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PATOPHYSIOLOGY AND LATEST TREATMENT OPTIONS OF VASCULITIS: A LITERATURE REVIEW

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ABSTRACT

Excessive inflammation in the vascular can cause an autoimmune process in vasculitis. Vasculitis can cause damage to the tissues and organs that are vascularized. Although therapy with glucocorticoids is effective for remission, complications that often occur early in patients can thwart the therapy. More detailed and interrelated understanding of the disease will further encourage the development in the quality of medical procedures to be given to patients so that it is expected to improve the prognosis of patient condition. This literature review aimed to explain the topic starting from the prevalence of vasculitis, followed by the underlying risk factors and the development of the current diagnostic and management chart. The method of review is a searching articles from various databases in *PubMed*, *Google Scholar*, and *ScienceDirect* with a year range of 2014-2025. Based on the various literature obtained, the diagnosis and selection of management in vasculitis are influenced by heterogeneous disease classifications, with glucocorticoids remaining the standard treatment that continues to be associated with various long-term complications. Diagnosis can involve serological examinations such as *Anti Neutrophilic Cytoplasmic Antibody* (ANCA) and vascular imaging. In addition to initial therapy with glucocorticoids, further management is determined based on the phase of treatment and the patient's response to selected therapy. Various new regimens have been developed as alternatives to glucocorticoids, adjuvants to therapy, or to help reduce the long-term effects of immune system suppression. Based on the results of the therapy to patients, the prognosis and complications of vasculitis are largely influenced by comorbidities and the long-term effects of glucocorticoid use. Further studies are needed, especially in determining the reference values of laboratory tests used for diagnosis, determining the exact therapeutic doses, and strategy to treat complications that occur in patients.

Keywords: AAV, autoantibody, glucocorticoid, HSP, PAN, vasculitis

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INTRODUCTION

Inflammation is the physiological defence process against various potentially damaging factors in order to maintain ideal conditions, such as against pathogens, chemical compounds, or physical injuries (Chen *et al*., 2017). Excessive inflammation can lead to chronic conditions such as many of non-communicable diseases including cardiovascular disease, fatty liver, diabetes, and cancer (Furman *et al.,* 2019). In this case, autoimmune reactions can be one of the causes of excessive inflammation or as a separate result of hyperinflammation by immune cells (Xiang *et al.,* 2023). Inflammation and autoimmune are two processes that are often been linked in a number of diseases. One disease that is a combination of inflammatory and autoimmune reactions is vasculitis.

Vasculitis is an autoimmune condition with heterogeneous aetiologies characterized by inflammation and destruction of the vasculature and can cause ischemia and damage to various tissues and organs that are vascularized (Redondo-Rodriguez *et al*., 2022; Watts *et al.,* 2022). A study in 2022 concluded that the incidence of all types of *Antineutrophilic Cytoplasmic Antibody* (ANCA)-*associated Vasculitis* (AAV) was 17.2 per 1 million people per year, with the most prevalent AAV type being *Granulomatosis with Polyangiitis* (GPA) (Redondo-Rodriguez *et al.,* 2022).

Until this current time, the pathophysiology of vasculitis has been widely understood. However, the description of the pathophysiology of vasculitis is often distinguished based on the many separated type of vasculitis. This shows the complexity of the natural course of the disease. The impact of the complexity of the disease can be showed by the increasing incidence of delayed diagnosis in patients. Also, vasculitis presents with various clinical manifestations, and therapy with glucocorticoids is still the main choice in treating the disease. Although therapy with glucocorticoids is evidenced to be effective for disease remission, complications that often occur earlier in patients can thwart the therapy.

Therefore, a more effective method to diagnose accurately in the most efficient time possible is needed as a patient management approach. More detailed and interrelated understanding of the disease will further encourage an increase in the quality of medical procedures provided to patients so that it is expected to improve the patient's prognosis.

To cover the gaps, this literature review aimed to explore in more detail the prevalence of vasculitis cases and the factors involved in the changes of the trends that occur. In addition, the author will also discuss about the development of diagnostic and management algorithms that have developed to date to be used as a basic benchmark in evaluating and treating patients in both primary and secondary facilities. The limitations used are primary vasculitis which includes diseases in large, medium, and small blood vessels.

METHOD OF LITERATURE REVIEW

The method of review is a search for articles from various databases in *PubMed*, *Google Scholar*, and *ScienceDirect*. The keywords used in the search are "vasculitis", "pathophysiology", "management", "epidemiology", "AAV", "ANCA", "clinical manifestations", and "prognosis and complication". The range of publication years included is 2014-2025. All types of articles including meta-analysis, literature review, original research, case reports, and clinical guidelines will be included. Articles included must be relevant to the topic of primary vasculitis, use studies with human subjects, and at least have a complete abstract. The languages included are limited to Indonesian and English. References cited in the articles found earlier will also be considered. All articles found are

manually selected by the author team based on the relevance of the topic and the quality of the information presented and the selection of the final articles is done purposively.

RESULT AND DISCUSSION

Definition and Epidemiology

Vasculitis is an autoimmune condition with heterogeneous causes characterized by inflammation and destruction of the vascular system—either arteries, veins, capillaries, or a combination of the three—which can cause ischemia and damage to the tissues and organs it vascularizes (Redondo-Rodriguez *et al.,* 2022; Watts *et al.,* 2022). Vasculitis has undergone several nomenclature updates until the nomenclature used in this article was the *International Chapel Hill Consensus Conference* (ICHCC) nomenclature in 2012[1] (Jennette *et al*., 2013). Based on this nomenclature, the first case describing suspected systemic vasculitis was presented in 1866. The case described a 27-year-old male patient with complaints of pyrexia, severe myalgia, abdominal pain, and multiple mononeuritis[2] who died 6 weeks after the onset of symptoms. The patient was subsequently classified as having *Polyarteritis Nodosa* (PAN), a type of vasculitis. Meanwhile, research in the form of case reports on one type of vasculitis, namely AAV, first began in 1982, followed by the discovery of new cases regarding other classifications of AAV including GPA and other types of vasculitis (Jennette *et al.,* 2013; Carette, 2022).

Along with the improvement in the quality of health services related to early diagnosis and integrated management of vasculitis patients, the patient survival rate has increased quite significantly from <75% in the 1900s to ~95% in 2010. In this regard, studies on the relationship between patient quality of life and vasculitis diagnosis and treatment need to be further studied. Factors include multimorbidity that can occur, multiple diagnoses at the same time, including increased duration of care and hospital costs in line with a decrease in patient quality of life scores. Research underlines aspects of inability to do work, physical activity, sensation of fatigue, including neurological involvement and damage to various organ systems including the ears, nose, throat, lungs, skin, kidneys, and eyes in the evaluation of the quality of life of patients with vasculitis. The use of medication as an initial treatment for vasculitis such as glucocorticoids is also considered to have a negative impact on the quality of life of patients with the emergence of medication effects that are not limited to weight gain, muscle weakness, and increased susceptibility to infection (Aitken and Basu, 2020).

So far, the classification of vasculitis is determined based on the morphology of blood vessels (Table 1), namely large blood vessels, medium blood vessels, and small blood vessels throughout the body (Jennette *et al.,* 2013; Melduni *et al.,* 2020).

Table 1. Classification and definition of vasculitis based on size category of vessels

Size of vessels	Type of vasculitis	Definition	Citation
Small	AAV	Primary vasculitis characterized by the presence of ANCA encoded by the PR3 and MPO genes; further	(Brogan and Eleftheriou,

[1] The nomenclature referred to is listed in Table 1 in the cited citation

[2] A condition of nerve disorders due to blockage of nerve axons following vascular inflammation; asynchronous and asymmetric nerve disorders

		classified as *Granulomatosis with Polyangiitis* (GPA), *Eosinophilic Granulomatosis with Polyangiitis* (EGPA)/*Churg-Strauss Syndrome*, and *Microscopic Polyangiitis* (MPA)	2018; Nakazawa *et al.*, 2019)
	HSP	*IgA vasculitis;* vasculitis that often occurs in children is a non-granulomatous inflammation of the vessels characterized by IgA deposits in the skin, joint synovial, intestinal, and urinary systems	(Sestan and Jelusic, 2023)
	CLA	Vasculitis in arterioles, capillaries, and venules with neutrophil infiltrate with fibrinoid necrosis and nuclear fragments, and occurs in the cutaneous system	(Fraticelli, Benfaremo and Gabrielli, 2021)
	CGV	Vasculitis due to deposition of abnormal proteins, mainly types II and III, with most cases associated with chronic hepatitis C virus infection	(Goglin and Chung, 2016)
Medium	PAN	Vasculitis is mainly at the branching sites of large arteries, can be primary or secondary, generally affects patients aged > 50 years	(Virgilio *et al.*, 2016; Halabi *et al.*, 2021)
	KD	Vasculitis that occurs frequently in children is characterized by neutrophil infiltration in non-granulomatous inflammation	(Gorelik *et al.*, 2022)
Large	GCA	Granulomatous arteritis affecting the walls of the second to fifth branch arteries of the aorta	(Weyand and Goronzy, 2013; Gloor *et al.*, 2022)
	TAK	Granulomatous aortitis is characterized by thickening of the media and adventitia layers accompanied by infiltration of young immune cells	(Watanabe *et al.*, 2020; Gloor *et al.*, 2022)

Abbreviations:
AAV: *Antineutrophil Cytoplasmic Antibody-Associated Vasculitis;* HSP: *Henoch-Schonlein Purpura;* CLA: *Cutaneus Leukocytoclastic Angiitis;* CGV: *Cryoglobulinemic Vasculitis;* PAN: *Polyarteritis Nodosa;* KD: *Kawasaki Disease;* GCA: *Giant Cell Arteritis;* TAK: *Takayasu Arteritis*

A meta-analysis study stated that the prevalence of all AAV types studied was 198 per 1 million people, with GPA (96.8 per 1 million people) having the highest prevalence compared to MPA (39.2 per 1 million people) and EGPA (15.6 per 1 million people) (Redondo-Rodriguez *et al.*, 2022). In Indonesia itself, a case report was published in 2020 regarding an adult female patient with a diagnosis of one type of vasculitis, namely HSP, which was confirmed using the *European Alliance of Associations for Rheumatology* (EULAR) criteria (Table 2) (Matius, 2020). Another known case report is an 18-year-old woman with a diagnosis of TAK using the *American College of Rheumatology* (ACR) criteria. The patient showed clinical manifestations in the form of recurrent fever, postprandial abdominal pain, lower extremity claudication, and differences in systolic blood pressure between the two arms (Lusida, Kurniawan and Nugroho, 2020; Maz *et al.*, 2021).

Table 1. EULAR criteria in diagnose of vasculitis *Henoch-Schonlein Purpura*

Criteria	Description
Mandatory	Purpura or petechiae predominantly in the lower extremities
Additional (at least 1)	Generalized abdominal pain with acute onset
	Histopathology examination shows leukocytoclastic vasculitis or proliferative glomerulonephritis with predominantly IgA deposits
	Acute onset of arthritis or arthralgia
	Renal involvement with clinical manifestations of proteinuria or haematuria
Establishing a diagnosis	If there are mandatory criteria accompanied by ≥ 1 additional criterion

Polyarteritis Nodosa (PAN) is a vasculitis that primarily affects medium-sized arteries in the branching section and is categorized as a systemic, cutaneous, or secondary form caused by hepatitis B/C virus infection, rheumatoid arthritis, or leukaemia. In PAN, injury to the arterial wall leads to aneurysm[3], vascular irregularity, haemorrhage, or thrombosis that can progress to ischemia in the distal part. Vasa vasorum from the arterial supply of the peripheral nervous system are the most common predilection sites for inflammation so that 85% of PAN patients show symptoms of peripheral paralysis. The prevalence of PAN occurs in 30 per 1,000,000 people. The characteristics of PAN that distinguish it from other types of vasculitis are that it does not involve the lungs, arterial circulation restriction, negative ANCA laboratory examination, and the absence of granulomatous inflammation (Virgilio *et al.,* 2016; Halabi *et al.,* 2021).

Antineutrophilic Cytoplasm Antibody (ANCA)-Associated Vasculitis (AAV) is a type of primary vasculitis characterized by the presence of ANCA antibodies. ANCA antibodies are encoded by the proteinase 3 (PR3) and myeloperoxidase (MPO) related genes in neutrophils that cause excessive inflammation in small vessels (Brogan and Eleftheriou, 2018; Nakazawa *et al.,* 2019).

Giant Cell Arteritis (GCA) is a granulomatous arteritis that affects the second to fifth branches of the aorta. Inflammatory lesions are centred on the walls of the arteries and aorta and are generally characterized by cellularity consisting of activated macrophages and T cells that elicit maladaptive responses. Patients with GCA usually report clinical manifestations in the form of muscle pain in selective territories, fever, weight loss to *failure to thrive* (FTT) (Weyand and Goronzy, 2013; Gloor *et al*., 2022). One study showed the incidence of GCA in patients aged 50 years and over in Finland was 7.5 per 100,000 people (Sharma, Mohammad and Turesson, 2020).

Meanwhile, in *Takayasu Arteritis* (TAK), granulomatous aortitis is characterized by thickening of the media and adventitia layers that can be more differentiated than GCA. In TAK, the majority of infiltrating cells come from young immune cells, including CD8+ and natural killer cells—compared to GCA which is produced by the aging immune system. Therefore, patients with TAK are usually diagnosed at a younger age with a peak incidence in the 3rd decade (Watanabe *et al.,* 2020; Gloor *et al*., 2022).

[3] Abnormal protrusion in the artery wall due to structural weakness

Etiology and Risk Factors

In general, based on the cause, vasculitis can be categorized as primary vasculitis and secondary vasculitis. Primary vasculitis means without a known definite cause and is only a basic pathological nature of tissue injury. Meanwhile, secondary vasculitis, which includes infectious and paraneoplastic vasculitis, is caused by a known underlying disease or cause (Langford, 2010; Mamfaluti *et al.*, 2023). The most basic cause of vasculitis is an erroneous inflammatory response by immune cells to specific triggers that been presented in the involved blood vessels. Various specific aetiologies depend on the type of vasculitis discussed. Microorganisms including bacteria such as *Mycobacterium spp.* and *Staphylococcus aureus*[4], viruses such as *cytomegalovirus* and *hepatitis B virus*[5], and fungi and parasites are known to play a role as inflammatory triggers in various types of vasculitis. However, the actual relationship between infection and vasculitis is not yet clearly understood considering that in addition to pathogenic infections as triggers for vasculitis, the recorded infections may also be the infections that can occur after the initial diagnosis of vasculitis in patients (Lian, Teoh and Tay, 2019; Theofilis *et al.*, 2022).

The literature[6] mentions a relationship between age and the incidence of vasculitis, specifically in patients with GCA and TAK. Because vasculitis is an autoimmune reaction, the senescent condition of immune cells tends to be susceptible to regulatory failure by, for example, *T cell regulators* and *B cell regulators* which are important in the immunosuppressive process, which can lead to an erroneous and excessive inflammatory response. In aging blood vessels, there is also an increase in the production of *reactive oxygen species* (ROS) which can amplify the inflammatory process that occurs. TAK is known to be more common in patients aged 20 to 40 years, when the immune system is working at maximum potential. In contrast to GCA which is known to be more common in the elderly, especially the incidence increases after the age of 80 years (Gloor *et al.*, 2022).

Types of vasculitis in small blood vessels such as AAV can be induced as a side effect of certain medications such as *propylthiouracil* (Radic, Kaliterna and Radic, 2012; Nakazawa *et al*., 2019). Drugs such as *Angiotensin Converting Enzyme Inhibitors* (ACE-I), *clarithromycin*, and *Angiotensin-II Receptor Blockers* (ARBs) such as *losartan* have been reported as triggers for HSP vasculitis (Matius, 2020).

Pathophysiology

Several correlated factors cause inflammation leading to destruction and obstruction of blood vessels. This obstruction and destruction will eventually reduce perfusion to tissues and organs which will lead to damage as a result of extensive ischemia (Theofilis *et al.*, 2022).

One of the clear pathophysiologies of vasculitis is those that induced by infection. (Theofilis *et al.*, 2022) explained the mechanism of vasculitis caused by infection. The mechanism consists of direct and indirect pathogen invasion. Direct pathogen invasion is detected in the vascular wall and is characterized by the accumulation of smooth muscle cells, endothelial dysfunction, expression of ROS, cytokines, chemokines, cellular adhesion molecules, and vascular wall damage. Meanwhile, the indirect mechanism involves immune-mediated injury to the vascular wall, such as immune complexes bound to the vasculature that activate immune reactions by *T cells*, ANCA autoantibodies that activate immune

[4] Known as the most frequent culture result in patients with GPA

[5] As one of the causes of PAN

[6] Further schemes can be seen in the citation (Gloor *et al.*, 2022)

reactions by neutrophils, toxins that are still deposited which are superantigens, autoantigens, and immune responses in the form of hypersensitivity (Theofilis *et al*., 2022).

Furthermore, the infection that occurs can stimulate an autoimmune response through the virulence properties from the pathogen, such as superantigens by *S. aureus*. Superantigens can stimulate the production of autoantibodies by *B cells* that involved in the process of vascular endothelial necrotization in the mechanism of vasculitis. Meanwhile, several pathogens suspected of being involved through direct invasion mechanisms include *Pseudomonas aeruginosa* in the lungs and *Fusobacterium necrophorum* in the internal jugular vein after onset of pharyngitis (Theofilis *et al*., 2022).

In addition to being a direct impact of vascular inflammation due to infection, the continued series of inflammatory responses can lead to the formation of autoantibodies which then form a series of separate mechanisms in the pathophysiology of vasculitis. This can be seen in the case of AAV. (Nakazawa *et al.*, 2019) have explained in detail the mechanism of ANCA autoantibody formation and its relationship to the occurrence of clinical manifestations of AAV. Two types of antigens targeted by ANCA autoantibodies are PR3 and MPO (as previously mentioned). In response to infection, neutrophils—activated by proinflammatory cytokines such as *Tumour Necrosis Factor* (TNF)—will release *Neutrophil Extracellular Traps* (NETs) on their surface to eliminate the causative pathogen. PR3 and MPO are both contained in NETs along with other proteins and bound to DNA. After the infection is eradicated, NETs are normally degraded primarily by the enzyme DNAse I to prevent excessive exposure of NETs that can cause angiopathy. However, in some patients with genetic mutation susceptibility including patients with *Systemic Lupus Erythematosus* (SLE), the NETs that been produced become resistant to degradation by DNAse. In patients with MPA, DNAse production tends to be lower. These genetic mutations and high levels of NETs are accompanied by decreased tolerance of immune cells to PR3 and MPO antigens and eventually identified as *neoantigens* (Nakazawa *et al.*, 2019).

After increasing levels of PR3 and MPO in the blood, dendritic cells will present these two *neoantigens* to *CD4+ T cells*. The result of this *T cell* activation is the differentiation of *B cells* into plasma cells that produce specific ANCA antibodies against the targeted antigen type. The ANCA antibodies that have been produced bind to the antigen on the NETs. At the same time, other parts of the ANCA antibodies also bind to receptors on neutrophils, which directly increase neutrophil activation. This process then continues continuously—neutrophil hyperactivation increases NET production that will be responded to by ANCA—which results in the production of ROS that can injure blood vessel endothelial cells. In addition to the impact of excessive ROS production, longer exposure to NET in the vasculature can also damage the integrity of endothelial cells (Nakazawa *et al.*, 2019).

Clinical Manifestation

Since vasculitis is known to be a heterogeneous disease, clinical manifestations tend to be nonspecific and can only present with constitutional[7] symptoms that complicate and delay immediate diagnosis. Basically, each clinical manifestation describes the degree of damage

[7] Symptoms that can originate from any organ system, such as fever, fatigue, decreased appetite, and weight loss

that occurs to the vascular and other surrounding structures that are also affected at a certain location, especially the nervous system (Table 3). Common systemic symptoms include fatigue, fever, and weight loss. (Duarte *et al.,* 2023) summarize typical clinical manifestations according to the organ systems involved in the pathophysiology of AAV. In the musculoskeletal, the disease can be manifested as joint and muscle pain. Purpura, subcutaneous nodules, and bullae usually occur if vasculitis affects the skin. Symptoms in the neurological system include motor neuropathy and cranial nerve neuropathy and signs of meningitis (Pagnoux, 2016; Marzano *et al.,* 2017; Morita *et al.,* 2020; Duarte *et al.,* 2023).

In PAN, which is a necrotizing systemic vasculitis that usually affects medium-sized blood vessels, systemic symptoms may appear in the form of fever and weight loss. Clinical manifestations according to the organ system involved include peripheral neuropathy in the nervous system, nodules and livedo reticularis[8] in the cutaneous system, hypertension in the kidneys, and abdominal pain in digestive disorders (Chung, Gorelik, *et al.,* 2021).

Table 2. Clinical manifestation of types of vasculitis

Size of vessels	Type of vasculitis	Subjective symptoms	Objective signs	Citation
Small	AAV	Respiratory: sinus pain Musculoskeletal: joint and muscle pain Neurological: weakness, tingling	Respiratory: nasal discharge, cough, shortness of breath, wheezing, haemoptysis Orbital: scleritis Cucumber: purpura, nodules, bullae Neurological: signs of meningitis	(Pagnoux, 2016; Marzano *et al.*, 2017; Morita *et al.*, 2020; Duarte *et al.*, 2023)
	HSP	Gastrointestinal: intermittent epigastric pain—worsened by eating Musculoskeletal: knee and wrist joint pain	Cutaneous: purpuric patches on the skin, especially the lower extremities and buttocks, with symmetrical distribution Renal: haematuria	(Matius, 2020)
Medium	PAN	Neurological: neuropathy, sensory & motor deficits Digestive: abdominal pain	Systemic: fever, weight loss Size: nodules, livedo reticularis, ulcers, gangrene Urinology: hypertension, oliguria	(Chung, Gorelik, *et al.*, 2021)
Large	GCA	Cranial: headache, visual disturbances, mandibular claudication Extracranial: extremity claudication	Extracranial: loss of extremity pulses	(Maz *et al.*, 2021)

[8] Reddish-blue discoloration of the skin resembling a net

	TAK	Constitutional symptoms Vascular: claudication of the extremities	Vascular: loss of extremity pulses	(Maz *et al.*, 2021)

Diagnosis

Establishing the diagnosis of vasculitis is challenging due to the heterogeneity of symptoms and similarities in clinical manifestations with other medical conditions. This literature review only discusses the diagnosis of AAV, PAN, and HSP vasculitis. Various clinical guidelines and systematic studies summarize the diagnostic algorithms for AAV (Duarte *et al.,* 2023) and PAN (Chung, Gorelik, *et al.,* 2021).

The initial assessment of patients with suspected AAV begins with a complete history including past medical and medication history and possible exposure to chemicals or pathogenic infections. It is necessary to consider the possibility of secondary vasculitis that occurs as a complication of diseases such as tuberculosis, *Human Immunodeficiency Virus* (HIV), hepatitis, and others. Drugs that need to be suspected include *propylthiouracil*, *carbimazole*, *phenytoin*, and *allopurinol*. Further complementary diagnostic tests that will be crucial include assessment of haematological parameters, inflammatory markers, renal function tests and urinalysis, liver function tests, viral serology (to exclude PAN classification), ANCA serology (specific titres for anti-PR3 and anti-MPO), chest radiography, evaluation of lung function and bronchoscopy (such as the presence of neutrophilic alveolitis in MPA), and biopsies of the lungs, kidneys, and upper respiratory tract (can also be used to exclude PAN classification) (Duarte *et al.,* 2023). Haematology test results that may support the diagnosis of AAV include anaemia, leucocytosis, thrombocytosis, and eosinophilia in cases of EGPA. Active disease can show an increase in the *Erythrocyte Sedimentation Rate* (ESR) or *C-Reactive Protein* (CRP) although it can also be a manifestation of various other inflammatory cases. Renal involvement can be evidenced by proteinuria, haematuria, and increased serum creatinine. Patients with AAV can also show pulmonary symptoms that indicate the need for chest radiography to exclude other abnormalities or forms of disease complications (Berden *et al.,* 2012; Duarte *et al.,* 2023).

After an initial evaluation of the possibility of AAV, the next step is to assess the degree of disease activity. This can be done using the *Birmingham Vasculitis Activity Score* (BVAS) questionnaire. BVAS evaluates 10 specific components of the affected organ system along with clinical manifestations that may be occurring. BVAS is able to assess whether the disease is active during the last 4 weeks. A score ≥ 1 on the BVAS indicates active disease. Furthermore, scoring with the *Vascular Damage Index* (VDI) can assess the extent of the severity or damage caused by vasculitis to the general health condition of the patient. Patients who are newly diagnosed with vasculitis usually have a VDI score = 0. A score higher than that may indicate that the onset of the disease was more than 3 months ago and/or that there has been a deterioration in various organ systems since the onset of vasculitis. Meanwhile, a cumulative increase in VDI scores after diagnosis and treatment is implemented indicates the possibility of inadequate treatment results. A cumulative increase in VDI scores indicates the possibility of inadequate treatment results (Kermani *et al.,* 2016; Duarte *et al.*, 2023).

Until now, there has been no research that produces a definite cutoff value that can be used for the diagnosis of vasculitis based on ANCA levels in serum. However, ANCA

serology examination is usually indicated if there is a strong suspicion of AAV vasculitis and to reduce the percentage of false-positives, suspicion of various types of inflammation, or in vasculitis of unknown type (Chehroudi, Booth and Milman, 2018). Laboratory examination for the diagnosis of AAV can utilize *Indirect Immunofluorescence* (IIF) and *Enzyme-Linked ImmunoSorbent Assay* (ELISA) to detect the presence of anti-MPO and anti-PR3 antibodies. Typical immunofluorescence results are cytoplasmic-ANCA in anti-PR3 and perinuclear-ANCA in anti-MPO. The ANCA levels found are directly proportional to the degree of inflammation with higher levels indicating active disease or recurrence and the potential for poor response to therapy. In conclusion, the diagnosis of AAV can be confirmed if there are symptoms of AAV accompanied by at least 1 of: histological assessment of vasculitis; positive ANCA serology; or specific evidence of vasculitis (Duarte *et al.*, 2023).

The diagnosis of PAN is usually confirmed by tissue biopsy from the affected organ or angiography if tissue biopsy is not possible, as recommended in clinical guidelines (Chung, Gorelik, *et al.*, 2021). The histological picture found from the biopsy is a mixed inflammatory cell infiltrate in the blood vessel wall with fibrinoid necrosis without the presence of granulomas or giant cells. Angiography can show fusiform or saccular aneurysms and stenotic lesions in the arterial branches in several organ systems including the mesenteric artery, hepatic artery, and renal artery. In patients suspected of having abdominal vascular disorders in the form of gastrointestinal or urinary symptoms, angiographic assessment is recommended to confirm the diagnosis as well as for monitoring in patients with a history of severe PAN who have been asymptomatic. Meanwhile, in patients with suspected vascular involvement in the skin, a biopsy reaching the medium blood vessels in the dermis can be used to confirm the diagnosis. Nerve biopsy along with muscle biopsy is more recommended than muscle biopsy alone in patients who show symptoms of peripheral neuropathy (Chung, Gorelik, *et al.*, 2021).

Finally, the diagnosis of HSP vasculitis refers to the EULAR criteria which tend to be distinguishable from other diseases (Table 2).

Treatment

After establishing the correct diagnosis, understanding appropriate management actions forms a solid foundation for improving patient care outcomes. The treatment of patients with vasculitis generally requires multidisciplinary collaboration beyond general practitioners, involving specialists such as rheumatologists, nephrologists, neurologists, ophthalmologists, and pulmonologists, depending on the organ systems affected by the disease's heterogeneous pathophysiology (Chung, Gorelik, *et al*., 2021; Chung, Langford, *et al*., 2021; Maz *et al*., 2021; Gorelik *et al*., 2022).

In general, treatment aims to suppress the immune response, with carefully consideration of dosage and route of administration to avoid potentially severe side effects. The treatment period is typically divided into two phases: the remission induction phase, which involves more aggressive administration of immunosuppressant drugs to achieve remission within at least three months, followed by the maintenance phase, which aims to sustain remission, monitor progress, and minimize adverse effects of medication (Hellmich *et al*., 2024).

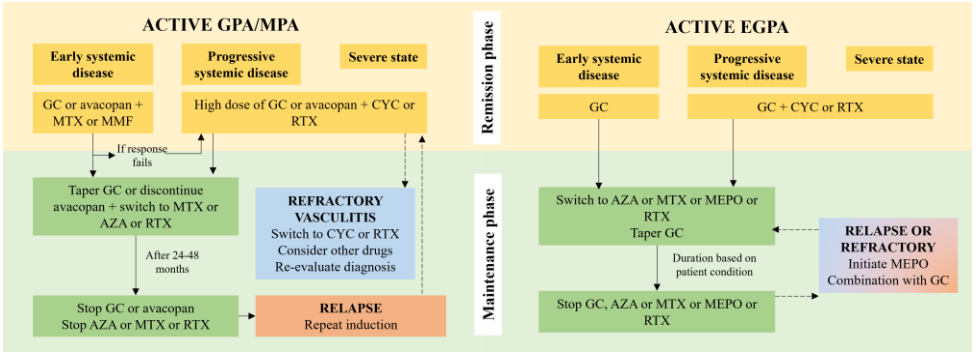

Figure 1 Recommended Treatment Regimens for AAV (adapted from (Duarte *et al.*, 2023))

The following section discusses the management of AAV. Readers are encouraged to consult the original reference (Duarte et al., 2023) for a comprehensive table outlining the medication options and dosages for the three subtypes of AAV (Figure 1).

During the remission induction phase in patients without suspected life-threatening conditions or risk of organ failure, a glucocorticoid (GC) regimen—such as prednisone, prednisolone, or methylprednisolone—combined with rituximab (RTX) may be administered. Prednisolone can be initiated at a dose of 75 mg/day and tapered down to an equivalent of 5 mg/day or adjusted according to patient tolerance[9]. In patients with GPA or MPA presenting with early systemic disease, RTX may be substituted with mycophenolate mofetil (MMF). In contrast, for patients with suspected organ-threatening or life-threatening involvement—such as renal or pulmonary complications—first-line therapy includes a combination of GC with either RTX or cyclophosphamide[10] (CYC). In these severe cases, adjuvant therapy such as plasmapheresis[11] may be considered to help reduce circulating ANCA levels. Recent studies have focused on strategies to minimize GC exposure due to their long-term adverse effects, particularly in frail patients (Chung, Langford, *et al*., 2021; Speer *et al*., 2021; Tsiakas *et al*., 2021; Duarte *et al*., 2023; Hellmich *et al*., 2024).

One of the newer regimens evaluated as an alternative to GC is avacopan. Avacopan functions by inhibiting the complement receptor C5a receptor, a proinflammatory mediator involved in immune cell activation, thereby reducing leukocyte migration along the inflammatory pathway. It has been shown to be effective in maintaining remission for up to 52 weeks and in reducing the relapse rate by 11%. Avacopan has been approved for use in adult patients with severe GPA or MPA, in combination with RTX or CYC, as a substitute for prednisolone. The recommended dosage is 30 mg twice daily (Duarte *et al*., 2023; Hellmich *et al*., 2024).

In patients with EGPA who do not present with life-threatening conditions, mepolizumab (MEPO) may be used as an alternative to prednisone, particularly for managing severe respiratory manifestations such as asthma. MEPO acts by inhibiting interleukin-5, which plays a key role in sustaining hypereosinophilia involved in the

[9] Continue to provide pharmacological effects for patients without increasing the risk of recurrence of disease onset
[10] The recommended dose for remission induction is 2.5 – 3 grams
[11] Removal of plasma from the body to remove antibodies that play a role in autoimmune disease; indicated in AAV patients with diffuse alveolar haemorrhage (DAH) or severe renal impairment

disease's pathogenesis. The recommended dosage for MEPO in patients over 12 years is 300 mg administered subcutaneously every four weeks (Wechsler *et a*l., 2017; Duarte *et al*., 2023; Hellmich *et al*., 2024).

Clinical guidelines recommend that immunosuppressive therapy be continued for at least 24 months following remission[12]. given the high risk of relapse in patients with AAV, maintenance therapy for up to 36 months is strongly emphasized. The goal of the maintenance phase is to prevents potential relapse and mitigate the cumulative side effects of drugs used during the remission induction phase, using a less aggressive immunosuppressive regimen. For all AAV subtypes, a gradual tapering of GC dosage is implemented during the maintenance phase. In patients with GPA, MPA, and EGPA who have achieved remission, RTX may still be used. for patients who are intolerance to RTX, azathioprine (AZA) is viable alternative. Additionally, leflunomide may be considered for those with contraindications to AZA (Duarte *et al*., 2023; Hellmich *et al*., 2024).

In principle, the therapeutic approach for various types of vasculitis follows a similia pattern, consisting of a remission induction phase followed by a maintenance phase. In GCA—the most common type of vasculitis in elderly patients—GCs are particularly effective in suppressing the exaggerated immune response driven by Th17 cells, as well as in reducing anemia, systemic symptoms, and acute inflammatory responses associated with GCA. GC therapy typically begins with a high initial dose followed by a gradual taper individualized to the patient's condition. Prednisolone is usually started at 40-60 mg/day and tapered to 15-20 mg/day after 2-3 months (Hellmich *et al*., 2024). However, GC monotherapy—especially when the dose is reduced to below 10 mg/day or discontinued entirely—can increase the risk of relapse. This often necessitates returning to the initial dose, particularly in patients with GC-dependent disease, in whom tapering to physiological levels proves difficult[13] (Mainbourg *et al*., 2020). The challenges in achieving and maintaining the lowest effective GC dose highlight the need for alternative treatment regimens, particularly in patients over 75 years of age, those receiving treatment for longer than two years, on individuals with comorbidities such as diabetes (Perrineau *et al*., 2021; Castañeda *et al*., 2022).

Several studies have reported favorable outcomes, including a reduction in relapse rates and a safe cumulative decrease in GC dosage, when combination therapy using GC and methotrexate[14] (MTX) as an adjuvant is employed. Another regimen shown to be effective as a GC-sparing agent is tocilizumab, which acts as an interleukin-6 receptor inhibitor. However, conflicting results from other studies highlight the need for further research to confirm the safety and efficacy of these agents in patients with GCA and other forms of vasculitis (Castañeda *et al*., 2022; Schmitt *et al*., 2022).

In patients diagnosed with HSP, the natural course of the disease—which often resolves spontaneously in both adult and paediatric populations—allows for supportive therapy to serve as the primary intervention. To alleviate joint pain, acetaminophen or Non-steroidal Anti-Inflammatory Drugs (NSAIDs) such as diclofenac may be administered, while carefully considering contraindications in patients with a history of gastrointestinal or renal

[12] The criteria for vasculitis remission are the absence of clinical manifestations in patients either during or having stopped using any immunosuppressive medication for at least 1 month

[13] Reducing the dose of GC in patients who have been dependent on GC for a long time for disease remission, in addition to increasing the risk of relapse for the associated disease, also takes into account the possibility of endogenous corticosteroid-producing adrenal gland insufficiency

[14] Dosage 10-15 mg/week

disorders. Adequate rest and elevation of the affected extremities may help reduce symptom severity, although the risk of recurrence persist. In paediatric patients who are no longer manageable with outpatient care alone, steroid therapy may provide symptom relief. Oral prednisolone at a dose of 1-2 mg/kg per day for two weeks may reduce abdominal and joint symptoms and promote more rapid resolution of HSP. In case of clinical deterioration, initiation of high-dose steroids in combination with immunosuppressants and intravenous immunoglobulin may be necessary to prevent further complications (Reamy, Williams and Lindsay, 2009; Putri and Awalia, 2022).

Clinical guidelines for the treatment of medium-vessel vasculitis, specifically PAN, are available in (Chung, Gorelik, *et al*., 2021). For patients newly diagnosed with active[15] and severe PAN, initial treatment with intravenous low-dose methylprednisolone is recommended. In such cases, GC therapy is preferably combined with CYC, administered either orally or intravenously. Studies has also demonstrated that the addition of CYC may reduce the toxic effects associated with prolonged GC use. For patients with contraindications to CYC, alternative non-glucocorticoid agents such as AZA or MTX may be considered. In cases of mild PAN, without life-threatening manifestations, low- to moderate-dose oral GC may be sufficient. GCs act by modifying cell membrane permeability and receptor activity to suppress inflammatory responses. In paediatric patients, pulse GC therapy is preferred over oral administration. Following disease remission, non-glucocorticoid therapy may be discontinued after 18 months, as most case of PAN tend to follow a monophasic[16] course. A comprehensive chart detailing the pan treatment algorithm is presented in (Chart 1).

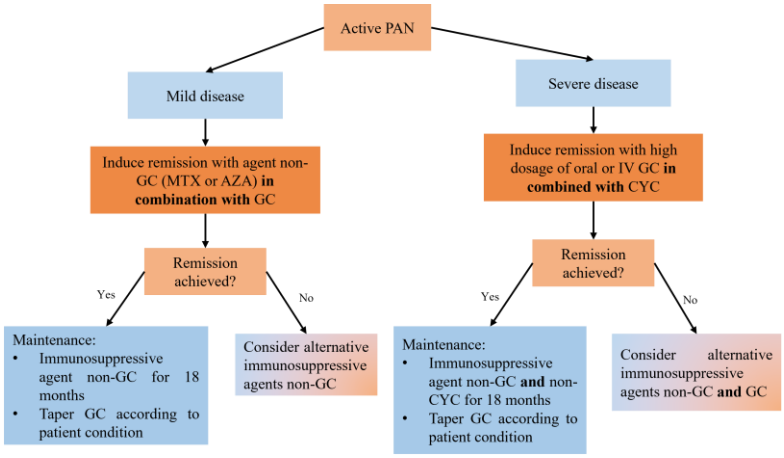

Chart 1 Treatment algorithm for active PAN (adapted from (Chung, Gorelik, *et al.*, 2021))

During the monitoring and evaluation phase following completion of the full therapeutic regimen, careful consideration must be given to the long-term effects of GC use. Potential side effects include adrenal suppression, hyperglycemia, dyslipidemia, cardiovascular disease, osteoporosis, psychiatric disorders, and immune suppression, which may increase the risk of opportunistic infections from various pathogens. Additional adverse

[15] Readers can review the assessment of vasculitis disease activity through various scoring systems such as VDI and BVAS for AAV

[16] The patient experienced only one inflammatory episode and it did not recur after remission was achieved

effects that may occur in certain patients include weight gain, insomnia, peptic ulcer disease, cataracts, hepatic steatosis (fatty liver), skin atrophy, growth or later developmental delays, and other manifestations that may emerge either early or later during the course of therapy (Alan and Alan, 2017).

Prognosis and Complication

The mortality rate in patients with AAV is 2.7 times higher than the general population (Tan *et al*., 2017). Around 40% of AAV patients die with vasculitis as one of the contributing factors in the chain of causes of mortality (Dagostin *et al.,* 2021). However, the survivability rate is currently increasing along with the success of diagnostic and treatment methods (Tan *et al.,* 2017). The median survival time since AAV diagnosis is estimated to be only 17.8 years (Álamo *et al.,* 2023). This survival duration must continue to be improved by reducing the duration of delayed diagnosis and accelerating good treatment responses. Infection characterized by high CRP levels, malignancy, impaired renal function characterized by creatinine levels, and the emergence of various comorbidities are significantly associated with poor prognosis in patients with vasculitis (Kronbichler *et al.,* 2020). Cardiovascular disease also accounts for 14% as the main cause of death in AAV patients (Álamo *et al.,* 2023). Along with the increase in hepatitis B vaccination coverage, the prevalence of PAN is considered to be decreasing. However, severe PAN diagnosis can increase the mortality rate by up to 40% within 5 years (Chung, Gorelik, *et al*., 2021).

Cardiovascular disease is one of the important comorbidities in vasculitis patients and is also a major cause of death. Research suggests that the incidence rate of venous thromboembolism is 8.9% in patients diagnosed with GPA with a median period of 2.1 months after diagnosis. Other studies have revealed a *relative risk* (RR) of 1.86 for myocardial infarction in patients diagnosed with AAV, with the elderly being one of the high-risk groups (Aviña-Zubieta *et al*., 2016; Kronbichler *et al.,* 2020). In patients with HSP, life-threatening complications that can occur, although rare and often complicate management include diffuse alveolar haemorrhage (DAH), venous thrombosis, and intestinal ischemia (Dhaliwal et al., 2020).

Prevention and Rehabilitation

Since most vasculitis diseases are autoimmune conditions, preventive measures are less feasible. Actions that can be considered include preventing risk factors for complications and the severity of accompanying symptoms in addition to the main manifestations of vasculitis. A study published in 2023 stated that there was an association between the use of prophylaxis in the form of *trimethoprim-sulfamethoxazole* (TMP/SMX) for *Pneumocystis jirovecii* infection and a reduced risk of severe infection in 82 AAV patients, with 68% of infections affecting the respiratory system. This reduction in infection severity was observed in both patients with therapy using RTX or CYC/AZA (Odler *et al.,* 2023).

Prevention of complications and efforts to reduce mortality rates are attempted by early detection of the disease and initiation of appropriate treatment indications, while preventing the risk of recurrence as is often the case in cases of vasculitis with GC dependence. Recurrence episodes in GCA are observed in patients with GC dependence and female gender. Studies have shown a 6-fold lower incidence of therapy failure in patients treated with a combination of GC such as *prednisone* plus the immunosuppressant *tocilizumab* compared to GC monotherapy (Dumont *et al.,* 2020; Abukanna *et al.,* 2023).

Rehabilitation in vasculitis patients is determined based on the type of disease suffered, treatment status, and severity of symptoms. In patients with PAN with nerve and muscle involvement, physical therapy can be applied to improve motor skills that are hampered by inflammation of the locomotor system (Chung, Gorelik, *et al.*, 2021).

SUMMARY

Vasculitis is a disease that consists of other more complex classifications, which can be simplified based on the size of the affected blood vessels. The complexity of the nature of the disease makes vasculitis a challenge in diagnosis and management. Although the diagnostic methods are heterogeneous, basically the management that is still valid and effective to date is the administration of glucocorticoids and adjuvants during the remission induction phase and maintenance phase. A number of new regimens have been studied for their benefits in reducing the effects of glucocorticoid toxicity while still improving patient outcomes. With the administration of long-term glucocorticoid therapy, clinical monitoring of patients and rehabilitation strategies become more important to consider immediately after the starting of the therapy. Collaboration and coordination of various specialties will be very helpful in directing the most appropriate treatment. Various aspects to be discussed further include determining the reference values of laboratory examinations used, dosage regimens that can be directly applied to patients, as well as a review of the prevalence of vasculitis in various age groups and its relationship to demographic factors and comorbidities.

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