To provide evidence-based recommendations and expert guidance for the management of patients with systemic polyarteritis nodosa (PAN).

Twenty-one clinical questions regarding diagnostic testing, treatment, and management were developed in the Patient population, Intervention, Comparator, and Outcome (PICO) question format for systemic, non-hepatitis B-related PAN. Systematic literature reviews were conducted for each PICO question. We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology to assess the quality of evidence and formulate recommendations. Each recommendation required consensus from at least 70% of the voting panel.

We present 16 recommendations and 1 ungraded position statement for PAN. Most recommendations are graded as “conditional” due to the paucity of evidence. These recommendations support early treatment of severe PAN with cyclophosphamide and glucocorticoids, limiting toxicity through minimizing long-term exposure to both cyclophosphamide and glucocorticoids, and the use of imaging and tissue biopsy for disease diagnosis. These recommendations endorse minimizing risk to the patient by using established therapy at disease onset, and also identifying new areas where adjunctive therapy may be warranted.

These recommendations provide guidance regarding diagnostic strategies, use of pharmacologic agents, and imaging for patients with PAN.

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that affects primarily medium-sized vessels [1]. Patients frequently present with systemic symptoms such as fever and weight loss, and the most common clinical presentations include neurologic manifestations such as mononeuritis multiplex and peripheral neuropathy, cutaneous manifestations such as nodules and livedo, renal manifestations including hypertension, and gastrointestinal manifestations including abdominal pain [2]. Diagnosis is generally confirmed by tissue biopsy of an affected organ, or angiography if tissue biopsy cannot be obtained. Typical histologic findings include mixed cell inflammatory infiltrates in the vessel wall and fibrinoid necrosis, with an absence of granulomas and giant cells.[3] Findings on angiography include saccular or fusiform aneurysms and stenotic lesions in the mesenteric, hepatic, and renal arteries and their subsequent branches. Although PAN is becoming increasingly rare due to the prevention of hepatitis B viral (HBV) infection,[3] it remains a potentially devastating diagnosis, with severe PAN having a mortality rate of 40% at 5 years.[3]

Given increasing options available to treat systemic vasculitis, the American College of Rheumatology and Vasculitis Foundation are supporting the development of guidelines for the management of large-, medium-, and small-vessel vasculitis. This report presents evidence-based recommendations for the diagnostic testing, treatment, and management of PAN as an exemplar of medium-vessel vasculitis. Of note, these guidelines focus on systemic PAN. Since HBV-associated PAN as well as cutaneous PAN are generally managed differently from systemic idiopathic PAN, they are excluded from this guideline.

Although this guideline may inform an international audience, these recommendations were developed considering the experience with and availability of treatment and diagnostic options in the United States (US) and are intended for rheumatologists within the US.

This guideline follows the ACR guideline development process (<https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines>) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence and develop recommendations.[4 , 5] ACR policy guided management of conflicts of interest and disclosures (<https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis>). Supplementary Appendix 1 presents a detailed description of the methods. Briefly, the Literature Review team undertook systematic literature reviews for pre-specified questions specifying the clinical population, intervention, comparator, and outcomes (PICO). An in-person Patient Panel of 11 individuals with different types of vasculitis, which included one participant with PAN, moderated by a member of

the Literature Review team, reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives and preferences. The expert panel provided expert knowledge to inform discussion of the PICO questions and findings of the literature review. The Voting Panel, comprised of nine adult rheumatologists, five pediatric rheumatologists, and 2 patients, reviewed the Literature Review team's evidence summaries and, bearing in mind the Patient Panel's deliberations, formulated and voted on recommendations. At least 70% consensus was required to obtain a recommendation.

How to interpret the recommendations: A strong recommendation is typically supported by moderate or high-quality evidence (e.g., multiple randomized controlled trials). For a strong recommendation, the recommended course of action would apply to all or almost all patients. Only a small proportion of clinicians/patients would not want to follow the recommendation. In rare instances, a strong recommendation may be based on low or very low certainty evidence. For example, an intervention may be strongly recommended if it is considered low-cost, without harms, and the consequence of not performing the intervention may be catastrophic. An intervention may be strongly recommended against if there is high certainty that the intervention leads to more harm than the comparison with low or very low certainty about its benefit [6].

A conditional recommendation is generally supported by lower quality evidence or a close balance between desirable and undesirable outcomes. For a conditional recommendation, the recommended course of action would apply to the majority of the patients, but the alternative is a reasonable consideration. Conditional recommendations added always warrant a shared decision-making approach. We specify conditions under which the alternative may be considered.

In some instances, the committee found that the evidence for a particular PICO question did not support a graded recommendation or did not favor 1 intervention over the other. However, the voting panel believed the PICO question addressed a commonly encountered clinical question and thus felt that providing guidance for this question was warranted. For these situations, we present 'ungraded position statements' which reflects general views of the voting panel.

In this evidence-based guideline, we explicitly use the best evidence available and present that in a transparent manner for the clinician reader/user [7]. In some instances, this includes randomized trials directly comparing the interventions under consideration. The GRADE system rates evidence that comes exclusively from the collective experience of the Voting Panel and patient panel members as "very low quality" evidence.

For each recommendation, Supplementary Appendix 2 provides details regarding the PICO questions and the GRADE evidence tables.

For the evidence report, the Literature Review team summarized 127 articles to address 21 PICO questions for PAN.

The following recommendations and ungraded position statements are for systemic PAN, and do not apply to isolated cutaneous or HBV-related PAN. Table 1 presents definitions of selected terms used in the recommendations, including definitions of severe and non-severe disease as well as dosing ranges for glucocorticoids. Table 2 presents the recommendations with their supporting PICO questions and level of evidence. Figure 1 provides key recommendations for the treatment for PAN. Of note, all but one of the recommendations are conditional primarily due to lack of high-quality evidence (e.g., randomized controlled trials) supporting the recommendation.

A. Vascular imaging, tissue biopsy, and diagnostic testing: Recommendation 1: In patients with suspected PAN, we conditionally recommend using abdominal vascular imaging to aid in establishing a diagnosis and determining the extent of the disease.

Evidence for the use of routine diagnostic imaging is limited with no comparative trials available. In single arm studies performed when diagnostic criteria for PAN were not well defined, vascular imaging, in tandem with clinical signs and pathology, helped validate the diagnosis[8], and determine disease severity.[9] This in turn can influence treatment decisions. Moreover, obtaining vascular imaging at disease onset facilitates identification of new vascular involvement during relapses. Vascular imaging may not be warranted if patients present with isolated findings such as mononeuritis multiplex or myopathy, or if there are no clinical features suggestive of abdominal arterial involvement (such as absence of gastrointestinal or genitourinary symptoms including renovascular hypertension). For children, clinicians should be mindful of minimizing repeated radiation exposure.

Clinicians currently use both conventional catheter-based dye angiography and non-invasive methods such as computed tomography or magnetic resonance angiography (CTA or MRA) to diagnose PAN.[10 – 12] Conventional angiography is the current gold standard due to its ability to provide better resolution but can be associated with complications, albeit at a very low rate.[13 , 14] However, the resolution for non-invasive modalities is improving, and CTA or MRA may provide additional information regarding the vessel wall that conventional angiography does not. Specifically, CTA may be able to visualize more of the distal branches of the mesenteric arteries than MRA, but MRA may be preferred in certain clinical situations (e.g., need to avoid iodinated contrast). In patients with a negative CTA or MRA but a high degree of suspicion for abdominal involvement, it is reasonable to consider conventional angiography.

Recommendation 2: In patients with a history of severe PAN with abdominal involvement who become clinically asymptomatic, we conditionally recommend follow-up abdominal vascular imaging.

Follow-up imaging permits assessment of disease control and treatment response. In the view of the voting panel, follow-up imaging is particularly important when baseline imaging demonstrates aneurysmal disease. The timing of follow-up imaging is dependent, in part, on clinical factors, such as the extent and severity of vascular abnormalities, overall disease course, and response to therapy. However, indefinite routine vascular imaging should be avoided if the abdominal vascular disease is shown to be quiescent.

Recommendation 3: In patients with suspected PAN involving the skin, we conditionally recommend obtaining a deep skin biopsy (i.e., a biopsy reaching the medium sized vessels of the dermis) over a simple/superficial skin punch biopsy to aid in establishing a diagnosis.

Indirect evidence (found in non-randomized studies, or studies in which findings were not primary aims) suggests that evaluation of deeper tissue is more effective at establishing the diagnosis of PAN.[15 , 16], since deeper tissue sample more likely captures a medium vessel. A deep skin biopsy can be performed by a dermatologist as a deep (or “double”) punch biopsy and does not necessarily require invasive resection. This recommendation had strong support from the voting panel but remains conditional due to limited evidence.

Recommendation 4: In patients with suspected PAN and peripheral neuropathy (motor and/or sensory), we conditionally recommend obtaining a combined nerve and muscle biopsy over nerve biopsy alone to aid in establishing a diagnosis.

Several studies suggest an increased yield with nerve and concurrent muscle biopsy as opposed to nerve biopsy alone.[15 – 20] However, the biopsy should sample involved tissue and not be performed “blind” (i.e., sampling tissue that does not appear to be clinically affected). Of note, biopsy of an affected purely sensory nerve (e.g., sural nerve) is favored to avoid motor deficits.

Recommendation 5: In patients with a history of peripheral motor neuropathy secondary to PAN, we conditionally recommend serial neurologic exams instead of repeated electromyography/nerve

conduction studies (e.g., every 6 months) to monitor disease activity.

This recommendation is based on the opinion of the voting panel due to a lack of published evidence addressing the issue. Repeated electromyography in a patient with stable symptoms is not recommended due to the invasive nature of this study. However, repeated electromyography/nerve conduction study would be warranted if there were uncertainty as to whether a new (or worsening) process was developing.

Recommendation 6: In patients with newly diagnosed, active, severe PAN, we conditionally recommend initiating treatment with pulse intravenous glucocorticoids over high-dose oral glucocorticoids.

Several single arm and comparative studies that evaluated medical therapy were confounded by use of other medications and not controlled for pulse intravenous or high-dose oral glucocorticoid use.[20 – 22] However, for active and severe disease specifically, patients may benefit from the additional mechanism of action of high dose pulse glucocorticoids. That is, glucocorticoids may rapidly alter cell membrane and receptor function to promote suppression of inflammation once the glucocorticoid receptor is saturated.[23] The Voting Panel noted that this recommendation was focused on patients with active severe disease. For many patients with disease that is not associated with life-threatening manifestations (such as immediate risk of visceral infarct), oral glucocorticoids would be preferred due to lower overall glucocorticoid burden. For pediatric patients, pulse glucocorticoid therapy in other systemic immune disorders appears to have a favorable side effect profile, in that it is not associated with infections or other morbidity more so than oral glucocorticoids. [24]

Recommendation 7: In patients with newly diagnosed, active, severe PAN, we conditionally recommend initiating treatment with cyclophosphamide and high-dose glucocorticoids over high-dose glucocorticoids alone.

In newly diagnosed severe PAN, a single observational study as well as indirect evidence suggests that cyclophosphamide use has benefits over glucocorticoid therapy alone, with no differences seen between oral or intravenous cyclophosphamide.[25 , 26] Additionally, the use of additional cycles of cyclophosphamide may provide a medium term benefit (3 years) against relapse, although this benefit wanes by 10 years.[21] Use of cyclophosphamide may mitigate glucocorticoid toxicity by decreasing the cumulative steroid dose.[27]

Recommendation 8: In patients with newly diagnosed, active, severe PAN, we conditionally recommend initiating treatment with cyclophosphamide with glucocorticoids over rituximab with glucocorticoids.

While case reports have recently raised the question as to whether rituximab use in PAN may have effect, the efficacy of rituximab in PAN remains uncertain due to the lack of comparative or large single arm studies of rituximab for this disease.

Recommendation 9: In patients with newly diagnosed, active, severe PAN unable to tolerate cyclophosphamide, we conditionally recommend treating with other non-glucocorticoid immunosuppressive agents with glucocorticoids over glucocorticoids alone.

Indirect evidence, due to data being gleaned from secondary outcomes from prior trials,[25 , 28] suggest that the combination of non-glucocorticoid immunosuppressive agents, such as azathioprine or methotrexate, with glucocorticoids is superior to glucocorticoids alone. Mycophenolate has not been well studied. No direct trials comparing glucocorticoid use with non-glucocorticoid combination therapy are available. In general, patients with severe PAN should be treated with cyclophosphamide over other immunosuppressive agents[26] but in patients unable to tolerate cyclophosphamide, another agent, such as azathioprine or methotrexate, is

recommended over glucocorticoid monotherapy. Use of non-glucocorticoid immunosuppressive therapy may provide a glucocorticoid sparing effect and minimize glucocorticoid toxicity, which is particularly significant in pediatric populations.

Recommendation 10: In patients with newly diagnosed, active, non-severe PAN, we conditionally recommend treating with non-glucocorticoid immunosuppressive agents and glucocorticoids over glucocorticoids alone.

In cases of non-severe disease, patient's age, clinical condition, and their values and preferences are important factors in assessing treatment. Although some patients achieve remission on glucocorticoids alone, a substantial number of patients ultimately require additional non-glucocorticoid therapy, which is usually azathioprine or methotrexate.[20] This recommendation contradicts management recommendations based on the Five Factor Score[29], in which patients without factors of severe disease can be treated with glucocorticoids alone. We favor use of non-glucocorticoid therapy in non-severe disease since the addition of non-glucocorticoid therapy may minimize glucocorticoid use and subsequent toxicity.

Recommendation 11: In patients with newly diagnosed, active, severe PAN, we conditionally recommend against using plasmapheresis combined with cyclophosphamide and glucocorticoids over cyclophosphamide and glucocorticoids alone.

A single trial conducted in 1995 evaluated the use of plasmapheresis in PAN, but did not discriminate between PAN and hepatitis B virus-associated PAN.[30] Confidence intervals in this study were very wide. Thus, evidence supporting the use of plasmapheresis in non-hepatitis B virus-associated PAN is unavailable and the benefit unclear. Plasmapheresis could be considered in catastrophic cases unresponsive to the recommended aggressive immunosuppressive therapies and may have a role in the management of hepatitis B-related PAN.

Recommendation 12: In patients with PAN in remission on non-glucocorticoid immunosuppressive therapy, we conditionally recommend discontinuation of non-glucocorticoid immunosuppressive agents after 18 months over continued (indefinite) treatment.

Evidence for this recommendation is based on a single study that was performed in 1979.[28] Although a significant number of patients with PAN relapse, the majority experience monophasic disease.[20] Indefinite treatment may therefore not be needed. Patients need to be in a sustained remission (Table 1) before discontinuing therapy.

Ungraded Position Statement A: The optimal duration of glucocorticoid therapy for PAN (e.g., tapering off by 6 months or longer than 6 months) is not well established, and thus the duration of therapy should be guided by the patient's clinical condition, values, and preferences.

In PAN, studies to determine the optimal length of time for glucocorticoid utilization have not been performed. In studies of other types of vasculitis (e.g. [31]), faster tapers led to more flares, which were often not organ threatening and may have been mild. The patient panel preferred a longer taper as a prime concern was disease control rather than glucocorticoid toxicity. Thus, duration of glucocorticoid use should be influenced by the patient's clinical condition, values, and preferences.

Recommendation 13: In patients with severe PAN refractory to treatment with glucocorticoids and non-glucocorticoid immunosuppressive agents other than cyclophosphamide, we conditionally recommend switching the non-glucocorticoid immunosuppressive agent to cyclophosphamide over increasing glucocorticoids alone.

With the effectiveness of cyclophosphamide in new-onset severe PAN[26], indirect evidence suggests that cyclophosphamide should be used in patients with PAN that has evolved from a non-severe presentation to one that is severe and does not respond adequately to other

immunosuppressive agents.

Recommendation 14: In patients with newly diagnosed PAN who have achieved remission with cyclophosphamide, we conditionally recommend transitioning to another non-glucocorticoid immunosuppressive agent over continuing with cyclophosphamide.

Due to its toxicity, cyclophosphamide therapy should not continue indefinitely, and should generally be limited to 3–6 months per course.[21] Based on the experience in ANCA-associated vasculitis, transitioning to another less toxic agent such as methotrexate or azathioprine is recommended once remission has been obtained. Given the lack of clinical trials investigating remission maintenance in PAN, this recommendation was based on expert experience.

Recommendation 15: In patients with PAN with nerve and/or muscle involvement, we conditionally recommend physical therapy.

Indirect published evidence for PAN is available for this recommendation from studies in inflammatory myositis. Based on this, we conditionally recommend this intervention due to its potential benefit and minimal risk. Physical therapy may be more beneficial for those with more substantial motor involvement. Patients on the voting panel expressed a high degree of enthusiasm for physical therapy as a modality for recovery and rehabilitation, in that they felt they had personally experienced benefit from physical therapy.

Recommendation 16: In patients with clinical manifestations of Adenosine Deaminase 2 deficiency (DADA2), we strongly recommend treatment with TNF-alpha inhibitors over glucocorticoids alone.

Adenosine Deaminase 2 deficiency (DADA2) was first described with a series of patients with an early onset (often childhood) PAN-like vasculitis.[32] DADA2 is characterized by recurrent strokes and skin changes and diagnosed using ADA2 sequencing or ADA2 functional assays, and ADA2 mutations have been identified in patients diagnosed with systemic PAN[33]. Although only one case series has been published, the strong signal of benefit by TNF-alpha inhibitors provide evidence that treatment with TNF-alpha inhibitors instead of conventional immunosuppressive agents such as cyclophosphamide prevents strokes.[32 , 34] Thus, physicians should consider DADA2 in the setting of a PAN-like syndrome with strokes, and if confirmed, we strongly recommend use of TNF-alpha inhibitors. The committee voted for a 'strong' recommendation despite the small number of cases, stressing the prevention of severe adverse events.

This is the first guideline issued by the American College of Rheumatology, in conjunction with the Vasculitis Foundation, for the management of systemic polyarteritis nodosa. These recommendations constitute a guide to help physicians treat patients with this disease. Because many recommendations are conditional, a patient's clinical condition, values, and preferences should influence the management decisions that are made. These recommendations should not be used by any agency to restrict access to therapy or require that certain therapies be utilized prior to other therapies.

Classic systemic PAN, although rare, remains a disease with a high mortality rate[22]. Thus recommendations in this guideline indicate that patients with severe disease should be treated with cyclophosphamide and glucocorticoids. However, when patients present with non-severe disease, (i.e., without life- or organ-threatening manifestations such as renal insufficiency, tissue ischemia), alternative immunosuppressive agents and a glucocorticoid-sparing regimen is reasonable for remission induction. Use of diagnostic procedures such as angiography, EMG/NCS, and nerve and muscle biopsy are recommended to aid in diagnosis. However, use of routinely repeated procedures during periods of disease quiescence is discouraged.

PAN has become increasingly rare, and no large clinical trials focused solely on idiopathic (non-HBV-associated) PAN have been published. In addition, studies of PAN conducted prior to the

recognition of microscopic polyangiitis (MPA) may have included patients with MPA and should be interpreted with caution. Many recommendations were based on expert experience of the voting panel and/or trials that were performed several years and, in some cases, decades ago. Strong recommendations will require larger interventional studies, but will be challenging to conduct given the rarity of this disease.

The process of developing these guidelines has brought to our attention other gaps in our understanding of the optimal treatment for PAN. These gaps include the role of longitudinal vascular imaging studies, the comparative effectiveness of non-glucocorticoid immunosuppressive agents, and the lack of biomarkers to inform disease activity or treatment response. Therefore, we encourage continued research in this disease. Specific areas to investigate include: Determining the role of longitudinal vascular imaging in assessing disease activity and determining disease prognosis

Conducting randomized clinical trials (including comparative efficacy trials) to assess the efficacy of non-glucocorticoid immunosuppressive agents, as well as identify the optimal dosing, duration, and population that would benefit from these agents

Developing novel, targeted, and/or glucocorticoid sparing therapies with minimal toxicity

Identifying biomarkers to inform assessment of disease activity and prognosis

In summary, the American College of Rheumatology and Vasculitis Foundation present these recommendations to assist physicians in managing polyarteritis nodosa, and this guideline can serve as a touchstone for basic principles of management. We hope this guideline will evolve as new research is conducted and new diagnostic and treatment strategies for PAN are identified.

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Definitions for selected terms used in the recommendations for polyarteritis nodosa (PAN).

Recommendations for the management of polyarteritis nodosa (PAN).

PICO= Population Intervention Comparator Outcome question used in GRADE methodology. Please refer to Supplementary Appendix 2 for the PICO questions developed for PAN.

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