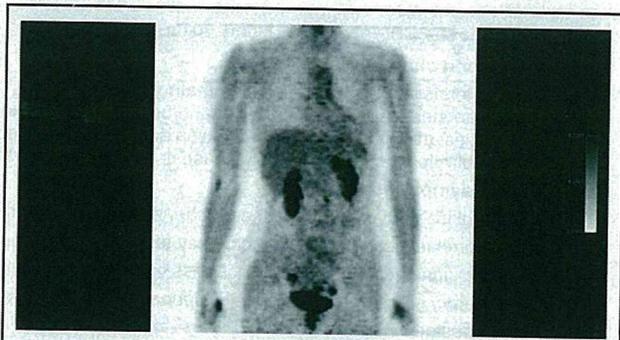Figure 5. DSA of a patient with Takayasu arteritis. DSA, digital subtraction angiography.

Figure 6. 3D-CT image of a patient with Takayasu arteritis. 3D-CT, three-dimensional computed tomography.

tion and heart failure due to aortic insufficiency secondary to aortic annular dilatation.[17]

When young female patients present with fever and malaise, the following should be evaluated in considering the possibility of Takayasu arteritis.

(1) Difference in pulse rate and blood pressure between the right and left arms
(2) Presence/absence of vascular bruits
(3) Presence/absence of heart murmurs, especially aortic insufficiency murmur

Figure 7. PET image of a patient with Takayasu arteritis. In the PET image, significant accumulation of radioactivity is observed in the ascending aorta and aortic arch. PET, positron emission tomography.

(4) Presence/absence of signs/symptoms of cerebral ischemia

2 Laboratory Findings

There are no typical changes in hematological or biochemical parameters specific to Takayasu arteritis. Disease activity of Takayasu arteritis should be evaluated according to level of C-reactive protein (CRP), sedimentation, leukocyte count, and gamma globulin level as well as the presence/absence of anemia. In addition to evaluation of inflammation, patients should be evaluated for tendency toward thrombosis, ie, platelet aggregation activity, fibrinogen, prothrombin time (PT), activated partial thromboplastin time (APTT), and antithrombin III. Immunological examination may reveal increases in immunoglobulins (IgG and IgA) and increase in complement components (C3 and C4). Significant positive associations of Takayasu arteritis with human leukocyte antigen (HLA)-B52 and HLA-B39 have been observed. It is in particular believed that patients with HLA-B52 exhibit more severe lesions than those without it.
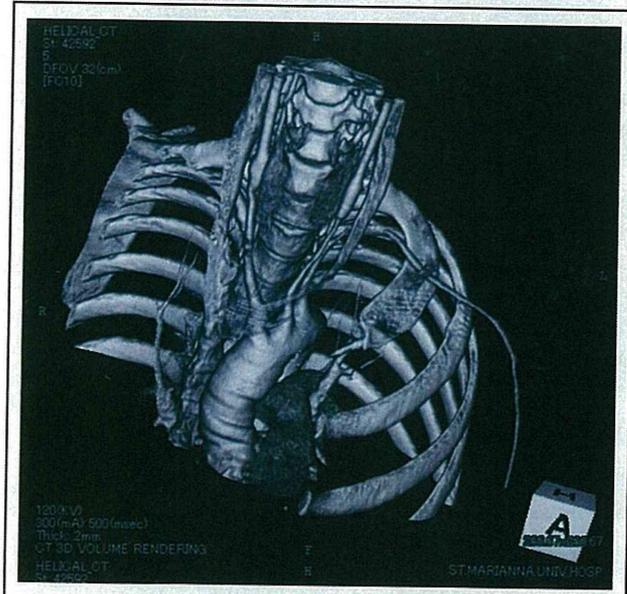
The presence/absence of stenosis and dilatation of blood vessels should be evaluated with methods of angiography, such as digital subtraction angiography (DSA) and three-dimensional computed tomography (3D-CT). F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful in the topographic diagnosis of vessel wall lesions (Figures 5–7).

5. Diagnostic Methods and Criteria (Table 5)

6. Policies and Guidelines of Treatment

1 Medical Treatment (Figure 8)

Glucocorticoid treatment is the gold standard in the medical treatment of Takayasu arteritis. Patients generally respond well to glucocorticoid. The typical initial dose is approximately 20 to 30 mg/day PSL, though the dose should be adjusted according to the age and constitution of the patient.[18] When clinical and laboratory findings continue to improve for ≥2 weeks after the initiation of glucocorticoid therapy, the dose should be tapered by about 5 mg every other week, during which time periodic evaluation of severity and disease activity should be performed. The typical maintenance dose is 5 to 10 mg/day PSL, and withdrawal from glucocorticoid therapy should be attempted whenever possible (Level A, Class I).

Table 5. Diagnostic Criteria for Takayasu Arteritis

1. Definition and characteristics

Takayasu arteritis is a non-specific inflammatory disease of unknown etiology that causes stenosis, occlusion, or dilatation of the aorta and its major branches, pulmonary arteries, and/or coronary arteries. Its main clinical manifestations include ischemic disorders of organs supplied by vessels with stenosis or occlusion and aneurysms caused by dilatation of affected arteries. Signs and symptoms differ widely by the location of affected vessels. This disease is particularly prevalent among young women.

2. Signs and symptoms

(1) Cerebral ischemia: Dizziness, headache, syncope, and hemiplegia, etc.

(2) Upper limb ischemia: Pulse deficit, easy fatigability in the upper limbs, numbness of fingers, cold sensation, and upper limb pain

(3) Cardiac signs and symptoms: Shortness of breath, palpitations, chest pressure, angina, arrhythmia

(4) Respiratory signs and symptoms: Dyspnea, bloody sputum

(5) Hypertension

(6) Visual signs and symptoms: Transient or persistent visual impairment, loss of vision

(7) Lower limb signs and symptoms: Intermittent claudication, weakness, easy fatigability in the lower limbs

(8) Pain: Neck pain, back pain, lower back pain

(9) Systemic signs and symptoms: Fever, generalized malaise, easy fatigability, lymphadenopathy (cervical)

(10) Skin signs and symptoms: Erythema nodosum

3. Important diagnostic findings

(1) Abnormal pulse and blood pressure in the upper limbs (decrease or loss of pulse in the radial artery, and significant difference in blood pressure between the right and left arms)

(2) Abnormal pulse and blood pressure in the lower limbs (increase or decrease of pulse in the femoral artery, decrease in blood pressure, and difference in blood pressure between the upper and lower limbs)

(3) Vascular bruits in the neck, back, or abdomen

(4) Heart murmurs (mainly due to aortic insufficiency)

(5) Hypertension in young patients

(6) Funduscopic changes (hypotensive fundus, hypertensive fundus, reduced visual acuity)

(7) Facial atrophy, nasal septal perforation (especially in severe cases)

(8) Inflammatory findings: Low-grade fever, cervical pain, generalized malaise

4. Supportive diagnostic findings

(1) Inflammatory reactions: Elevated erythrocyte sedimentation rate, elevated CRP, leukocytosis, increase in gamma globulin

(2) Anemia

(3) Immune disorder: Increase in immunoglobulins (IgG, IgA), increase in complement components (C3, C4)

(4) Coagulation/fibrinolytic system: Hypercoagulation (abnormal fibrinolysis), increase in platelet activity

(5) HLA: HLA-B52, B39

5. Characteristic findings of diagnostic imaging

(1) Calcification of the aorta: Plain chest X-ray, CT

(2) Thickening of the thoracic aortic wall: Plain chest X-ray, CT, MRA

(3) Occlusion/stenosis of arteries: DSA, CT, MRA
Branches of the aortic arch: From focal to diffuse stenosis
Descending aorta: Diffuse stenosis (atypical aortic coarctation)
Abdominal aorta: Diffuse stenosis (atypical aortic coarctation)
          Continuous stenosis of the descending aorta and upper abdominal aorta is often observed
Branches of the abdominal aorta: Ostial stenosis

(4) Dilatation lesions: DSA, ultrasonography, CT, MRA
Ascending aorta: Diffuse dilatation, complication by aortic insufficiency
Brachiocephalic artery: From diffuse to focal dilatation
Descending aorta: Diffuse dilatation with uneven vascular walls, from beaded pattern of dilatation and stenosis to focal dilatation

(5) Pulmonary arterial lesions: Pulmonary scintigraphy, DSA, CT, MRA

(6) Coronary artery lesions: Coronary angiography

(7) Multiple lesions: DSA

6. Diagnosis

(1) Definitive diagnosis is made by diagnostic imaging (DSA, CT, MRA).

(2) When angiography reveals multiple lesions with occlusion or dilatation of the aorta and its primary branches in young patients, Takayasu arteritis (aortitis syndrome) should be considered the most likely diagnosis even if no inflammation reaction is observed.

(3) If both the angiographic findings in Item (2) and inflammation reaction are observed, the diagnosis of Takayasu arteritis (aortitis syndrome) should be made.

(4) Patients with the above-noted clinical and laboratory findings in whom the following diseases can be ruled out should be diagnosed as having Takayasu arteritis.
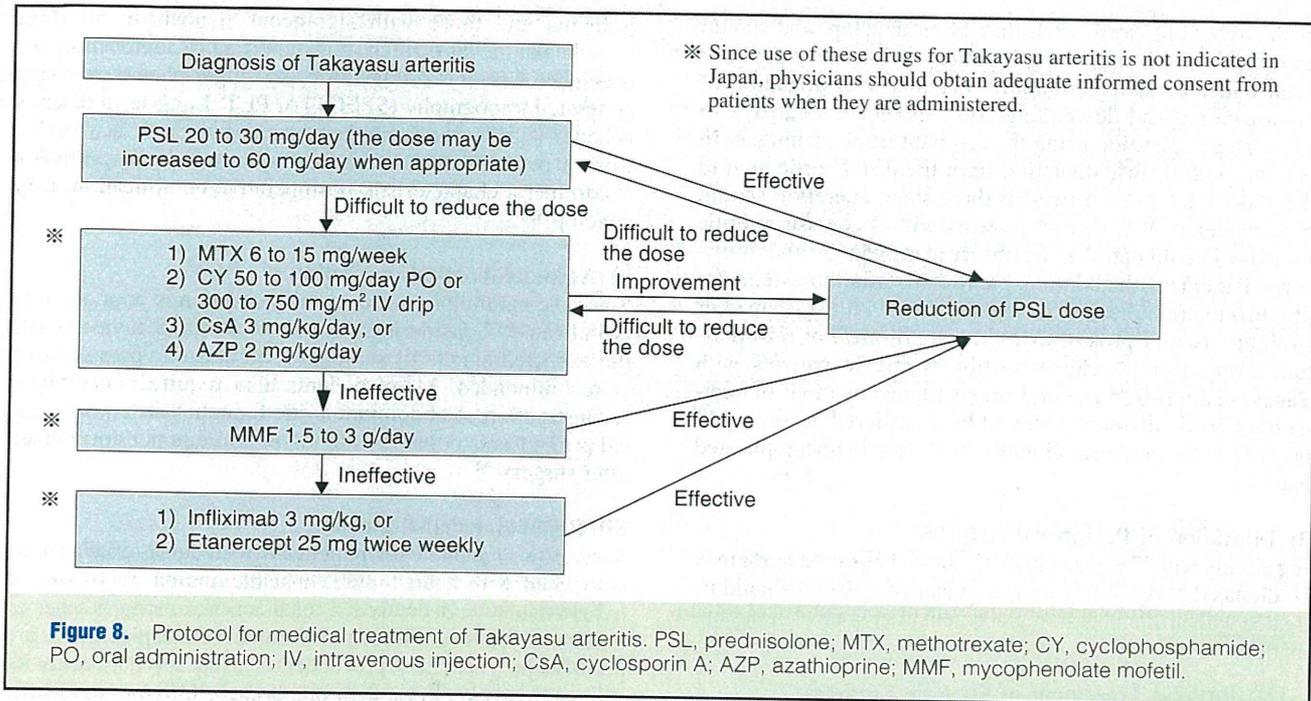
7. Conditions to be included in the differential diagnosis of Takayasu arteritis

(1) Arteriosclerosis	(2) Inflammatory abdominal aortic aneurysm
(3) Vascular Behcet's disease	(4) Syphilitic mesaortitis
(5) Temporal arteritis (Giant cell arteritis)	(6) Congenital vascular anomaly
(7) Bacterial aneurysm	

Report of the Intractable Vasculitis Study Group of the MHLW in 1998.
MHLW, Ministry of Health, Labour and Welfare (formerly Ministry of Health and Welfare).
CRP, C-reactive protein; Ig, immunoglobulin; HLA, human leukocyte antigen; CT, computed tomography; MRA, magnetic resonance angiography; DSA, digital subtraction angiography.

Figure 8. Protocol for medical treatment of Takayasu arteritis. PSL, prednisolone; MTX, methotrexate; CY, cyclophosphamide; PO, oral administration; IV, intravenous injection; CsA, cyclosporin A; AZP, azathioprine; MMF, mycophenolate mofetil.

However, patients with HLA-B52 often exhibit resistance to glucocorticoid and require treatment at high doses.[19] Since organ infarction due to vascular stenosis, aortic insufficiency, hypertension, and/or pulmonary hypertension may occur, appropriate treatment for these conditions is also necessary. For patients with glucocorticoid resistance and those who require dose reduction of glucocorticoid due to ADRs to treatment, oral or intravenous CY[20] or oral treatment with MTX,[21] azathioprine,[22] and/or cyclosporine[23] is added. Recently, treatment with mycophenolate mofetil,[24] anti-tumor necrosis factor (TNF-α) therapy,[25] and peripheral stem cell transplantation[26] have been attempted. However, there are concerns about ADRs to these drugs, such as bone marrow suppression and renal disorder, as well as the increased risk of infection in patients using these drugs together with glucocorticoids. Since these treatments are not covered by NHI of Japan, and currently available data are limited to the results of investigations in small numbers of patients, physicians should obtain adequate informed consent from patients when they use these methods, and should observe patients carefully for any adverse events.

2 Surgical Treatment

Surgical treatment of occlusions and dilatations due to Takayasu arteritis should in principle be performed during periods in which patients do not exhibit severe inflammation and are not on glucocorticoid therapy.[27-35] However, when surgical treatment needs to be performed promptly due to severe signs and symptoms, it should be performed after a sedimentation rate of ≤30 mm/hr and CRP of ≤1.0 mg/dL have been achieved with glucocorticoid therapy. When inflammatory responses continue after surgery, glucocorticoid should be administered to prevent dysraphia and control and prevent recurrence of inflammation. Patients should undergo CT of the trunk annually to observe the condition of reconstructed areas and the remaining aorta.

(1) Surgical Treatment of Cardiac and Dilatated Lesions

1) Cardiac Lesions

Aortic regurgitation develops when the aortic cusps are thickened or shrunken. Valve replacement should be considered for patients with a regurgitation fraction of ≥three-quarters. Although mechanical valves are often used, bioprosthetic valves are used for elderly patients and young female patients who wish to become pregnant. When inflammation cannot be controlled, affected vessels should be replaced with a valved conduit (Bentall surgery) even when aortic root dilatation is absent.[31-33] When anginal pain and significant coronary stenosis are present, coronary revascularization should be performed.[36-40] When coronary artery bypass grafting (CABG) is performed, the type of grafts and site of proximal anastomosis should be carefully selected. In Takayasu arteritis, ostial lesions are especially prevalent in patients with coronary lesions. Coronary ostial endarterectomy and coronary ostial patch angioplasty are useful in some patients.[40] For patients with pulmonary hypertension due to pulmonary artery stenosis, pericardial patch angioplasty or reconstruction with vascular prostheses should be performed. Mass-like dilatation of the pulmonary arteries may occur. When pulmonary arterial lesions are treated during surgery of other lesions, the affected lesion should be partially resected and directly sutured.

2) Aortic Root Dilatation

Surgical treatment of thoracic aortic aneurysm[41-43] is indicated for patients with aortic aneurysm with a maximum short axis of ≥50 mm on CT of the trunk, a pronounced tendency toward dilatation, a ruptured aneurysm, and/or a symptomatic aneurysm. Whether surgery is indicated should be carefully evaluated in patients with aortic root dilatation with encircling calcification. Patients with aortic root dilatation should be treated with aortic root replacement (Bentall surgery). In the treatment of patients with Takayasu arteritis, valve preservation should in general be avoided. Spindle-shaped dilatation

of the ascending aortic arch may often develop, and should be treated with hemiarch replacement or total-arch replacement under median sternotomy. Patients with dilatation of the ascending and descending aorta should be treated with a two-stage operation using the elephant trunk technique. In patients with diffuse dilatation from the distal aortic arch to the abdominal aorta, a two- or three-stage operation should be considered. It is rare in patients with Takayasu arteritis for mass-like dilatation to be observed only in the abdominal aorta. Patients with abdominal aortic dilatation to a diameter of ≥40 mm are indicated for replacement with a Y-shaped or straight vascular prosthesis by transperitoneal or retroperitoneal approach. Aortic dissection is rare in patients with Takayasu arteritis.[44] The indications for and methods of treatment of aortic dissection should be considered according to the criteria for treatment of aortic dissection in uncomplicated patients.

3) Dilatation of Peripheral Arteries

In patients with Takayasu arteritis, branches of the aorta may be dilatated.[45] Arteries with a diameter of ≥30 mm should be treated with artificial graft replacement after control of inflammation.

(2) Surgical Treatment of Stenotic Lesions

1) General Descriptions

i) Surgical Treatment

Bypass surgery is the standard technique.[46] Surgery should be performed when inflammation is not present and the grafts should be anastomosed to intact vessels. Branches of the aortic arch are bypassed with artificial grafts, while the renal arteries are bypassed with artificial grafts or venous grafts.[47] Since the incidence of aneurysm at the site of anastomosis is high, patients should be followed for a long period of time after bypass surgery.

ii) Vascular Interventions

Bifurcated lesions often lead to restenosis, and stenting for such lesions does not improve the outcome.[48] Stenting is mainly indicated for discrete lesions and high-risk patients. It has been reported that the use of stents in the treatment of aortic coarctation may improve both the early and long-term outcomes of patients with Takayasu arteritis.[49–51]

2) Descriptions of Individual Diseases

i) Bifurcated Lesions in the Aortic Arch

Surgery is indicated for patients with symptomatic cerebral ischemia and those with significant stenosis in all three branches of the aortic arch. It is important to demonstrate the presence of cerebral ischemia using single photon emission computed tomography (SPECT) or PET. Long-term patency is better with bypass from the ascending aorta than with that from a patent branch of the aortic arch.[52] Hyperperfusion syndrome, a characteristic postoperative complication, may develop.[53]

ii) Atypical Aortic Coarctation

Since the natural prognosis of this condition is poor, surgery is indicated. Considering the risk of surgical invasion and the expected benefit of surgery, aorto-aortic bypass grafting is recommended. Many patients also require concomitant reconstruction of abdominal aortic branches. The postsurgical prognosis is poor when blood pressure is not normalized after surgery.[54]

iii) Renal Arterial Lesions

Surgery is indicated for patients with renal arterial lesions associated with heart failure, unstable angina, renovascular hypertension, or decreased renal function, among other conditions. Bypass grafting and renal autotransplantation are performed. The latter procedure is used for patients with lesions involving more than one branch. In bypass grafting, infrarenal aortic bypass surgery with vein grafts is frequently performed.[55,56]

iv) Mesenteric Arterial Lesions

Although it is believed that surgery is indicated for patients with symptomatic mesenteric arterial lesions, reports for many patients subjected on this have not yet been published.

7. Prognosis

The penetration of advanced examination techniques such as magnetic resonance angiography and CT has enabled physicians to diagnose and treat patients with Takayasu arteritis promptly, and the prognosis of this disease has improved significantly. The prognosis of Takayasu arteritis is affected by the presence/absence of renal arterial stenosis, aortic coarctation, aortic valve insufficiency, and aneurysms. Patients with such lesions should be treated from the early phase of disease with appropriate medical treatment and, when appropriate, appropriate surgical treatment to improve long-term outcome.

III Buerger Disease

1. Definition and Epidemiology

The diagnosis of Buerger disease is based on the criteria for diagnosis published by the Intractable Vasculitis Study Group of the MHLW (described below). Buerger disease causes segmental lesions in arteries and veins of the extremities, and is observed in young and middle-age males in their 20s to 40s. Pathologically, it is characterized with diffuse, inflammatory, hyperplastic, and nonsuppurative changes affecting all layers of affected vessels as well as thrombotic occlusion of lesions.[57] Although it has been estimated that the annual incidence of Buerger disease is 4 to 5 patients in 100,000, since the late 1970s new cases of it have decreased rapidly. In 2006, about 8,000 patients with Buerger disease were certified as having a Specific Disease. Age at onset is mainly in the 20s to 40s, and patients have a history of smoking and are mostly male. Although the percentage of manual workers tends to be high, there are no characteristics suggestive of a relationship with any particular occupation. There are no

genetic factors or geographical differences known to be associated with the disease, either. It has been suggested that Buerger disease is associated with periodontal disease, though no epidemiological data have supported this association. Although Buerger disease is present worldwide, it is especially prevalent in South Asia, East Asia, and Turkey. The presence of racial/ethnic differences in prevalence has been suggested.[58]

2. Pathogenesis

Factors possibly involved in the onset of Buerger disease include smoking, infection, nutritional disorder, autoimmunity, and activation of vascular endothelial cells.[59–61] The involvement of microcirculation disorder and racial/ethnic factors has also been pointed out.[62,63] Smoking is an important factor associated with exacerbation of Buerger disease. There is a significant correlation between smoking and major amputation.[58] Smoking is known to cause vasospasm and hypercoagulation.[58,64] The involvement of syphilis was suggested in the past.[65,66] Apical periodontitis is present in 75% of patients with Buerger disease,[67] and in many patients the types of bacteria detected in periodontal tissues are also detected in biopsy specimen obtained from arterial lesions.[68] In addition, patients exhibit increases in hematocrit and blood viscosity, decrease in deformability of erythrocytes, and activation of platelets.[69] It has been reported that serum concentrations of anti-endothelial cell antibodies and ANCA are increased during the active phase of Buerger disease, and that these findings are useful in the diagnosis of the disease and evaluation of disease activity.[63] There are associations between Buerger disease and HLA-A9, HLA-B5, HLA-A1, HLA-B8, and HLA-DR4.[70–72] There is a negative association between this disease and HLA-B12.[73] The incidence of Buerger disease is low among individuals with HLA-DPB1*0401 and those with HLA-DRB*1302.[74]

3. Pathologic Findings

Buerger disease is a vasculitis affecting muscular-type arteries, especially medium- or small-sized arteries, in the extremities and is characterized by the occurrence of segmental thrombotic lumen occlusions associated with various degrees of inflammation. It is frequently associated with migrating thrombophlebitis.

Its most characteristic acute-phase finding is thrombosis associated with marked infiltration by neutrophils. The lumens of affected vessels are often occluded by thrombi.

During the sub-acute phase, the lesions are infiltrated mainly by macrophages and lymphocytes. In some cases, granulomatous inflammation involving foreign body giant cells, Langhans giant cells, and/or activated histiocytes may be observed. The lumen of affected arteries in the amputated extremities of patients with chronic-phase Buerger disease are narrowed or occluded with severe fibrous thickening of the tunica intima. The thick tunica intima during the chronic phase of Buerger disease exhibits only slight inflammation, and recanalization may occasionally be observed. Buerger disease should be differentiated from nonspecific thrombosis, thromboembolism, and aortosclerosis based on pathological findings and clinical/epidemiological characteristics.

Table 6. Incidences of Ischemic Signs/Symptoms of Buerger Disease[75]

	Incidence
(1) Location	
Upper limbs only	5.1%
Lower limbs only	74.7%
Upper and lower limbs	20.2%
(2) Affected arteries	
Ulnar artery	11.5%
Anterior tibial artery	41.4%
Posterior tibial artery	40.4%
(3) Initial signs and symptoms	
Paresthesia, cold sensation, cyanosis	37%
Plantar claudication	15%
Sural claudication	16%
Pain at rest	10%
Ulcer/gangrene	19%
(4) Signs/symptoms observed during the entire course of Buerger disease	
Ulcer/gangrene	72%
Migrating phlebitis	43%
Upper limb lesions	90%

4. Clinical Features and Laboratory Findings

1 Ischemic Signs/Symptoms

(1) Ischemic Signs/Symptoms in the Lower Limbs

1) Cold sensation: Cold sensation in the toes is particularly prevalent.
2) Paresthesia: Numbness of the fingers, toes, feet, and hands is especially prevalent.
3) Skin color change: The skin color of affected fingers and toes turns red (rubor) regardless of the position of the lower limbs. Red fingers/toes are observed even when the limbs and the trunk are kept in a horizontal position, and not just when the hands and legs are kept down.
4) Intermittent claudication: A condition involving fatigue, pain, and/or muscle "cramping" that develops after a certain amount of exercise, and makes it impossible to continue exercise.
5) Pain at rest: Unbearable stinging pain that disturbs sleep.
6) Ulcer/gangrene: These conditions often develop in the fingers and toes especially around nails, and are often caused by mechanical stimuli, burns, and medical procedures.

(2) Ischemic Signs/Symptoms in the Upper Limbs

Signs/symptoms of Buerger disease may develop in the upper as well as the lower limbs. However, it is believed that the signs/symptoms in the fingers, hands, and arms are milder than those in the lower limbs.

2 Incidence of Ischemic Signs/Symptoms

Table 6 lists the incidences of ischemic signs/symptoms by type.[75]

3 Hematological Examination

There are no specific hematological findings characteristic of Buerger disease.

Table 7. Physical Findings of Buerger Disease

(1) Appearance: Atrophy of the fingers and toes, underdeveloped nails, difference in hair growth between the right and left sides, and migrating phlebitis

(2) Auscultation: Iliac artery, femoral artery, and popliteal artery

(3) Palpation: Decreased skin temperature in the extremities, fingers, and toes, and decrease or loss of pulse in peripheral arteries

(4) Provocation tests: Positive Allen's test, positive straight leg-raising test

Table 8. Noninvasive Testing for Buerger Disease

A. Functional diagnosis

(1) Blood pressure (upper arm, fingers, ankle joint, toes): Doppler method, pulse wave method

(2) Skin perfusion pressure: Laser Doppler method

(3) Skin oxygen saturation: Percutaneous oxygen partial pressure monitoring

(4) Skin temperature: Thermography

(5) Skin blood flow: Laser Doppler method

(6) Muscle oxygen saturation: Near-infrared spectroscopy

(7) Blood flow: Air plethysmography, strain gauge plethysmography

B. Morphologic diagnosis

(1) Magnetic resonance angiography

(2) Contrast three-dimensional computed tomography (3D-CT)

Table 9. Angiographic Findings of Buerger Disease

(1) In the lower limbs, lesions are observed only in the knee joint or lower leg. In the upper limbs, no lesions are observed in the upper arm above the elbow.

(2) Chronic obstruction associated with secondary thrombi is observed.

(3) The arterial wall on the proximal side of the lesion is smooth and is not rough with a moth-eaten appearance, calcification, or other atherosclerotic changes.

(4) Abrupt or tapering occlusion of arteries is observed.

(5) Corkscrew, tree-root, or bridging configuration of collateral vessels is observed.

(6) Accordion-like appearance of arteries is a characteristic sign of Buerger disease.

4 Involvement of Visceral Arteries

Buerger disease mainly affects medium- or small-sized arteries and veins in the extremities, and rarely affects visceral arteries.

5. Diagnostic Methods and Criteria
(Tables 7–12)

Physical findings (**Table 7**) are important in the diagnosis of Buerger disease. When the presence of Buerger disease is suspected, appropriate noninvasive examinations (**Table 8**) should be conducted to determine whether further examination for the disease should be performed. Morphologic diagnosis is especially important. Patients should be examined for the presence/absence of angiographic findings characteristic of Buerger disease (**Table 9**). Physicians should use the criteria for diagnosis (**Table 10**), and perform differential

Table 10. Diagnostic Criteria for Buerger Disease

(1) Age at onset less than 50 years

(2) History of smoking

(3) Occlusions observed in the popliteal artery or its distal branches

(4) Patients with arterial occlusions or a history of migrating phlebitis

(5) Patients not complicated by hypertension, dyslipidemia, or diabetes

Patients who meet the five criteria above and have negative findings for collagen disease may be diagnosed as having Buerger disease. Female patients and non-smokers require careful differential diagnosis.

Table 11. Conditions to Be Differentiated From Buerger Disease

1. Arteriosclerosis obliterans
2. Traumatic arterial thrombus
3. Popliteal artery entrapment syndrome
4. Popliteal artery adventitial cyst
5. Systemic lupus erythematosus
6. Scleroderma
7. Vascular Behcet's disease
8. Thoracic outlet syndrome
9. Atrial fibrillation

Table 12. Severity Classification of Buerger Disease

Stage I:	Although numbness, cold sensation, decrease in skin temperature and changes in skin color such as pallor and ischemic rubor are present, the patient has no limitations in activities of daily living after smoking cessation and drug treatment.
Stage II:	In addition to the signs and symptoms noted above, the patient has intermittent claudication of the plantar region or lower leg. However, after smoking cessation and drug treatment, limitations to activities of daily living do not significantly affect the social life of the patient.
Stage III:	Changes in skin color of fingers and toes and localized ulcer or necrosis or severe intermittent claudication are observed. Conventional drug treatment is not effective in maintaining activities of daily living required for social life.
Stage IV:	Due to painful ulcer, the patient has limitations to activities of daily living required for social life. When treatment does not stabilize or improve symptoms, hospitalization is required.
Stage V:	The patient has severe pain due to ulcer or necrosis and requires intensive medical and surgical treatment in a hospital setting (eg, smoking cessation, bed rest, drug treatment, pain control, wound treatment, lumbar sympathectomy, bypass surgery, amputation of fingers, toes, or lower legs, and therapeutic angiogenesis).

Report of the Intractable Vasculitis Study Group of the MHLW in 1998.
MHLW, Ministry of Health, Labour and Welfare (formerly Ministry of Health and Welfare).

diagnosis to rule out the diseases listed in **Table 11**. The classification of severity of Buerger disease (**Table 12**) should be used to perform appropriate treatment and provide instructions on lifestyle.

6. Policies and Guidelines of Treatment

1 Policies of Treatment

The policies of treatment of Buerger disease published by the Intractable Vasculitis Study Group of the MHLW are as follows.

(1) Principles of Treatment
1) Encourage smoking cessation, and avoid passive smoking.
2) Keep the affected legs/arms and the entire body warm, and avoid exposure to cold temperatures.
3) Perform walking training and exercise therapy regularly.

(2) Treatment Policies for Primary Healthcare Institutions
1) Patients with mild disease should be treated orally with drugs and followed up.
   I. When signs/symptoms are stabilized or improved, oral drug treatment should be continued.
   II. When signs/symptoms are exacerbated, patients should be referred to secondary or tertiary healthcare institutions.
2) Patients with severe disease should be referred to secondary or tertiary healthcare institutions.

(3) Treatment Policies for Secondary/Tertiary Healthcare Institutions
1) Patients with mild disease and patients who have improved with oral drug treatment should continue to be treated with oral drugs.
2) Patients with exacerbation and those with severe disease should in principle be treated in the hospital setting.
   I. Injectable drugs should be combined with oral drugs.
   II. During treatment, angiography should be performed for differential diagnosis.
   III. For patients with severe disease not responding to drug therapy, appropriate treatment such as revascularization, sympathectomy, ganglion blocking, and toe amputation should be selected.

2 Treatment

(1) Drug Treatment
Oral drugs should be administered for about 3 months. When signs/symptoms are improved, treatment should be continued. Oral drugs commonly used in the treatment of Buerger disease are cilostazol, beraprost sodium, sarpogrelate hydrochloride, limaprost alfadex, and ticlopidine hydrochloride. Injectable drugs include alprostadil alfadex (PGE1-CD) and alprostadil (lipoPGE1). When no improvement is observed with infusion therapy, arterial administration of these drugs is performed.

(2) Exercise Therapy
Exercise therapy supervised by a physical therapist is useful. Various types of exercises are used. Typically, treadmill walking at a 12 percent incline at a speed of 2.4 km/hr is continued until walking causes moderate pain. Following rest for about 5 minutes, treadmill walking should be restarted. Exercise therapy for 30 to 60 minutes (including walking and rests) should be performed 3 times a week. At home, patients should walk for a distance of about 80% of the maximum walking

Table 13. Fontaine Classification	
Fontaine classification	Clinical findings
Stage I	Numbness, cold sensation
Stage II	Intermittent claudication
Stage III	Rest pain
Stage IV	Ulcer, necrosis

distance. Following a rest for 3 to 5 minutes, patients should walk for the same distance. Efficacy should be evaluated after 3 to 6 months of walking exercise.

(3) Revascularization
When absence of improvement or exacerbation is observed after conservative therapy including drug therapy for pain at rest and ulcers, revascularization should be performed.

(4) Sympathectomy
Sympathectomy is performed for the treatment of painful ischemic ulcers limited to the toes and fingers for which revascularization is not feasible. In treatment of the upper limbs, the lower third of the stellate ganglion and the second and third thoracic sympathetic ganglions are removed, while in treatment of the lower limbs the second and third lumbar sympathetic ganglions are removed.[76,77]

(5) Pain Control
Patients with severe pain should first be treated with oral analgesics. When pain cannot be controlled with oral drugs, a peridural catheter should be threaded into the epidural space for continuous epidural anesthesia.[78]

(6) New Treatments Under Development
Therapeutic angiogenesis is attracting attention as a method of treatment for patients with Buerger disease. Gene therapy, autologous bone marrow (mononuclear cell) transplantation, peripheral mononuclear cell transplantation, and autologous endothelial progenitor cell (EPC) transplantation are under investigation.

7. Prognosis

1 Prognosis of Limb Ischemia
The prognosis of limb ischemia depends on the level of progression according to the Fontaine classification (Table 13). A nationwide questionnaire survey by the Intractable Vasculitis Study Group of the MHLW in 2003 revealed that 63% of patients with Buerger disease present with findings corresponding to Fontaine stage III or IV, while only 37% of patients present with Fontaine stage I or II findings.[79] Accordingly, 70% of patients with Buerger disease experience at least one episode of ischemic ulcer or necrosis. At the time of the questionnaire, amputation was considered when pain in ischemic limbs could not be controlled even after surgery or when necrosis had expanded. The questionnaire indicated that 8.8% of patients underwent major amputation[79] and 20.5% of patients underwent toe amputation. It is believed that the upper limbs are less frequently affected by ischemia than the lower limbs. Major amputation of the upper limbs is quite rare.

2 Factors Contributing to Exacerbation and Improvement
It has been pointed out that continuation of smoking shortens

the symptom-free period and induces exacerbation of Buerger disease. Patients who quit smoking after the onset of this disease do not experience exacerbations and often respond to treatment designed to achieve long-term remission, while those who continue smoking do not respond to treatment and undergo amputation at a significantly higher rate than those who quit smoking. Improvement may be achieved after cessation of external mechanical stimulation and elimination of other mechanisms of injury.

3 Prognosis of Non-Ischemic Limbs

In almost all patients, Buerger disease affects at least two limbs. Although the number of patients without limb ischemia is therefore very small, patients with mild, Fontaine stage I disease without severe ischemia rarely experience severe disease when they are able to quit smoking completely.

4 Concomitant Diseases and Life Expectancy

Since Buerger disease is an inflammatory condition that affects the peripheral arteries and major arteries in the extremities but rarely affects the visceral arteries that supply main organs, life expectancy is fairly long. Since many patients with Buerger disease are smokers, patients should be carefully observed for lung cancer and esophageal cancer, which are known to be associated with smoking, to ensure long life expectancy. In the nationwide survey by the Intractable Vasculitis Study Group of the MHLW, the prevalences of diabetes, hypertension, dyslipidemia, cerebrovascular disorder, ischemic heart disease and arteriosclerosis obliterans among patients with Buerger disease were 13.7%, 29.6%, 15.2%, 8%, 6%, and 5%.[79] Physicians should be aware that patients with Buerger disease may have concomitant diseases common to individuals of the same age, and should use a multidisciplinary approach in treating elderly patients.

IV Temporal Arteritis (Giant Cell Arteritis)

1. Definition and Epidemiology

Temporal arteritis or giant cell arteritis typically develops elderly individuals ≥50 years of age, and affects the aorta and its branches, which are large or medium in size. Extracranial arteries, especially the superficial temporal arteries, are also frequently affected. The most devastating complication of temporal arteritis is irreversible loss of vision.[80]

Temporal arteritis typically develops in individuals ≥50 years of age. A survey in Japan in 1997 revealed that the male to female ratio is 1:1.7, with a mean age at onset of 71.5±10.8 years.[81,82]

2. Pathologic Findings

Pathologically, giant cells and inflammatory cells infiltrate the vascular intima, and the affected vessels are obliterated by thickened intima.[83]

3. Clinical Features and Laboratory Findings

The most important subjective symptoms are jaw claudication and diplopia, and characteristic objective findings are tenderness and pulsation of the temporal arteries. Elevated sedimentation rate and increased CPR are observed.[83] Headache is often unilateral and pulsating. Visual impairment develops in about 40% of patients, and loss of vision develops in about 10 to 20% of patients. About 30% of patients have symptoms of polymyalgia rheumatica (PMR), including stiffness and pain in the neck, shoulders, and lower back.[84] Since this disease is associated with non-specific systemic signs and symptoms such as fever and weight loss, careful differential diagnosis is required for elderly patients.

When temporal arteritis affects the posterior ciliary arteries, ophthalmic arteries, and/or central retinal arteries, serious visual impairment occurs. One such complication is arteritic anterior ischemic optic neuropathy, which causes unilateral or bilateral acute serious visual impairment.[85,86] In 30% of patients, transient amaurosis occurs as a preceding symptom. In patients who manifest the disease as unilateral visual impairment, bilateral visual impairment will develop within several days or weeks if glucocorticoid treatment is not started promptly.[87-89] Since the prognosis regarding visual acuity is poor, patients must be diagnosed and treated promptly. About 10% of patients complain of diplopia, which is believed to be caused by an oculomotor disorder manifesting as ischemic external ophthalmoplegia or ischemia of the brainstem.

Table 14. ACR Criteria for the Classification of Temporal Arteritis (Proposed by the ACR in 1990)[84]

Criteria	Definition
1. Onset age of 50 years or older	Development of clinical features or laboratory findings beginning at age 50 or older
2. New headache	New onset of, or new type of, localized headache
3. Temporal artery abnormality	Tenderness to palpation or decreased pulsation of temporal artery, unrelated to arteriosclerosis of cervical arteries
4. Elevated ESR	ESR ≥50 mm/hr by Westergren method
5. Abnormal artery biopsy	Biopsy specimen of artery revealing vasculitis characterized by predominant mononuclear or granulomatous inflammation with multinucleated giant cells
For purposes of classification, a patient is said to have temporal arteritis if at least 3 of these 5 criteria are present.*	

*Evaluation of criteria should be performed at the discretion of the treating physician.
ACR, American College of Rheumatology; ESR, erythrocyte sedimentation rate.

4. Diagnostic Methods and Criteria

1 Criteria for Diagnosis

Temporal arteritis is diagnosed according to the criteria for the classification of temporal arteritis published by the ACR in 1990 (**Table 14**).[84] Since temporal arteritis develops mainly in elderly patients and its clinical features and laboratory findings are nonspecific, histological findings of temporal artery biopsy samples are important for confirming the diagnosis. In the clinical setting, differential diagnosis to rule out the diseases listed below is important. Since visual symptoms may continue to progress to irreversible loss of vision, physicians should ensure that their patients understand that development of visual symptoms is possible, and should ensure good collaboration between specialists in internal medicine and ophthalmology in treating patients with such symptoms promptly.

2 Biopsy

Histological findings for the temporal arteries are important in ensuring correct diagnosis of temporal arteritis. Histological examination has a false-negative rate of about 15%. Since noncontiguous segmental lesions often develop, it is important to prepare serial sections of biopsy specimens.[80] Recommendations for biopsy are as follows:

(1) Timing: Samples should be obtained prior to glucocorticoid therapy. However, positive findings may be observed in samples obtained on days 14 to 28 of glucocorticoid therapy.

(2) Size of temporal artery samples: Samples with a length of ≥2 cm are preferable.

(3) Relationship between histological findings and clinical signs/symptoms: Mandibular pain, abnormal temporal arteries, and systemic signs/symptoms correlate with positive histological findings. The severity of intimal thickening is associated with visual impairment.

(4) Bilateral biopsy is not necessary. Biopsy specimen may be obtained from one side alone.

3 Diagnostic Imaging

Magnetic resonance imaging (MRI), FDG-PET, and ultrasonography are useful. PET is quite useful, and 83% of patients with temporal arteritis have PET-positive lesions in the subclavian arteries, aorta, and femoral arteries.

4 Differential Diagnosis

Temporal arteritis is a cause of FUO in elderly patients. It is important to differentiate temporal arteritis from malignant tumors, Takayasu arteritis, MPA, Wegener's granulomatosis, and infections.

5. Policies and Guidelines of Treatment

1 Glucocorticoid

Typically PSL is administered at a dose of 1 mg/kg.[90] Due to their small body size, about half of patients with temporal arteritis are treated with PSL at ≤40 mg/day in Japan. The response rate in patients receiving ≤40 mg/day was 82.9%, and quite similar to that in patients receiving PSL at ≤60 mg/day (88.2%).[82,85,91–94] It has been reported that some patients start PSL therapy at ≥80 mg/day, and undergo tapering of the dose to maintenance levels over 4 years to avoid loss of vision.[95,96]

The following initial doses are recommended.

- Patients without visual, central nervous system (CNS), or cranial nerve symptoms: PSL at 30 to 40 mg/day (Level B, Class I)
- Patients with visual, CNS, or cranial nerve symptoms: PSL at 1 mg/kg/day (Level B, Class I)

Following 3 to 4 weeks of initial treatment, doses of glucocorticoid should be tapered according to clinical signs/symptoms, sedimentation rate, and CRP. The rate of decrease should be 10 mg every other week to 20 mg/day, 2.5 mg every other week to 10 mg/day, and 1 mg every 4 weeks from 10 mg/day. The maintenance dose should be ≤10 mg/day. Many patients are able to discontinue glucocorticoid therapy.[83,97]

2 Steroid Pulse Therapy (Level B, Class IIb)

The efficacy of steroid pulse therapy in the treatment of temporal arteritis is controversial.[98] Some reports have noted that steroid pulse therapy does not exert long-term efficacy, while one study reported that patients receiving steroid pulse therapy had better outcomes than those receiving conventional steroid therapy in terms of the number of patients whose dose of PSL could be decreased to ≤5 mg/day, the number of patients with steroid-free remission, and average and total doses of steroids, and adverse events were similar.[99] At present, steroid pulse therapy should be selected for patients with visual symptoms (with severe visual impairment: Level B, Class I) and patients with or at a high risk for CNS or cranial nerve signs/symptoms.[82,100]

3 Steroid-Sparing Agents: Methotrexate (Level B, Class IIb)

While in one study treatment with MTX and glucocorticoids could not control temporal arteritis or enable decrease in doses of glucocorticoids, another report noted that MTX was effective in maintaining remission of temporal arteritis and decreasing the total dose of glucocorticoids.[101,102] Patients received glucocorticoids every other day in the former study, and received glucocorticoids daily, as in many cases in Japan, in the latter. Since the usefulness of alternate-day treatment with glucocorticoids in patients with temporal arteritis is questionable, addition of MTX is considered useful.[103–107] Treatment with MTX should be tried for patients who cannot be treated with sufficient amounts of glucocorticoids due to ADRs and those who require prompt tapering of glucocorticoids.

In the case of other steroid-sparing agents such as azathioprine, CY and cyclosporine, no reports suitable for evaluation of their usefulness in the treatment of temporal arteritis are available.

4 Low-Dose Aspirin (Level B, Class IIa)

A retrospective, non-randomized study in 166 patients has been conducted to investigate the effects of low-dose aspirin on the cranial ischemic complications of temporal arteritis.[4] The incidences of ischemic complications at onset and during the course of disease were significantly lower in patients receiving low-dose aspirin therapy than in those not receiving it. Since low-dose aspirin therapy does not pose a significant risk and cranial ischemic complications are important complications that affect ADL and QOL of patients with temporal arteritis, the authors are tempted to recommend the addition of low-dose aspirin in the treatment of temporal arteritis, although the results of randomized clinical studies are required to draw firm conclusions regarding the usefulness of this.

5 Anti-TNF-α Drugs (Level B, Class IIb)

There have been several cases in which anti-TNF-α agents

were effective in treating intractable temporal arteritis.[108–110] However, a phase II clinical study of anti-TNF-α in patients with temporal arteritis was discontinued since an interim analysis did not reveal usefulness of treatment.[111] There is no evidence supporting the use of anti-TNF-α agents for patients with temporal arteritis. Well-designed clinical studies of such agents are awaited.

6. Prognosis

Complications of temporal arteritis reported in Japan in-

cluded infections (15.3%), digestive ulcer (6.8%), cerebral infarction (5.2%), and malignant tumors.[97] Although temporal arteritis had been considered a transient condition for which treatment may be completed in 2 years, it has been reported that both this disease and PMR repeatedly recur. The most common causes of death in patients with temporal arteritis in Japan are malignant tumors, infections, and geromarasmus, in descending order.

V Polyarteritis Nodosa

1. Definition and Epidemiology

1 Definition

Polyarteritis nodosa (PAN) is a disease that induces necrotizing vasculitis in medium- or small-sized vessels but is associated with neither arteriolitis nor capillaritis (including glomerulonephritis). It was first reported by Kussmaul and Maier in 1866 as periarteritis nodosa.[112] They initially termed the condition "periarteritis" because of the presence of peri-

arterial inflammation forming nodules around the arteries in various organs. However, since further research revealed that inflammation is present affected arteries, the disease came to be called PAN. Among conditions previously classified as PAN, microscopic polyangiitis (MPA),[113] Wegener's granulomatosis,[114] and Churg-Strauss syndrome[115] have been identified as separate conditions, and the current concept of PAN has been established.

2 Epidemiology

PAN is quite a rare disease compared with MPA. It is estimated, based on the results of surveys including those conducted by the Specific Disease Epidemiology Study Group of the MHLW,[116] that the annual number of new cases of PAN in Japan is 0.5/1,000,000 population, with a prevalence of 11.7/1,000,000 population. The age at onset of PAN is lower than that of MPA, and male patients are predominant.[117] PAN associated with hepatitis B, which has often been reported in Europe and the United States, is considered rare in Japan.

2. Pathogenesis and Pathologic Findings

The main finding of PAN is inflammation of medium- and small-sized arteries. It does not affect arterioles, venules, and capillaries. PAN is not associated with glomerulonephritis, differentiating it from MPA. The typical histological finding of PAN is necrotizing angiitis characterized by fibrinoid necrosis in the tunica media.

However, the histological findings of PAN change over time, and are classified into Stages I to IV according to the criteria proposed by Arkin[118] (**Figure 9**).

In Stage I (degenerative stage), there are findings of serous exudative inflammation including swelling of the intima and media, and subintimal deposition of fibrin or hyaline-like material. In addition, swollen and degenerated smooth muscle cells in the tunica media and degenerated elastica interna are observed.

Stage II (acute inflammatory stage) is characterized by necrosis of the media and fibrin deposition. Fibrin deposition has extended to the adventitia, followed by the inflammation of polymorphonuclear leukocytes, eosinophils, lymphocytes, and plasma cells. Then, fibrinoid degeneration is observed in some or all layers of the vascular wall. Rupture, destruction, or disappearance of the elastica interna is observed, with or without thrombus. When the disease progresses rapidly, aneurysms may occur.

In Stage III (granulation tissue stage), the adventitia is
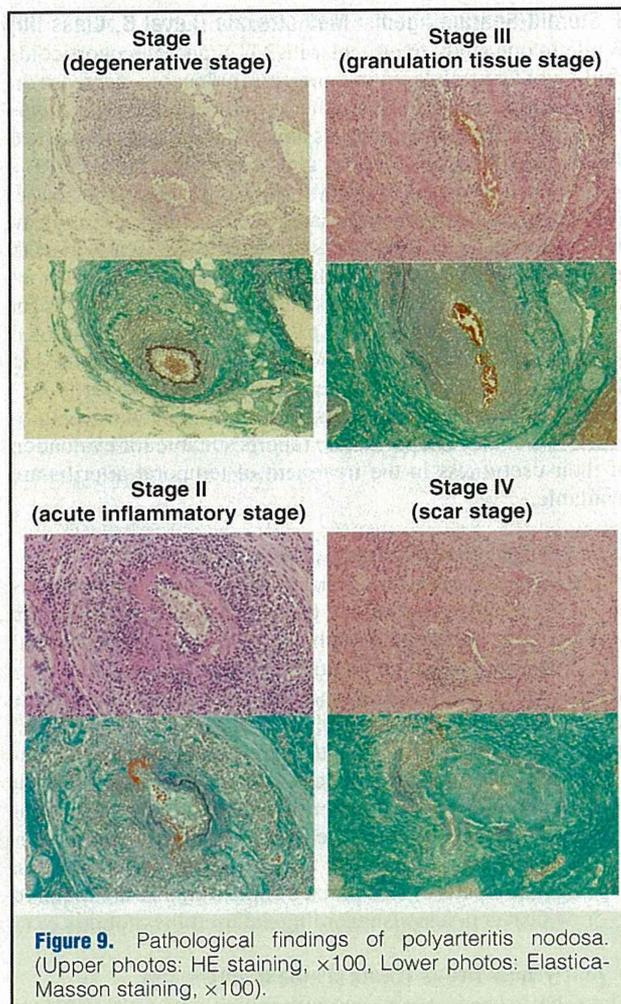
Figure 9. Pathological findings of polyarteritis nodosa. (Upper photos: HE staining, ×100, Lower photos: Elastica-Masson staining, ×100).

Stage I (degenerative stage)

Stage III (granulation tissue stage)

Stage II (acute inflammatory stage)

Stage IV (scar stage)

infiltrated with macrophages and fibroblasts, and granulation tissue is formed. In the intima, migration of myointimal cells (with phenotypic transformation of smooth muscle cells) and infiltration of fibroblasts are observed, and luminal stenosis due to intimal thickening occurs. Since intimal thickening may extend longitudinally as well as circularly, it should be noted that medial injury may not be observed in some sections of affected blood vessels.

In Stage IV (scar stage or healed granulation tissue stage), fibrous thickening of the intima, fibrosis of the media, and granulomatous scarring of the adventitia are observed. Organizing thrombus and recanalization may also be observed. These findings represent the end-stage of inflammation.

Arkin's classification was used to establish the Criteria for Histological Assessment of Necrotizing Vasculitis by the Pathology Group of the MHLW (formerly Ministry of Health and Welfare) Specific Disease Systemic Vascular Disorder Study Group in 1988, and is still used. However, it should be noted that the nature and severity of lesions may vary even in the same individual by affected site, and that pathologic staging may not always be consistent with clinical staging.

3. Clinical Features and Laboratory Findings

Since PAN is a systemic vasculitis, its signs and symptoms vary greatly. Typically, patients exhibit systemic signs and symptoms due to inflammation as well as signs and symptoms of inflammation by affected organs and those of organs due to ischemia or infarction.

1 Systemic Manifestations
(1) Fever: Patients often have a continuous fever of 38 to 39°C, but rarely have chills and shivering such as those observed during acute infection.
(2) Weight loss: The degree of weight loss depends on the severity of fever and the duration from onset to diagnosis.
(3) Hypertension: About 20% of patients develop hypertension.

2 Visceral Signs/Symptoms
(1) Kidneys: Renal involvement is the most important visceral finding and develops in more than 50% of patients.[119] Patients with typical PAN, which affects medium- and small-sized arteries from the renal arteries to interlobular arteries, manifest renin-mediated hypertention. Patients do not exhibit typical manifestation of glomerulonephritis.
(2) CNS: CNS signs/symptoms develop in about 20 to 30% of patients, typically in the form of cerebral infarction, which may cause hemiplegia and disturbance of consciousness.[120] Both intracranial hypertension and vascular injury may provoke cerebral infarction.
(3) Heart: Although it has been reported that the lesions of coronary artery due to PAN cause myocardial infarction, conduction disorder, and pericarditis, the incidence of these complications is low.
(4) Respiratory system: Respiratory signs/symptoms are not prevalent, but have occasionally developed in recent cases, mostly in association with interstitial pneumonitis.
(5) Gastrointestinal system: Abdominal pain and gastrointestinal hemorrhage are the most common signs and symptoms. Gastrointestinal perforation and intestinal infarction are particularly severe conditions and are predictive of poor prognosis.[121,122] Individual organs such as the gall-

bladder, pancreas, and appendix may also be involved.
(6) Peripheral nerves: Signs/symptoms of mononeuritis or mononeuritis multiplex mainly in the extremities are prevalent (≥50% of patients).[119] The most common symptom is sensory disturbance. Many patients complain of "numbness" of the extremities, and hypoesthesia and hyperesthesia are also common. When peripheral nervous involvement progresses to movement disorder, irreversible paralysis may occur.
(7) Skin: More than 50% of patients have various cutaneous signs/symptoms, which develop in the extremities especially the lower legs and feet. Subcutaneous nodules are prevalent among patients with PAN. Erythema nodosum, purpura, and livedo reticularis are common, and intractable skin ulcer may develop in some patients. A type of vasculitis limited to skin, termed cutaneous polyarteritis nodosa (cPAN), differs from systemic PAN.
(8) Joints and muscles: About 80% of patients complain of joint or muscle pain and stiffness. Joint deformity and destruction do not occur. Muscular signs and symptoms, such as myalgia and muscular weakness, develop at an incidence similar to that of articular signs/symptoms. Pain and weakness may be specifically pronounced in the gastrocnemius muscle. Biopsy of the gastrocnemius muscle may often demonstrate the presence of vasculitis.
(9) Others: Testicular pain has often been reported in foreign reports, though it is rare in Japan. Otitis media and sinusitis may develop, though they are rare. Uveitis, iritis, episcleritis, and retinal hemorrhage may occur.

3 Laboratory Findings
(1) Blood: No specific autoantibodies or other serological markers are associated with PAN. Leukocytosis, anemia, and thrombocytosis occur in many patients. Leukocytosis is mainly caused by an increase in neutrophils. Eosinophils, which were previously described as increased substantially, do not in fact increase significantly. Inflammatory findings such as elevation in CRP and enthrocyte sedimentation rate are pronounced. Blood urea nitrogen (BUN) and creatinine increase as renal involvement progresses. In many patients, serum albumin level may decrease and hypergammaglobulinemia may develop. Serum complement level often increases.
(2) Urinalysis: Although proteinuria and hematuria may be observed, patients do not exhibit typical findings of glomerulonephritis.
(3) Special examinations
   1) ANCA: In patients with typical PAN affecting only medium- or small-sized arteries, the incidence of ANCA is low (≤20%).
   2) Hepatitis B surface antigen (HBsAg): Although one subgroup of PAN is associated with hepatitis B virus infection,[123] the prevalence of HBsAg positive PAN is quite low in Japan.
(4) Histological findings: On biopsy, the presence of fibrinoid necrosis in medium- and small-sized arteries should be confirmed. Biopsy samples are often obtained from affected muscles and kidneys. In patients with mononeuritis multiplex or myalgia of the lower limbs, biopsy of the gastrocnemius muscle often reveals characteristic findings.
(5) Imaging: PAN is characterized by multiple small aneurysms, stenoses and occlusions in association with inflammation in the medium- and small-sized arteries. These lesions are often observed in the branches of the abdomi-

Table 15. Diagnostic Criteria for Polyarteritis Nodosa (Report of the Intractable Vasculitis Study Group of the MHLW, 2006 Revised)

[Diagnostic features]

(1) Major clinical findings

  1) Fever (≥38°C continued ≥2 weeks) and weight loss (≥6 kg over ≤6 months)

  2) Hypertension

  3) Rapidly progressive renal failure, renal infarction

  4) Cerebral hemorrhage, cerebral infarction

  5) Myocardial infarction, ischemic heart disease, pericarditis, heart failure

  6) Pleurisy

  7) Gastrointestinal hemorrhage, intestinal infarction

  8) Mononeuritis multiplex

  9) Subcutaneous nodule, skin ulcer, gangrene, purpura

  10) Polyarthralgia (polyarthritis), myalgia (myositis), muscular weakness

(2) Histological finding

Fibrinoid necrosis in medium- and small-sized arteries

(3) Angiographic findings

Multiple microaneurysms, stenoses, and occlusions in branches of the abdominal aorta (characteristically in renal arterioles)

(4) Diagnosis

  1) Definite

    Patients with ≥2 major clinical findings and the histological finding

  2) Probable

    (a) Patients with ≥2 major clinical findings and the angiographic findings

    (b) Patients with ≥6 major clinical findings including item 1)

(5) Suggestive laboratory findings

  1) Leukocytosis (≥10,000/μL)

  2) Thrombocytosis (≥400,000/μL)

  3) Elevated sedimentation rate

  4) Strongly positive CRP

(6) Diseases to be ruled out

  1) Microscopic polyangiitis

  2) Wegener's granulomatosis

  3) Allergic granulomatous angiitis

  4) Kawasaki disease

  5) Collagen disease (SLE, RA, etc)

  6) Purpura

[Notes]

(1) Histologically, polyarteritis nodosa has been classified into Stage I (degenerative stage), Stage II (acute inflammatory stage), Stage III (granulation tissue stage), and Stage IV (scar stage).

(2) Clinically, patients in Stages I and II exhibit signs and symptoms of severe inflammation of systemic vessels, while patients in Stages III and IV exhibit signs and symptoms of ischemia of affected organs.

(3) The diseases to be differentiated from polyarteritis nodosa also demonstrate necrotic vasculitis, but may be clearly differentiated from it on the basis of characteristic findings and laboratory results.

MHLW, Ministry of Health, Labour and Welfare; CRP, C-reactive protein; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.

nal aorta such as renal arteries, mesenteric arteries, and hepatic arteries and their branches, and may be observed on angiography.[124] Recently, magnetic resonance angiography and ultrasonography have been used to confirm abnormal vascular wall structure.

4 Severity of PAN

Several criteria for the classification of severity have been proposed to predict the prognosis of PAN and to select treatment strategies. The Birmingham Vasculitis Activity Score (BVAS)[125] and the Five Factor Score (FFS)[121] are fairly commonly used in many countries. These scoring systems rate the condition of visceral organs and the severity of symptoms to determine the severity of PAN. In Japan, the Intractable Vasculitis Study Group of the MHLW has proposed the "Severity Classification of Polyarteritis Nodosa and Microscopic Polyangiitis" as well as the Progressive Renal Disorder Study Group of the MHLW has proposed the "Severity Classification of Renal Disorder".

4. Diagnostic Methods and Criteria

The criteria for diagnosis of PAN proposed by the Intractable Vasculitis Study Group of the MHLW (revised in 2006, **Table 15**) should be used.
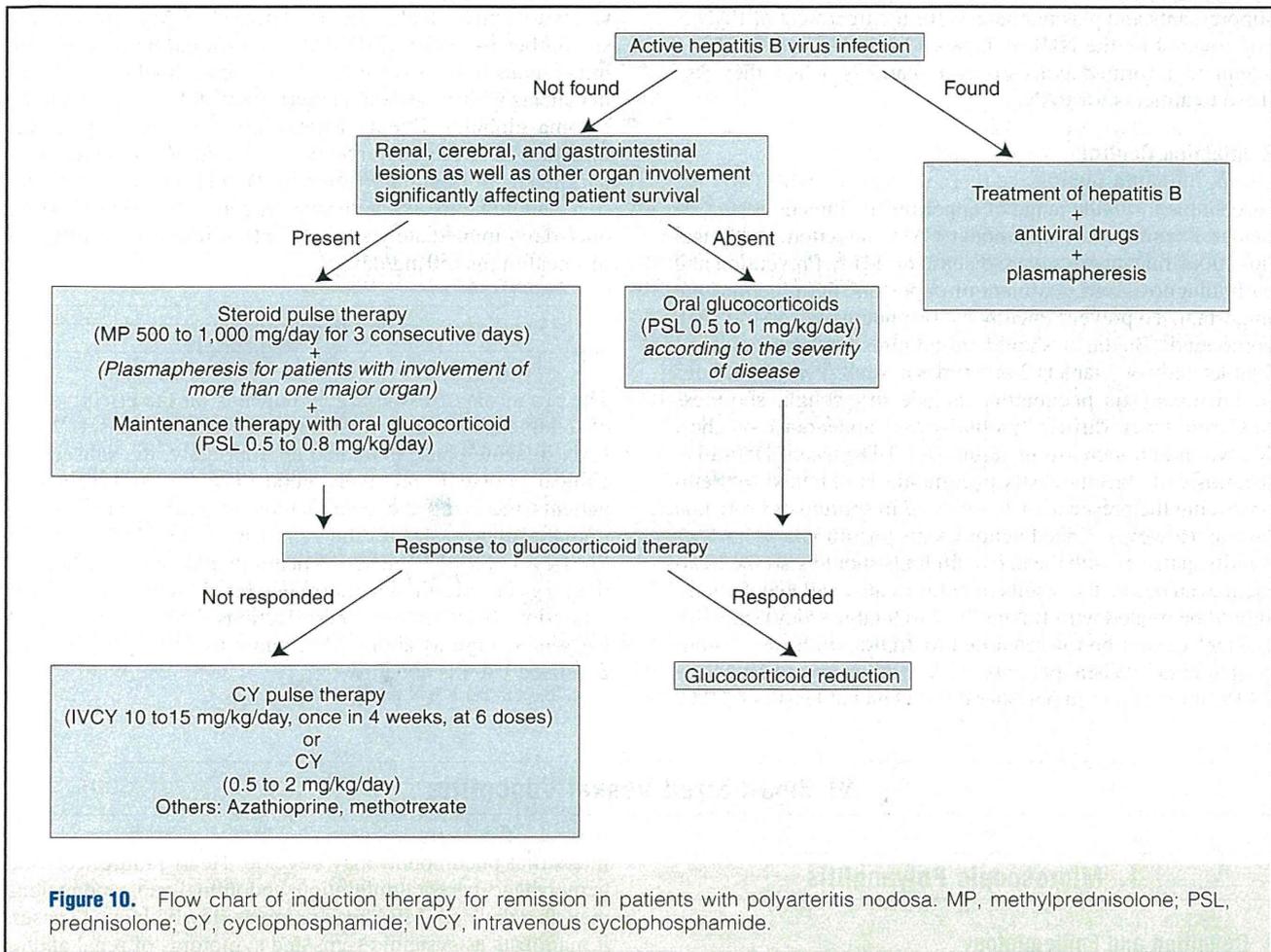
PAN is not associated with the presence of particular antibodies, such as ANCA in patients with MPA and Wegener's granulomatosis. Accordingly, differential diagnosis should be conducted according to the clinical, laboratory and imaging findings, and biopsy of affected organs should be performed whenever possible for definitive diagnosis. Differentiation between PAN and MPA is especially important. According to the Chapel Hill Consensus Conference (CHCC) in 1994, PAN is "a necrotizing vasculitis in which there is arteritis in medium- and small-sized arteries without involvement of smaller vessels such as arterioles, capillaries and venules".[113] Accordingly, when the presence of capillaritis such as glomerulonephritis is demonstrated, PAN may be ruled out.

5. Policies and Guidelines of Treatment

The treatment consists of induction therapy for remission and maintenance therapy of remission. In both phases, glucocorticoid should primarily be used (Class IIb, Level C).[126,127] When glucocorticoid therapy is not satisfactory effective, patients should also additionally receive immunosuppressants (Class IIb, Level C).[126,127] Patients associated with hepatitis B should receive antiviral therapy and plasmapheresis (Class IIb, Level C).[128,129] **Figure 10** is a summarized flow chart of induction therapy for remission in patients with PAN.

1 Induction Therapy for Remission

(1) Glucocorticoid: PSL should be administered orally at a dose of 0.5 to 1 mg/kg/day (40 to 60 mg/day) depending on the severity of PAN. Patients with visceral involvement in the kidneys, brain, and/or gastrointestinal tract that significantly affect their survival should be treated with steroid pulse therapy, ie, intravenous high-dose methylprednisolone treatment (intravenous infusion of methylprednisolone 500 to 1,000 mg/day + 5% glucose solution 500 mL/day over 2 to 3 hours, repeated for 3 consecutive days). Following pulse therapy, PSL should be administered at 0.5 to 0.8 mg/kg/day.[130]

Figure 10. Flow chart of induction therapy for remission in patients with polyarteritis nodosa. MP, methylprednisolone; PSL, prednisolone; CY, cyclophosphamide; IVCY, intravenous cyclophosphamide.

(2) Patients not responding to glucocorticoid: CY should be administered orally or intravenously at a dose of 0.5 to 2 mg/kg/day. Intravenous cyclophosphamide (IVCY) should be administered at a dose of 10 to 15 mg/kg/dose (500 to 600 mg/dose) with 500 mL of physiological saline or 5% glucose solution over 2 to 3 hours, once every 4 weeks, 6 times, approximately.[131,132]

During IVCY therapy, leukocyte count should be monitored to adjust the dose so as to avoid decrease in it to ≤3,000/mm³. Since CY is excreted through the kidneys, the dose should be decreased when it is administered to patients with a decrease with renal dysfunction (Class IIb, Level C).[133] **Table 16** shows the recommended doses of IVCY according to age and renal function. It has been reported that IVCY is equivalent to oral CY in terms of efficacy, while the incidence of ADRs is lower in IVCY than in oral CY.[134]

Other immunosuppressants, such as azathioprine and MTX, are used in the treatment of PAN (Class IIb, Level C).[134] These drugs are excreted through the kidneys, as well. Azathioprine should be administered at lower doses to patients with decreased renal function, and MTX is contraindicated for patients with renal failure.

(3) Patients with severe PAN involving more than one major organ such as the lung, kidneys, gastrointestinal tract, and pancreas should be treated with steroid pulse therapy and plasmapheresis to improve life expectancy (Class IIb, Level C).[135,136]

Table 16. Recommended Doses of Cyclophosphamide Pulse Therapy According to Age and Renal Function

Age	Serum Cr <3.4 mg/dL	Serum Cr >3.4 mg/dL
<60 years	15 mg/kg/pulse	12.5 mg/kg/pulse
60 to <70 years	12.5 mg/kg/pulse	10 mg/kg/pulse
≥70 years	10 mg/kg/pulse	7.5 mg/kg/pulse

Information Center for Japan Intractable Disease: http://www.nanbyou.or.jp/sikkan/025_2_i.htm
Source: Information from the Immune Disorder Study Group (Intractable Vasculitis Study Group).
Cr, creatinine.

(4) Patients with active hepatitis B should be treated with antiviral drugs and undergo plasmapheresis to remove immune complexes (Class IIb, Level C).[130,131]

2 Maintenance Therapy of Remission

After induction of remission by initial treatment the dose of glucocorticoid (PSL) should be tapered carefully over time to maintenance doses (5 to 10 mg/day)and patients are observed for recurrence. The duration of treatment with glucocorticoid and/or immunosuppressants should not generally exceed 2 years (Class IIb, Level C).[137] Treatment with CY should be limited to 3 to 6 months. Following the induction of remission, CY should be switched to azathioprine, an agent with a lower incidence of ADRs, which should be administered for 6 to 12 months (Class IIb, Level C).[138] The use of immuno-

suppressants and plasmapheresis for the treatment of PAN is not covered by the NHI of Japan. Physicians should obtain adequate informed consent from patients when they use these treatments for PAN.

3 Infection Control

During immunosuppressive therapy, patients with PAN are susceptible to a wide range of opportunistic infections. In particular, Pneumocystis pneumonia, CMV infection, and fungal infections may cause severe disease or death. Prevention and early diagnosis and treatment of opportunistic infections are important. To prevent Pneumocystis pneumonia, SMX/TMP compound (Baktar®) should be administered at a dose of 1 tablet daily or 2 tablets 2 or 3 times a week. Typical findings of Pneumocystis pneumonia include dry cough, shortness of breath, fever, diffuse "ground-glass" appearance on chest X-ray, and an increase in serum β-1,3-D-glucan. Definitive diagnosis of Pneumocystis pneumonia is obtained by demonstrating the presence of *P. jirovecii* in sputum or bronchial lavage. However, since Pneumocystis pneumonia progresses rapidly, patients with the above findings should start the treatment even before the results of cultures are available. Patients should be treated with Baktar® (12 to 9 tablets/day) or, when Baktar® cannot be tolerated due to ADRs, with intravenous pentamidine. When patients with similar conditions have CMV antigenemia in peripheral blood and at least one CMV

antigen-positive leukocyte is detected, CMV pneumonia should be suspected. CMV infection should be treated with intravenous infusion of ganciclovir (dose should be reduced in patients with renal dysfunction) or anti-CMV hyperimmune gamma globulin. Deeply located mycosis (eg, Aspergillus infections and Candida infections) should be prevented with gargling with liquid amphotericin B, and, in cases of infection, should be treated with oral itraconazole (100 to 200 mg once daily immediately after a meal) or intravenous infusion of micafungin 150 mg/day.

6. Prognosis

The prognosis of PAN largely depends on the effectiveness of treatment during the first 3 months after the onset. When PAN in acute phase is treated appropriately, the subsequent clinical course is relatively good. The 5-year survival of patients receiving the combination of glucocorticoids and immunosuppressants for the treatment of PAN is 80% (Class IIb, Level C).[119,131] Causes of death include cerebral hemorrhage, gastrointestinal hemorrhage, renal failure, myocardial infarction, heart failure, and infections. The relapse rate of PAN is as high as about 40%, while that of hepatitis virus B-related PAN is about 8%.

VI Small-Sized Vessel Vasculitis

1. Microscopic Polyangiitis

1 Definition and Epidemiology

MPA is a vasculitis that causes inflammation of the walls of small vessels (arterioles, venules and capillaries) in various visceral organs, which may result in thrombi and bleeding and as a consequence of this ischemia and necrosis of tissues perfused by affected vessels, and also causes systemic inflammation. In Japan, MPA develops in about 1,400 patients each year. The incidence in Japan is somewhat higher than in Western countries. There is no marked gender difference in incidence. The most common age at onset is in the fifth and sixth decades.[139]

2 Pathogenesis and Pathologic Findings

The etiology of MPA is unknown. However, since autoantibodies to enzymes present in the ANCA, especially ANCA to MPO have been detected in patients with this condition,[140] it is believed that an abnormality in the immune system plays a role in the development of MPA, as in other collagen diseases. MPA is not a hereditary disease.

3 Clinical Features and Laboratory Findings

The signs and symptoms of MPA include those of systemic inflammation such as fever, generalized malaise, and weight loss, as well as arthralgia, myalgia, rash (including purpura and skin ulcer), numbness, and paralysis of the extremities (peripheral nerve disorders). Although no renal signs or symptoms are observed during the early phase of the disease, occult blood in the urine, proteinuria, poor renal function (rapidly progressive nephritis), and hypertension may develop. Pulmonary disorders such as cough, shortness of breath, anemia, and bloody sputum (due to pulmonary alveolar hemorrhage and

interstitial pneumonia) may develop. Heart failure, cerebral hemorrhage, cerebral infarction, abdominal pain, and melena may also develop. MPA may progress slowly. In many cases, it manifests as systemic signs and symptoms of renal and/or pulmonary disorders after a substantial length of time during which only occult blood and findings of chronic interstitial pneumonia are observed. Definitive diagnosis of MPA requires histological findings of necrotic crescentic glomerulonephritis and other typical findings. MPA may be diagnosed early by detecting the presence of ANCA in blood.[140]

4 Diagnostic Methods and Criteria (Table 17)

5 Policies and Guidelines of Treatment

Treatment of MPA consists of induction therapy for remission and maintenance therapy of remission. Induction therapy for remission is performed to eliminate the activity of the vasculitis. Patients with injury of major organs such as the kidneys and lungs due to vasculitis are treated with high-dose glucocorticoids and CY, an immunosuppressant.[138] When treatment is begun promptly after the diagnosis, remission can be expected in about 3 to 6 months. Plasmapheresis may also be performed for patients with more severe disease.[141] Following remission, doses of glucocorticoids are promptly decreased, and CY is switched to other milder immunosuppressants to maintain remission for 1 to 2 years. Since vasculitis may recur, periodic examinations are necessary. Although MPA may be fatal if not treated, remission may be achieved when patients are diagnosed early and received adequate initial therapy. When renal involvement has become severe, renal failure may develop and hemodialysis may become necessary. Since organ disorder may progress after ineffective treatment and infections may further exacerbate the disease, infection control is important.

6 Prognosis

In Japan, 30% of patients with MPA die within 6 months after onset. 1-year mortality is 35% overall, 45% in patients with systemic MPA, and 10% in those with renal-limited MPA. Mortality in the second year after onset and thereafter is low. Major causes of death are infections, pulmonary alveolar hemorrhage, and renal failure.

2. Wegener's Granulomatosis

1 Definition and Epidemiology

Wegener's granulomatosis is an intractable vasculitis characterized clinically and pathologically by (1) necrotizing granulomatous inflammation in the nose, eyes, ears, and upper respiratory tract (E) as well as in the lungs (L), (2) focal segmental necrotizing glomerulonephritis in the kidneys (K), and (3) systemic necrotizing vasculitis in medium- and small-sized arteries, and was first reported by Wegener, a pathologist in Germany, in 1939.[114] The most common age at onset is in the third to fifth decades, and no gender difference is observed in incidence.[142] Although autoimmune disorder is believed to play a part in the development of Wegener's granulomatosis, the exact mechanisms of onset are unknown.

2 Pathogenesis and Pathologic Findings

In 1985, van der Woude et al reported that cytoplasmic (c)(PR3)-ANCA is highly prevalent in patients with Wegener's granulomatosis.[143] The ANCA-cytokine sequence theory has been proposed as a mechanism of development of necrotizing vasculitis, granuloma, and necrotizing crescentic glomerulonephritis in patients with Wegener's granulomatosis.[113]

3 Clinical Features and Laboratory Findings

Wegener's granulomatosis is diagnosed on the basis of (1) upper respiratory tract (E) signs and symptoms such as epistaxis, purulent nasal discharge, and saddle nose; (2) pulmonary (L) signs and symptoms such as cough, bloody sputum, chest pain, and lung nodules, infiltrates, and cavities on conventional chest X-ray; (3) renal (K) signs[114] and symptoms such as hematuria, oliguria, and rapidly progressive nephritis; and (4) signs and symptoms suggestive of vasculitis such as purpura, polyarthritis, and polyneuritis; as well as the presence/absence of typical histological findings of (1) necrotizing granulomatous inflammation associated with infiltration of giant cells in E, L, K lesions; (2) necrotizing crescentic glomerulonephritis without Ig deposits; and (3) necrotizing granulomatous vasculitis in small arteries and arterioles and c(PR3)-ANCA.

4 Diagnostic Methods and Criteria (Table 18)

5 Policies and Guidelines of Treatment

Combined treatment with glucocorticoid and immunosuppressants has improved the life expectancy of patients with Wegener's granulomatosis significantly.[142] It is important to adjust immunosuppressive therapy according to the type of Wegener's granulomatosis to ensure appropriate treatment and management and prevent infections, respiratory failure, and recurrence/flare-up of the disease, which may be frequent.[144-146]

6 Prognosis

When not treated, 90% of patients with severe Wegener's granulomatosis associated with multiple organ dysfunction

Table 17. Diagnostic Criteria for Microscopic Polyangiitis

Major clinical findings
1. Rapidly progressive glomerulonephritis
2. Pulmonary hemorrhage or interstitial pneumonia
3. Visceral signs/symptoms other than renal/pulmonary manifestations
   Purpura, subcutaneous hemorrhage, gastrointestinal hemorrhage, mononeuritis multiplex, etc.

Major laboratory findings
1. Positive MPO-ANCA
2. Positive CRP
3. Proteinuria, hematuria, elevation in BUN, elevation in serum creatinine
4. Chest X-ray findings: Infiltrations (alveolar hemorrhage), interstitial shadows

Histological findings
Necrosis of arterioles, capillaries and postcapillary venules, and infiltration of inflammatory cells into tissues surrounding vessels

Diagnosis
1. Definite
   a) Patients with ≥2 major clinical findings and positive histological finding
   b) Patients with ≥2 major clinical findings including Items 1 and 2 and positive MPO-ANCA
2. Probable
   a) Patients with 3 major clinical findings
   b) Patients with one major clinical finding and positive MPO-ANCA

Diseases to be ruled out
1. Classical polyarteritis nodosa
2. Wegener's granulomatosis
3. Allergic granulomatous angiitis (Churg-Strauss syndrome)
4. Goodpasture syndrome

Notes
1. In many patients, infection (mainly upper respiratory infection) develops one or two weeks prior to manifestation of major clinical findings.
2. Items 1 and 2 of the major clinical findings develop simultaneously in about half of patients, and either of the two develops first in the remaining patients.
3. In many patients, MPO-ANCA titer is related to disease activity.
4. Early discontinuation of treatment may be associated with recurrence of disease.

Modified from Report of the Intractable Vasculitis Study Group of the MHLW in 1998, p.241, 1999.
MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibodies; CRP, C-reactive protein; BUN, blood urea nitrogen; MHLW, Ministry of Health, Labour and Welfare (formerly Ministry of Health and Welfare).

will die within 2 years after onset. Although remission may be achieved in 90% of patients who are treated with CY plus glucocorticoid, the condition recurs frequently. Major causes of death are sepsis and respiratory infection.

3. Allergic Granulomatous Angiitis (Churg-Strauss Syndrome)

1 Definition and Epidemiology

Allergic granulomatous angiitis (Churg-Strauss syndrome) is a disorder characterized by bronchial asthma and peripheral eosinophilia followed by various signs and symptoms of vas-

Table 18. Diagnostic Criteria for Wegener's Granulomatosis

Criteria for diagnosis

1) Major clinical findings
   (1) Upper respiratory tract (E) signs/symptoms
   E: Nose (Purulent rhinorrhea, bleeding, saddle nose), eyes (eye pain, reduced visual acuity, exophthalmos), ears (otitis media), oropharyngeal pain (ulcer, hoarse voice, airway obstruction)
   (2) Pulmonary (L) signs/symptoms
   L: Bloody sputum, cough, dyspnea
   (3) Renal (K) signs/symptoms
   K: Hematuria, proteinuria, rapidly progressive renal failure, swelling, hypertension
   (4) Signs/symptoms of vasculitis
   (1) Systemic findings: Fever ≥38°C for ≥2 weeks) and weight loss (≥6 kg in ≤6 months)
   (2) Visceral findings: Purpura, polyarthritis (polyarthralgia), episcleritis, mononeuritis multiplex, ischemic heart disease, gastrointestinal hemorrhage, pleurisy

2) Major histological findings
   (1) Necrotizing granulomatous inflammation with infiltration of giant cells in E, L, K lesions
   (2) Necrotizing crescentic glomerulonephritis without immunoglobulin deposits
   (3) Necrotizing granulomatous vasculitis in small-sized arteries and arterioles

3) Major laboratory findings
   Positive for PR3-ANCA (c-ANCA using the fluorescent antibody technique)

Diagnosis

1) Definite
   (1) Patients with ≥3 major clinical findings in E, L, K including visceral findings of E, L, and K
   (2) Patients with ≥2 major clinical findings in E, L, K or vasculitis and at least one of the major histological findings (1) to (3)
   (3) Patients with ≥1 major clinical findings in E, L, K or vasculitis and at least one of the major histological findings (1) to (3) and positive c(PR3)-ANCA

2) Probable
   (1) Patients with ≥2 major clinical findings in E, L, K or vasculitis
   (2) Patients with ≥1 major clinical findings in E, L, K or vasculitis and one of the major histological findings (1) to (3)
   (3) Patients with 1 major clinical finding in E, L, K or vasculitis and positive c(PR3)-ANCA

Supportive laboratory findings
   (1) Leukocyte count, elevation in CRP
   (2) Elevation in BUN and serum creatinine

Conditions to be ruled out
   (1) Granulomatous disorder in E and L due to other causes (such as sarcoidosis)
   (2) Other vasculitis syndromes (eg, microscopic polyangiitis, allergic granulomatous angiitis [Churg-Strauss syndrome])

Notes
   (1) Wegener's granulomatosis with visceral findings for E, L, K organs is referred to as systemic Wegener's granulomatosis, while that with findings of one or two of E, L is referred to as localized Wegener's granulomatosis.
   (2) Signs and symptoms of systemic Wegener's granulomatosis often develop in the order of E, L, then K.
   (3) Shortly after onset, infection mainly with Staphylococcus aureus often occurs in E and L lesions.
   (4) CT and MRI are useful in diagnosing space-occupying lesions due to granuloma formation in E and L.
   (5) PR3-ANCA titer is often correlated with disease activity.

Report of the Intractable Vasculitis Study Group of the MHLW, revised in 1998.
PR3, proteinase-3; ANCA, antineutrophil cytoplasmic antibodies; c-ANCA, cytoplasmic pattern of antineutrophil cytoplasmic antibodies; CRP, C-reactive protein; BUN, blood urea nitrogen; CT, computed tomography; MRI, magnetic resonance imaging; MHLW, Ministry of Health, Labour and Welfare (formerly Ministry of Health and Welfare).

culitis. The most common age at onset is in the third to sixth decades. Allergic granulomatous angiitis develops in about 100 new patients per year in Japan.

2 Pathogenesis and Pathological Findings

The etiology of allergic granulomatous angiitis is unknown. However, it is believed that antigenic stimulation of the airway activates T cells, which in turn activate eosinophils which produce tissue-injuring factors that cause bronchial asthma, peripheral nerve disorders, and other effects of eosinophilia.

3 Clinical Features and Laboratory Findings

Clinically, bronchial asthma and eosinophilia develop first, and then various signs and symptoms of vasculitis occur. Mononeuritis multiplex develops in most patients.

4 Diagnostic Methods and Criteria

A diagnosis of allergic granulomatous angiitis is made on the basis of bronchial asthma and eosinophilia, which develop in the early phase of the disease, and typical signs and symptoms of vasculitis. The diagnosis may be confirmed with histopathological findings (**Table 19**).

Table 19. Diagnostic Criteria for Allergic Granulomatous Angiitis (Churg-Strauss Syndrome)

Definition

This condition is a vasculitis first differentiated from classic polyarteritis nodosa by Churg-Strauss. Churg-Strauss syndrome is a condition associated with signs and symptoms of bronchial asthma, eosinophilia, and vasculitis, while allergic granulomatous angiitis is associated with the following characteristic histological findings.

Criteria for diagnosis

1) Major clinical findings

  (1) Bronchial asthma or allergic rhinitis

  (2) Eosinophilia

  (3) Signs/symptoms of vasculitis: Fever ≥38°C for ≥2 weeks), weight loss (≥6kg in ≤6 months), mononeuritis multiplex, gastrointestinal hemorrhage, purpura, polyarthralgia (polyarthritis), myalgia, and muscular weakness

2) Typical clinical course

  Major clinical findings (1) and (2) develop first, followed by major clinical finding (3).

3) Major histological findings

  (1) Presence of granulomatous or fibrinoid necrotizing vasculitis in microvascular associated with significant infiltration of eosinophils in the surrounding tissues

  (2) Presence of extravascular granuloma

Diagnosis

1) Definite

  (1) Patients with ≥1 major clinical findings of either bronchial asthma or allergic rhinitis, eosinophilia, and vasculitis and with ≥1 major histological findings (allergic granulomatous angiitis)

  (2) Patients with 3 major clinical findings and a typical clinical course (Churg-Strauss syndrome)

2) Probable

  (1) Patient with 1 major clinical finding and 1 major histological finding (allergic granulomatous angiitis)

  (2) Patients with 3 major clinical findings without typical clinical course (Churg-Strauss syndrome)

Supporting laboratory findings

  (1) Leukocytosis ≥10,000/μL

  (2) Thrombocytosis ≥400,000/μL

  (3) Elevated serum IgE ≥600U/mL

  (4) Positive MPO-ANCA

  (5) Positive rheumatoid factor

  (6) Pulmonary infiltration shadows on X-ray (these findings may not always be observed in patients)

Conditions to be differentiated from allergic granulomatous angiitis

Pulmonary eosinophilia syndrome and other types of vasculitis syndromes (eg, Wegener's granulomatosis and polyarteritis nodosa) should be ruled out.

Notes

  (1) Peripheral eosinophil count exceeds 2,000 μg/mL in patients not receiving glucocorticoid therapy, but will return to the normal range following glucocorticoid therapy.

  (2) Bronchial asthma is not limited to atopic-type asthma and is often severe. Duration from the onset of bronchial asthma to manifestation of vasculitis is often ≤3 years.

  (3) Various chest X-ray findings such as nodular shadows and diffuse granular shadows may be noted.

  (4) Pulmonary hemorrhage and interstitial pneumonia may occur in some patients.

  (5) Hematuria, proteinuria, and rapidly progressive nephritis may develop in some patients.

  (6) Bronchial asthma often persists following remission of vasculitis syndromes.

  (7) Sequelae often persist in patients with mononeuritis multiplex.

Report of the Intractable Vasculitis Study Group of the MHLW, revised in 1998.
MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibodies; MHLW, Ministry of Health, Labour and Welfare (formerly Ministry of Health and Welfare).

5 Policies and Guidelines of Treatment

The treatment of first choice is high-dose glucocorticoid therapy. Steroid pulse therapy is also effective. High-dose IVCY therapy may be effective in the treatment of intractable allergic granulomatous angiitis.[147] Intravenous gamma globulin may also be effective.[148]

6 Prognosis

The main causes of death are gastrointestinal hemorrhage, cerebral hemorrhage, and myocardial infarction. Motor paralysis due to mononeuritis multiplex may persist for a long period of time.

4. Henoch-Schönlein Purpura

1 Definition and Epidemiology

Henoch-Schönlein purpura is a nonthrombocytopenic purpura characterized by dermal, arthral, and abdominal signs and symptoms, and is often complicated by nephritis. It is the most prevalent vasculitis in children (systemic small-sized vessel vasculitis), and develops most frequently in children 4 to 7 years of age.[149]

2 Pathogenesis and Pathological Findings

The involvement of viral/bacterial infections and drug/food

Table 20. Diagnostic Criteria for Henoch-Schönlein Purpura[150]

Criteria	Definition
1. Palpable purpura	Slightly raised "palpable" hemorrhagic skin lesions; not related to thrombocytopenia
2. Age ≤20 years at disease onset	Patient age ≤20 years at onset of symptoms
3. Bowel angina	Diffuse abdominal pain, worse after meals, or the diagnosis of bowel ischemia, usually including bloody diarrhea
4. Wall granulocyte infiltration on biopsy	Histologic changes including granulocytes in the walls of arterioles and venules

Proposed by the American College of Rheumatology, 1990.
Note: For purposes of classification, a patient is said to have Henoch-Schönlein purpura if at least 2 of these 4 criteria are met. The meeting of any 2 or more criteria is associated with a sensitivity of 87.1% and specificity of 87.7%.

Table 21. Classification of Cryoglobulinemia[152]

	Type I	Type II	Type III
Composition	Simple Monoclonal IgM or IgG IgA, light chains in some cases	Mixed Immune complexes composed of monoclonal IgM (RF) and polyclonal IgG	Mixed Immune complexes composed of polyclonal IgM (RF) and polyclonal IgG
Pathology	Microthrombi	Immune complex vasculitis	Immune complex vasculitis

Related conditions	• Lymphoproliferative disorders
	  Multiple myeloma
	  Macroglobulinemia
	  Others
		• Essential
		• Infectious
		Viral: Hepatitis A, B, and C, infectious mononucleosis, post-streptococcal glomerulonephritis, leprosy, syphilis, Lyme disease, Schistosoma japonicum infection, toxoplasma infections, malaria, etc.
		• Collagen disease, including systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, and Sjögren syndrome
		• Lymphoproliferative disorders, such as macroglobulinemia, chronic lymphocytic leukemia, and malignant lymphoma
		• Others, such as membranoproliferative glomerulonephritis and sarcoidosis	

Percentage	25%	25%	50%

Ig, immunoglobulin; RF, rheumatoid factor.

allergy has been demonstrated in some patients. Henoch-Schönlein purpura is assumed to be an IgA immune complex disease. Histologically, it is characterized by infiltration of inflammatory cells into tissues surrounding small vessels and deposition of IgA in vascular walls.

3 Clinical Features and Laboratory Findings
Typical signs and symptoms include (1) symmetrical raised skin purpura, (2) pain and swelling of joints, (3) abdominal pain, vomiting, and bloody stool, and (4) nephritis (hematuria and proteinuria).

4 Diagnostic Methods and Criteria (Table 20)[150]
Although the diagnosis of Henoch-Schönlein purpura is not difficult when nonthrombocytopenic purpura, arthralgia, abdominal pain, and nephritis are present, it is difficult when dermal symptoms do not develop in the early phase of the disease.

5 Policies and Guidelines of Treatment
The prognosis of Henoch-Schönlein purpura is good, with a mortality of <1%. Bed rest and symptomatic treatment are used. When bacterial infections have triggered the disease, antibiotics should be administered. When the involvement of allergy is demonstrated, allergens should be avoided. When nephrotic syndrome or a decrease in renal function is present, renal biopsy should be performed to determine the optimal treatment strategy.

6 Prognosis
In the case of children, nephritis develops in about 50% of patients, but rarely progresses to end-stage renal failure. In the case of adults, nephritis develops in 85% of patients, and often progresses to end-stage renal failure, which has a poor prognosis.

5. Essential Cryoglobulinemia

1 Definition and Epidemiology
Simple (Type I) cryoglobulinemia is formed by monoclonal IgM (IgG), and is observed in patients with multiple myeloma and macroglobulinemia. In types II and III cryoglobulinemia, which are collectively referred to as mixed cryoglobulinemia, a monoclonal (type II) or polyclonal (type III) IgM (or IgG) rheumatoid factor forms complexes with polyclonal IgG. These types are observed in patients with infections (particularly in patients with hepatitis virus C infection)[151] and those with connective tissue disorders.

2 Clinical Features and Laboratory Findings
In type I cryoglobulinemia, Raynaud's phenomenon, cyanosis of the extremities, skin ulcers, myocardial infarction, or cerebral infarction may occur. Patients with type II or III cryoglobulinemia may have vasculitis syndrome as well as fever, malaise, muscular/joint signs and symptoms, purpura of the

Table 22. Diagnostic Criteria for Malignant Rheumatoid Arthritis (Rheumatoid Vasculitis)

Malignant rheumatoid arthritis is defined as the presence of extra-articular manifestations including vasculitis and intractable or severe clinical conditions in addition to established rheumatoid arthritis, and is diagnosed according to the following criteria.

A. Clinical features and laboratory findings

Mononeuritis multiplex	Sensory and/or motor disturbance may present.
Skin ulcer or infarction	Not including lesions due to infection or injury.
Finger gangrene Subcutaneous nodules	Subcutaneous nodules may be present in the apophyseal area, extensor surfaces, and tissues surrounding joints.
Episcleritis or iritis	Conditions confirmed by ophthalmologists, not including those due to other causes.
Exudative pleuritis or pericarditis	Not including those due to other causes such as infection. The presence of adhesions alone should not be considered a positive finding.
Myocarditis	Diagnosis should be made on the basis of clinical findings, inflammatory reactions, muscle enzyme levels, ECG, and echocardiography, among other parameters.
Interstitial pneumonia or pulmonary fibrosis	Diagnosis should be made on the basis of physical findings, chest X-ray, and pulmonary function testing, regardless of the extent of lesions.
Organ infarction	Infarction of intestine, myocardium, lungs, and other organs caused by ischemia or necrosis due to vasculitis.
Elevated rheumatoid factor	Rheumatoid factor should be positive at a titer of 1:2,560 or higher in ≥2 sessions of the RAHA or RAPA test (or ≥960 IU/mL on quantification of rheumatoid factor).
Decreased serum complement level or the presence of immune complexes in blood	A decrease in serum complement level should be demonstrated by a decrease in serum concentration of a complement component such as C3 and C4 or a decrease of CH50-induced complement activation in ≥2 sessions. The presence of immune complexes in blood should be demonstrated on the basis of C1q binding activity in ≥2 sessions (However, these examinations are not covered by the National Health Insurance of Japan, and are available only in limited institutions).

B. Histological findings

Biopsy of skin, muscle, nerve, or other affected organs should reveal the presence of necrotic vasculitis, granulomatous vasculitis, or occlusive endoangiitis in small- or medium-sized vessels.

Diagnosis
  When a patient meets the criteria for rheumatoid arthritis defined by the American College of Rheumatology in 1987, and
    (1) meets ≥3 items in "A. Clinical features and laboratory findings", or
    (2) meets ≥1 items in "A. Clinical features and laboratory findings" and "B. Histological findings",
  a diagnosis of malignant rheumatoid arthritis is made.
Conditions to be ruled out: Infections, amyloidosis, Felty's syndrome, systemic lupus erythematosus, polymyositis, and mixed connective-tissue disease, among others.

Report of the Intractable Vasculitis Study Groupof of the MHLW, 1989.
RAHA, rheumatoid arthritis hemagglutination; RAPA, rheumatoid arthritis particle agglutination; MHLW, Ministry of Health, Labour and Welfare (formerly Ministry of Health and Welfare).

extremities, livedo reticularis, ulcers, cold urticaria, and renal, pulmonary or neurological signs and symptoms (**Table 21**).[152]

3 Diagnostic Methods and Criteria
The diagnosis is made based on the presence of cryoglobulins in serum, and causative factors should be investigated. Examinations for monoclonal proteinemia, rheumatoid factors, and hypocomplementemia as well as histopathological findings for the skin and renal samples may provide useful findings.

4 Policies and Guidelines of Treatment
Treatment consists of avoiding cold temperatures, treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, immunosuppressants, and/or anticoagulants, and plasmapheresis, as well as treatment of causative conditions.

5 Prognosis
The prognosis of vasculitis due to mixed cryoglobulinemia is good in 50% of patients. However, patients may exhibit a serious clinical course, including development of hepatic or renal failure in a third of patients.[153]

6. Malignant Rheumatoid Arthritis (Rheumatoid Vasculitis)

1 Definition and Epidemiology
Rheumatoid arthritis (RA), a disease affecting multiple joints and causing joint destruction and functional disorder over time, may lead to intractable conditions including vasculitis and other extra-articular manifestations that are associated with poor life expectancy. These conditions are referred to as malignant rheumatoid arthritis (MRA).[154] It is believed that there are about 4,200 patients with MRA in Japan. Patients with MRA are slightly older than those with RA, and male patients are predominant.

2 Pathological Findings
MRA is classified into RA, polyarteritis nodosa (PN), and endoarteritis (EA) types according to the histopathological findings of vasculitis.

3 Clinical Features and Laboratory Findings
Clinically, patients with MRA may have subcutaneous nodules, ulcer, infarction or gangrene of skin, bleeding/purpura, mononeuritis multiplex, episcleritis, pleurisy, interstitial pneumonia, pericarditis, myocarditis, and/or intestinal, myocardial or pulmonary infarction, among other findings. Typical lab-

oratory findings include higher levels of rheumatoid factors than in RA and the presence of IgG rheumatoid factors. Decrease in serum complement levels and the presence of immune complexes in blood are also observed in many patients.

4 Diagnostic Methods and Criteria (Table 22)

5 Policies and Guidelines of Treatment

Treatment of MRA is performed using antirheumatic drugs, glucocorticoid, immunosuppressants, D-penicillamine, plasmapheresis, anticoagulants, and biological drugs. Treatment policies have been proposed based on the clinical conditions of individual patients.

6 Prognosis

The most common complications are infections, gastrointestinal ulcers, malignant tumors, and amyloidosis. The mortality of MRA is 43%, and its prognosis is poor. Major causes of death in patients with MRA are respiratory failure, infections, and heart failure.

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