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

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Objective. To provide evidence-based recommendations and expert guidance for the management of systemic polyarteritis nodosa (PAN).

Methods. Twenty-one clinical questions regarding diagnostic testing, treatment, and management were developed in the population, intervention, comparator, and outcome (PICO) format for systemic, non–hepatitis B–related PAN. Systematic literature reviews were conducted for each PICO question. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to assess the quality of evidence and formulate recommendations. Each recommendation required ≥70% consensus among the Voting Panel.

Results. We present 16 recommendations and 1 ungraded position statement for PAN. Most recommendations were 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 treatments, 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 identify new areas where adjunctive therapy may be warranted.

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

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INTRODUCTION

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that primarily affects medium-sized vessels (1). Patients frequently present with systemic symptoms such as fever and weight loss. The most common clinical presentations include neurologic manifestations such as mononeuritis multiplex and peripheral neuropathy, cutaneous manifestations such as nodules and livedo reticularis, renal manifestations such as hypertension, and gastrointestinal manifestations such as 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, it remains a potentially devastating diagnosis, with severe PAN having a mortality rate of 40% at 5 years (3).

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

METHODS

This guideline followed 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 the management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis). Supplementary Appendix 1 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41776/abstract) presents a detailed description of the methods. Briefly, the Literature Review team undertook systematic literature reviews for predetermined questions specifying the clinical population, intervention, comparator, and outcomes (PICO). An in-person Patient Panel of 11 individuals with different types of vasculitis (1 patient with PAN) was moderated by a member of the Literature Review team (ABD). This Patient Panel reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives and preferences. An Expert Panel provided expert knowledge to inform discussion of the PICO questions and findings of the literature review. The Voting Panel comprised 9 adult rheumatologists, 5 pediatric rheumatologists, and 2 patients; they reviewed the Literature Review team's evidence summaries and, bearing in mind the Patient Panel's deliberations, formulated and voted on recommendations. A recommendation required ≥70% consensus among the Voting Panel.

How to interpret the recommendations

A *strong* recommendation is typically supported by moderate- to high-quality evidence (e.g., multiple randomized controlled

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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 very low– to 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 very low or 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 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 one intervention over the other. However, the Voting Panel believed that 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 reflect general views of the Voting Panel.

In this evidence-based guideline, we explicitly used the best evidence available and present that in a transparent manner for the clinician reader/user (7). In some instances, this includes randomized trials in which the interventions under consideration are directly compared. 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 (5).

For each recommendation, details regarding the PICO questions and the GRADE evidence tables can be found in Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.41776/abstract).

RESULTS

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 the definition of severe and nonsevere disease, as well as dosing ranges for glucocorticoids. Table 2 presents the recommendations with their supporting PICO questions and levels of evidence. Figure 1 provides key recommendations for the treatment for PAN. All but 1 of the recommendations are conditional, primarily due to lack of high-quality evidence (e.g., randomized controlled trials) supporting the recommendation.

Vascular imaging, tissue biopsy, and diagnostic testing

Recommendation: For patients with suspected PAN, we conditionally recommend using abdominal vascular imaging to aid in establishing a diagnosis and determining the extent of disease.

Evidence for the use of routine diagnostic imaging is limited, with no comparative trials available. In single-arm studies that were performed when diagnostic criteria for PAN were not well defined,

Table 1. Definitions of selected terms used in the recommendations for PAN*

Term	Definition
Disease states	
Suspected disease	Clinical signs and/or symptoms suggestive of PAN and not explained by other conditions
Active disease	New, persistent, or worsening clinical signs and/or symptoms attributed to PAN and not related to prior damage
Severe disease	Vasculitis with life- or organ-threatening manifestations (e.g., renal disease, mononeuritis multiplex, muscle disease, mesenteric ischemia, coronary involvement, limb/digit ischemia)
Nonsevere disease	Vasculitis without life- or organ-threatening manifestations (e.g., mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis)
Remission	Absence of clinical signs or symptoms attributed to PAN, on or off immunosuppressive therapy
Refractory disease	Persistent active disease despite an appropriate course of immunosuppressive therapy
Relapse	Recurrence of active disease following a period of remission
Treatments	
IV pulse GCs	IV methylprednisolone 500–1,000 mg/day (adults) or 30 mg/kg/day (children; maximum 1,000 mg/day) or equivalent for 3–5 days
High-dose oral GCs	Prednisone 1 mg/kg/day (adults; generally up to 80 mg/day) or 1–2 mg/kg/day (children; generally up to 60 mg/day) or equivalent
Moderate-dose oral GCs	Prednisone 0.25–0.5 mg/kg/day (adults; generally 10–40 mg/day) or ~0.5 mg/kg/day (children; generally 10–30 mg/day) or equivalent
Low-dose oral GCs	Prednisone ≤10 mg/day (adults) or ≤0.2 mg/kg/day (children; maximum 10 mg/day) or equivalent
Non-GC immunosuppressive therapy	Azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil

* PAN = polyarteritis nodosa; IV = intravenous; GCs = glucocorticoids.

Table 2. Recommendations/statements for the management of PAN*

Recommendation/statement	PICO question informing recommendation and discussion	Level of evidence
Vascular imaging, tissue biopsy, and diagnostic testing		
Recommendation: For patients with suspected PAN, we conditionally recommend using abdominal vascular imaging to aid in establishing a diagnosis and determining the extent of disease.	1	Very low
Recommendation: For patients with a history of severe PAN with abdominal involvement who become clinically asymptomatic, we conditionally recommend follow-up abdominal vascular imaging.	19, 20	Very low
Recommendation: For patients with suspected PAN involving the skin, we conditionally recommend obtaining a deep-skin biopsy specimen (i.e., a biopsy reaching the medium-sized vessels of the dermis) over a superficial skin punch biopsy to aid in establishing a diagnosis.	2	Very low
Recommendation: For patients with suspected PAN and peripheral neuropathy (motor and/or sensory), we conditionally recommend obtaining a combined nerve and muscle biopsy over a nerve biopsy alone to aid in establishing a diagnosis.	3	Very low
Recommendation: For patients with a history of peripheral motor neuropathy secondary to PAN, we conditionally recommend serial neurologic examinations instead of repeated electromyography/nerve conduction studies (e.g., every 6 months) to monitor disease activity.	21	Very low
Treatment of active disease		
Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with IV pulse GCs over high-dose oral GCs.	4	Very low
Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with cyclophosphamide and high-dose GCs over high-dose GCs alone.	5, 6, 10	Very low to low
Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with cyclophosphamide and GCs over rituximab and GCs.	5, 6, 10	Very low to low
Recommendation: For patients with newly diagnosed active, severe PAN who are unable to tolerate cyclophosphamide, we conditionally recommend treating with other non-GC immunosuppressive agents and GCs over GCs alone.	8	Very low
Recommendation: For patients with newly diagnosed active, nonsevere PAN, we conditionally recommend treating with non-GC immunosuppressive agents and GCs over GCs alone.	12	Very low
Recommendation: In patients with newly diagnosed active, severe PAN, we conditionally recommend *against* using plasmapheresis combined with cyclophosphamide and GCs over cyclophosphamide and GCs alone.	7, 16	Low
Recommendation: For patients with PAN in remission who are receiving non-GC immunosuppressive therapy, we conditionally recommend discontinuation of non-GC immunosuppressive agents after 18 months over continued (indefinite) treatment.	13	Very low
Ungraded position statement: The optimal duration of GC 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.	11	Very low
Treatment of refractory disease		
Recommendation: For patients with severe PAN that is refractory to treatment with GCs and non-GC immunosuppressive agents other than cyclophosphamide, we conditionally recommend switching the non-GC immunosuppressive agent to cyclophosphamide, over increasing GCs alone.	17	Very low
Remission maintenance		
Recommendation: For patients with newly diagnosed PAN who have achieved disease remission with cyclophosphamide, we conditionally recommend transitioning to another non-GC immunosuppressive agent over continuing cyclophosphamide.	9	Very low
Other considerations		
Recommendation: For patients with PAN with nerve and/or muscle involvement, we conditionally recommend physical therapy.	14	Very low
Recommendation: For patients with clinical manifestations of DADA2, we strongly recommend treatment with tumor necrosis inhibitors over GCs alone.	18	Low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for polyarteritis nodosa (PAN), please refer to Supplementary Appendix 2 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41776/abstract). IV = intravenous; GCs = glucocorticoids; DADA2 = deficiency of adenosine deaminase 2.

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 disease relapse. 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 noninvasive methods such as computed tomography (CT) or magnetic resonance (MR) angiography to diagnose PAN (10–12). Conventional angiography is the current gold standard due to its ability to provide better resolution, but it can be

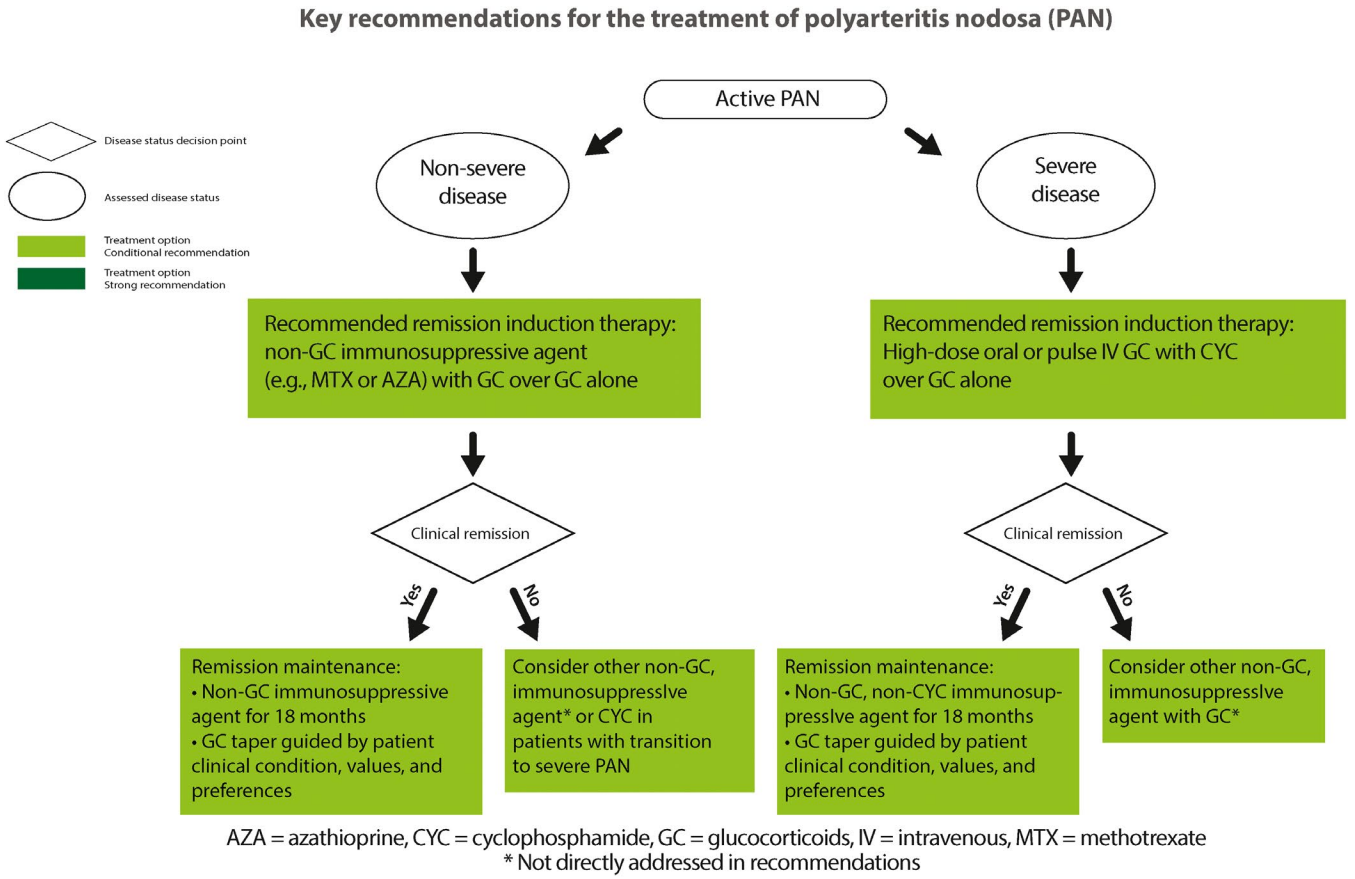

Figure 1. Key recommendations for the treatment of polyarteritis nodosa.

associated with complications, albeit at a very low rate (13,14). However, the resolution for noninvasive modalities is improving, and CT or MR angiography may provide additional information regarding the vessel wall that conventional angiography does not. Specifically, CT angiography may enable visualization of more of the distal branches of the mesenteric arteries than MR angiography, but MR angiography may be preferred in certain clinical situations (e.g., need to avoid iodinated contrast). In patients with a negative CT or MR angiogram result with a high degree of suspicion for abdominal involvement, it is reasonable to consider conventional angiography.

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

Indirect evidence (found in nonrandomized studies or studies in which findings were not primary aims) suggests that evaluation of deeper tissue is more effective at establishing a diagnosis of PAN (15,16), since a deeper-tissue sample is more likely to capture a medium-sized 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: For patients with suspected PAN and peripheral neuropathy (motor and/or sensory), we conditionally recommend obtaining a combined nerve and muscle biopsy over a 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 (15–19). 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: For patients with a history of peripheral motor neuropathy secondary to PAN, we conditionally recommend serial neurologic examinations 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.

Treatment of active disease

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

In several single-arm and comparative studies, evaluations of medical therapy were confounded by the use of other medications and did not control for IV pulse 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 and is not more strongly associated with infections or other morbidities compared to oral glucocorticoids (24).

Recommendation: For 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 and indirect evidence suggest that the use of cyclophosphamide has more benefits than glucocorticoid therapy alone, with no differences seen between oral and IV cyclophosphamide (25,26). Moreover, the use of additional cyclophosphamide cycles may provide a medium-term protection (3 years) against disease relapse, although this benefit wanes by 10 years (21). Use of cyclophosphamide may mitigate glucocorticoid toxicity by decreasing the cumulative steroid dose (27).

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

While case reports have recently raised the question about the efficacy of rituximab use in PAN (28–30), its efficacy in PAN remains uncertain due to the lack of comparative or large single-arm studies in this disease.

Recommendation: For patients with newly diagnosed active, severe PAN who are unable to tolerate cyclophosphamide, we conditionally recommend treating with other nonglucocorticoid immunosuppressive agents and glucocorticoids over glucocorticoids alone.

Indirect evidence (i.e., data obtained from secondary outcomes in prior trials [25,31]) suggests that the combination of nonglucocorticoid immunosuppressive agents, such as azathioprine or methotrexate, with glucocorticoids is superior to glucocorticoids alone. Mycophenolate mofetil has not been well studied in PAN. No direct trials comparing glucocorticoid monotherapy with nonglucocorticoid 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 nonglucocorticoid immunosuppressive therapy may provide a glucocorticoid-sparing effect and minimize glucocorticoid toxicity, which is particularly significant in pediatric populations.

Recommendation: For patients with newly diagnosed active, nonsevere PAN, we conditionally recommend treating with nonglucocorticoid immunosuppressive agents and glucocorticoids over glucocorticoids alone.

In cases of nonsevere disease, a patient's age, clinical condition, and their values and preferences are important factors in assessing treatment. Although some patients achieve disease remission while receiving glucocorticoids alone, a substantial number of patients ultimately require additional nonglucocorticoid therapy, usually azathioprine or methotrexate (20). This recommendation contradicts management recommendations based on the Five-Factor Score (32), in which patients without factors of severe disease can be treated with glucocorticoids alone. We favor the use of nonglucocorticoid therapy in nonsevere disease, since the addition of nonglucocorticoid therapy may minimize glucocorticoid use and subsequent toxicity.

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

In a single trial conducted in 1995, the use of plasmapheresis in PAN was evaluated, but a distinction between PAN and HBV-associated PAN was not made (33). Confidence intervals in this study were very wide. Thus, evidence supporting the use of plasmapheresis in non–HBV-associated PAN is unavailable and the benefit unclear. Plasmapheresis may be considered in catastrophic cases unresponsive to the recommended aggressive immunosuppressive therapies and may have a role in the management of HBV-related PAN.

Recommendation: For patients with PAN in remission who are receiving nonglucocorticoid immunosuppressive therapy, we conditionally recommend discontinuation of nonglucocorticoid immunosuppressive agents after 18 months over continued (indefinite) treatment.

Evidence for this recommendation is based on a single study that was performed in 1979 (31). Although a significant number of patients with PAN have disease relapse, the majority experience monophasic disease (20). Indefinite treatment may therefore not be needed. Disease needs to be in sustained remission (Table 1) before discontinuing therapy.

Ungraded position statement: 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 use have not been performed. In studies of other types of vasculitis (34), 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 primary 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.

Treatment of refractory disease

Recommendation: For patients with severe PAN that is refractory to treatment with glucocorticoids and nonglucocorticoid immunosuppressive agents other than cyclophosphamide, we conditionally recommend switching the nonglucocorticoid immunosuppressive agent to cyclophosphamide over increasing glucocorticoids alone.

Based on 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 nonsevere presentation to one that is severe and does not adequately respond to other immunosuppressive agents.

Remission maintenance

Recommendation: For patients with newly diagnosed PAN who have achieved disease remission with cyclophosphamide, we conditionally recommend transitioning to another nonglucocorticoid immunosuppressive agent over continuing 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 antineutrophil cytoplasmic antibody–associated vasculitis, transitioning to another less toxic agent such as methotrexate or azathioprine is recommended once disease remission has been attained. Given the lack of clinical trials investigating remission maintenance in PAN, this recommendation was based on expert experience.

Other considerations

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

Indirect 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: For patients with clinical manifestations of deficiency of adenosine deaminase 2 (DADA2), we strongly recommend treatment with tumor necrosis factor inhibitors over glucocorticoids alone.

DADA2 was first described in a series of patients with an early-onset (often childhood) PAN-like vasculitis (35). 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 as having systemic PAN (36). Although only 1 case series has been published, the strong signal of benefit of tumor necrosis inhibitors provides evidence that treatment with tumor necrosis inhibitors, instead of conventional immunosuppressive agents such as cyclophosphamide, prevents strokes (35,37). Thus, physicians should consider DADA2 in the setting of a PAN-like syndrome with strokes, and if confirmed, we strongly recommend use of tumor

necrosis factor inhibitors. The Voting Panel voted for a strong recommendation despite the small number of cases, stressing the prevention of severe adverse events.

DISCUSSION

This is the first guideline issued by the ACR, in conjunction with the VF, for the management of systemic PAN. 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). Therefore, recommendations in this guideline indicate that patients with severe disease should be treated with cyclophosphamide and glucocorticoids. However, when patients present with nonsevere disease (i.e., without life- or organ-threatening manifestations such as renal insufficiency and tissue ischemia), use of alternative immunosuppressive agents and a glucocorticoid-sparing regimen is reasonable for remission induction. Use of diagnostic procedures such as angiography, electromyography/nerve conduction studies, and nerve and muscle biopsy is recommended to aid in diagnosis. However, the use of routinely repeated procedures during periods of disease quiescence is discouraged.

PAN has become increasingly rare, and no large clinical trials that focused solely on idiopathic (non–HBV-associated) PAN have been published. In addition, studies of PAN conducted prior to the recognition of microscopic polyangiitis may have included such patients 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 due to 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 nonglucocorticoid immunosuppressive agents, and the lack of biomarkers to inform disease activity or treatment response. Therefore, we encourage continued research in this disease. Future study and specific areas to investigate include the following: 1) determining how informative longitudinal vascular imaging is for assessing disease activity and determining disease prognosis; 2) conducting randomized clinical trials (including comparative efficacy trials) to assess the efficacy of nonglucocorticoid immunosuppressive agents, as well as identifying the optimal dosing, duration, and population that would benefit from these agents; 3) developing novel, targeted, and/or glucocorticoid-sparing therapies with minimal toxicity; and 4) identifying biomarkers to inform assessment of disease activity and prognosis.

In summary, the ACR and the VF present these recommendations to assist physicians in managing PAN, 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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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Chung and Gorelik had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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