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EVGLastican van Gieson
EULAREuropean League Against Rheumatism
FDGfluorodeoxyglucose

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Abbreviations

AAV ANCA-associated vasculitis
ACR American College of Rheumatology
ADA adalimumab
ANCA anti-neutrophil cytoplasmic antibody
AZA azathioprine
bDMARDs biologic disease-modifying anti-rheumatic drugs
c-ANCA cytoplasmic ANCA
CG cryoglobulin
CHCC Chapel Hill Consensus Conference
Cr creatinine
CT computed tomography
CRP C-reactive protein
CyA cyclosporine
CV cryoglobulinemia
CY cyclophosphamide
DMARDs disease-modifying anti-rheumatic drugs
eGFR estimated glomerular filtration rate
EGPA eosinophilic granulomatosis with polyangiitis
ESR erythrocyte sedimentation rate
ETN etanercept
EULAR European League Against Rheumatism
EVG Elastica van Gieson
FDG fluorodeoxyglucose
GC glucocorticoid
GCA giant cell arteritis
GBM glomerular basement membrane
GPA granulomatosis with polyangiitis
GRADE Grading of Recommendations, Assessment, Development and Evaluation
GWAS genome-wide association study
HBV hepatitis B virus
HCV hepatitis C virus
HE hematoxylin and eosin
HLA human leukocyte antigen
HUV hypocomplementemic urticarial vasculitis
HUVS hypocomplementemic urticarial vasculitis syndrome
IFX infliximab
IL interleukin
IVCY intravenous cyclophosphamide
IVIG intravenous high-dose immunoglobulin
LV-GCA large-vessel giant cell arteritis
MMF mycophenolate mofetil
MPA microscopic polyangiitis
MPO myeloperoxidase
mPSL methylprednisolone
I. Background of the Guidelines

Vasculitis is a general term for diseases that cause inflammation in the blood vessels themselves. Table 1 shows the 2012 revised version of Chapel Hill Consensus Conference (CHCC) classification (CHCC2012). In 2007, the Guidelines for Management of Vasculitis Syndrome were published by a joint working group staffed primarily by the Japanese Circulation Society and the Research Committee on Intractable Vasculitis of the MHLW of Japan. This time, based on the subsequent development of basic and clinical research, the 2017 totally revised version of the Guidelines for Management of Vasculitis Syndrome and the digest version is published 9 years after the publication of its first version. This digest version plainly describes important points and is compiled for quick reference in daily clinical practice. We hope that it is of use in clinics.

2. Basic Principles for Preparation of the Guidelines

1.1 Target Diseases

Vasculitis is commonly referred to as CHCC2012 (Table 1), and is classified into large, medium, and small vessel vasculitides based on the size of the affected blood vessel. The present guidelines cover large vessel vasculitis (Takayasu arteritis and giant cell arteritis), Buerger disease, a medium-vessel vasculitis (polyarteritis nodosa) and small vessel vasculitides [anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis {microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA)}, immune complex small vessel vasculitis (anti-GBM disease, cryoglobulinemic vasculitis, IgA vasculitis (Henoch-Schönlein), IgAV), immune complex SVV, Anti-glomerular basement membrane (anti-GBM) disease* Cryoglobulinemic vasculitis, CV* IgA vasculitis (Henoch-Schönlein), IgAV* Hypocomplementemic urticarial vasculitis, HUV (anti-C1q vasculitis)*] [Jennette JC, Falk RJ, Bacon PA, et al., Arthritis Rheum 2013.]

Table 1. Categories and Diseases of Vasculitis Adopted by CHCC2012

| Large vessel vasculitis, LVV | Takayasu arteritis, TAK* |
|-----------------------------|--------------------------|
| Giant cell arteritis, GCA*   |                          |
| Medium vessel vasculitis, MVV | Polyarteritis nodosa, PAN* |
| Kawasaki disease, KD         |                          |
| Small vessel vasculitis, SVV | Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, AAV |
|                             | Microscopic polyangiitis, MPA* |
|                             | Granulomatosis with polyangiitis (Wegener’s), GPA* |
|                             | Eosinophilic granulomatosis with polyangiitis (Churg-Strauss), EGPA* |
|                             | Immune complex SVV |
| Variable vessel vasculitis, VVV | Anti-glomerular basement membrane (anti-GBM) disease* |
| Behçet’s disease, BD*        | Cryoglobulinemic vasculitis, CV* |
| Cogan’s syndrome, CS         | IgA vasculitis (Henoch-Schönlein), IgAV* |
| Single-organ vasculitis, SOV | Hypocomplementemic urticarial vasculitis, HUV |
| Cutaneous leukocytoclastic angiitis | (anti-C1q vasculitis)* |
| Cutaneous arteritis          |                          |
| Primary central nervous system vasculitis |                          |
| Isolated aortitis            |                          |
| Others                      |                          |
| Vasculitis associated with systemic disease | Lupus vasculitis |
|                             | Rheumatoid vasculitis*   |
|                             | Sarcoid vasculitis       |
| Others                      |                          |
| Vasculitis associated with probable etiology | Hepatitis C virus-associated cryoglobulinemic vasculitis* |
|                             | Hepatitis B virus-associated vasculitis |
|                             | Syphilis-associated aortitis |
| Drug-associated immune complex vasculitis | Drug-associated ANCA-associated vasculitis |
| Drug-associated ANCA-associated vasculitis | Cancer-associated vasculitis |
| Others                      |                          |

2.1 Target Diseases

Vasculitis is commonly referred to as CHCC2012 (Table 1), and is classified into large, medium, and small vessel vasculitides based on the size of the affected blood vessel. The present guidelines cover large vessel vasculitis (Takayasu arteritis and giant cell arteritis), Buerger disease, a medium-vessel vasculitis (polyarteritis nodosa) and small vessel vasculitides [anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis {microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA)}, immune complex small vessel vasculitis (anti-GBM disease, cryoglobulinemic vasculitis, IgA vasculitis (Henoch-Schönlein), IgAV), immune complex SVV, Anti-glomerular basement membrane (anti-GBM) disease* Cryoglobulinemic vasculitis, CV* IgA vasculitis (Henoch-Schönlein), IgAV* Hypocomplementemic urticarial vasculitis, HUV (anti-C1q vasculitis)*] [Jennette JC, Falk RJ, Bacon PA, et al., Arthritis Rheum 2013.]
The definition of clinical practice guidelines and the procedures for their preparation change with time. The World Health Organization (WHO) defines clinical practice guidelines as “any document developed by the World Health Organization containing recommendations for clinical practice or public health policy” and adopts the GRADE system for their preparation. The Minds Guidelines Center of Japan defines clinical practice guidelines as “a document that presents appropriate recommendations to assist patients and practitioners in making decisions regarding clinical practice of high importance, based on the body of evidence evaluated and integrated by systematic reviews and the balance between benefits and harms”.

### 2.2 Common Procedures for the Development of Clinical Practice Guidelines

The definition of clinical practice guidelines and the procedures for their preparation change with time. The World Health Organization (WHO) defines clinical practice guidelines as “any document developed by the World Health Organization containing recommendations for clinical practice or public health policy” and adopts the GRADE system for their preparation. The Minds Guidelines Center of Japan defines clinical practice guidelines as “a document that presents appropriate recommendations to assist patients and practitioners in making decisions regarding clinical practice of high importance, based on the body of evidence evaluated and integrated by systematic reviews and the balance between benefits and harms”.

### 2.3 Methods for the Development of the Present Guidelines

Although clinical practice guidelines are recommended to be developed using the GRADE or Minds system, it is extremely difficult to completely apply these methods to each of rare vasculitides. For these reasons, recommendations for the treatment of MPA and GPA were developed using the GRADE system, but the conventional review style was adopted for the other target diseases. The classification of recommendation and level of evidence for other target diseases were determined using the criteria shown in Tables 2 and 3.

## II. Takayasu Arteritis

### 1. Definition/Epidemiology/Subclassification

#### 1.1 Definition

Takayasu arteritis is a large vessel vasculitis that affects the aorta and its primary branches, coronary arteries, and pulmonary arteries. Its principal manifestations are systemic inflammation, pain due to vasculitis, and vascular stenosis, occlusion, and dilatation, and poses problems including disorders of various organs due to disturbance of the blood flow and aneurysms even after remission of inflammation. Its symptoms are diverse and non-specific, but its early diagnosis has become possible, and the prognosis has been improved.\(^5,6\)

#### 1.2 History

In 1908, Mikito Takayasu reported a 22-year-old woman as a case of “Peculiar changes of the central retinal vessels” (Figure 1).\(^7\) Absence of the pulses of the radial artery was pointed out. In 1951, Kentaro Shimizu, et al., amassed 25 cases and reported them under the name of “pulseless disease”.\(^8\) Hideo Ueda, et al., renamed the disease “aortitis syndrome”.\(^9,10\)

#### 1.3 Epidemiology

##### 1.3.1 Incidence by Age and Sex

In Japan, more than 6,000 patients with this disease have been registered, and about 300 new patients are counted annually (Figure 2).\(^11\) The male/female ratio is about 1:9, and the age of onset in women peaks around 20 years. The symptoms are not only diverse but also often non-specific, and many cases are still considered to be left undiagnosed.

##### 1.3.2 Geographic Differences

Takayasu arteritis is prevalent in Asia and Middle East, and females tend to be more often affected in both regions. While carotid artery lesions are characteristic in Japan and South America, hypertension due to lesions primarily affecting the abdominal aorta is frequently observed in Asian countries.

#### 1.4 Classification

The classification based on the distribution of vascular

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**Table 2. Classification of Recommendations**

| Class | Recommendation |
|-------|----------------|
| I     | Treatment should be administered |
| IIa   | It is reasonable to administer treatment |
| IIb   | Treatment may be considered |
| III   | Treatment should not be administered since it is not helpful and may be harmful |

**Table 3. Levels of Evidence**

| Level | Description |
|-------|-------------|
| A     | Data derived from multiple randomized clinical trials or meta-analyses |
| B     | Data derived from a single randomized trial or nonrandomized studies |
| C     | Only consensus opinion of experts |
lesions proposed by Numano et al. is used (Figure 3). The cases are divided into those with lesions in the 3 branches of the aortic arch and those with lesions also below the diaphragm. This classification is based on angiographic findings, but it should be noted that inflammatory thickening is diffusely observed also in regions with no marked changes in the vascular lumen.

2. Pathogenesis

Takayasu arteritis is estimated to be caused by destruction of elastic arteries, particularly, the aorta, by autoimmune mechanisms triggered by environmental factors including infection based on genetic factors.

2.1 Genetic Factors

HLA-B*52 has been reported to be related to the pathogenesis of this disease. In addition, SNP of the IL12B gene has recently been identified as a susceptibility factor.

2.2 Environmental Factors

Although an involvement of viral infection is suspected, viruses that may induce Takayasu arteritis have not been identified.

2.3 Mechanism of Vascular Damage

Cells including T cells, macrophages, and NK cells along with cytokine abnormalities are considered to damage the vascular wall, but detailed mechanism has not been elucidated.

3. Pathological Findings

Takayasu arteritis, which is classified as a large vessel vasculitis, often affects the aorta and its primary branches. Macroscopically, all layers of the vascular wall are thickened in

**Classification based on the site of the lesion**

![Diagram of vascular lesions]

**Types and their frequencies**

| Type  | Frequency (%) |
|-------|---------------|
| Type I| 28.0 ~ 35.9   |
| Type IIa| 9.4 ~ 16.3  |
| Type IIb| 8.5 ~ 16.6  |
| Type III| 0.9 ~ 7.3    |
| Type IV| 1.9 ~ 5.9     |
| Type V| 25.8 ~ 43.4   |

**Figure 3.** Types of Takayasu arteritis based on the distribution of vascular lesions and their frequencies (Cited from Hata A, et al. 1996, Mitsuaki Isobe, 2014, Watanabe Y, et al. 2015). Classification based on angiographic findings by Numano et al. Type I: Branches of the aortic arch. Type IIa: Ascending aorta, aortic arch and its branches. Type IIb: Ila lesions + thoracic descending aorta. Type III: Thoracic descending aorta, abdominal aorta, and/or renal arteries. Type IV: Abdominal aorta and/or renal arteries. Type V: Type IIb+IV (ascending aorta, aortic arch and its branches, and thoracic descending aorta as well as abdominal aorta and/or renal arteries). The presence of coronary artery lesions and pulmonary artery lesions is indicated by C(+) and P(+), respectively.
Figure 4. Gross appearance of the aorta with Takayasu arteritis 1. Brownish lesions showing coarse luminal surface are observed in the aortic arch and abdominal aorta. Skip lesions are formed as normal areas interpose between lesions. A teenage male.

Figure 5. Gross appearance of the aorta with Takayasu arteritis 2. The aorta shows a bark-like luminal surface and marked fibrotic thickening accompanied by calcification. A female in her 50s.

Figure 6. Histological findings of the aorta in Takayasu arteritis. Along with diffuse fibrosis of the adventitia, the outer side of the media is invaded by inflammation from the adventitia, resulting in scattered infarct foci in the media (outlined arrow). In the lesions, multinucleated giant cells appear in addition to histiocytes and lymphocytes, presenting an image of granulomatous inflammation. Giant cells phagocytose elastic fibers (filled arrow). (Left: HE staining, Right: anti-elastin antibody staining)

Figure 7. Histological findings of Takayasu arteritis. Histological findings of the aorta (Left) and brachiocephalic artery (Right). Along with diffuse fibrosis of the adventitia, moth-eaten loss of elastic fibers primarily on the outer side of the media is observed due to inflammation from the adventitia. Intimal thickening is localized at the sites of medial damage and not observed in areas where elastic fibers are intact. (EVG staining)
the affected arteries, and the luminal surfaces of the lesions show irregularities and macular or granular changes. Normal areas are often present between lesions (Figure 4). In the adventitia, vaguely circumscribed fibrotic thickening is notable. In the scar stage, the arterial wall develops plate-like calcification and presents a lead-pipe-like appearance (Figure 5).

Histologically, in an early stage, adventitial mononuclear cell infiltration accompanied by inflammatory cell infiltration to areas around the vasa vasorum is observed, and the media exhibits infarct lesions and granulomatous arteritis mixed with multinucleated giant cells that have phagocytosed fragmented elastic fibers (Figure 6). As a result of inflammation occurring on the adventitial side of the tunica media, elastic fibers of the media are lost in a moth-eaten pattern. While diffuse fibrosis is caused in the media and adventitia, the intima also develops marked thickening due to cell fibrosis, resulting in luminal stenosis (Figure 7).

In the scar stage, the adventitia is thickened due to marked fibrosis, and vasa vasorum with thickened wall is

| Table 4. Chief Complaints of Takayasu Arteritis at Onset |
|---------------------------|-----------------|
| Head and neck             | 365 (26.6)      |
| Dizziness/vertigo         | 129 (9.4)       |
| Headache                  | 113 (8.2)       |
| Syncope                   | 36 (2.6)        |
| Masseter claudication     | 5 (0.4)         |
| Neck pain                 | 133 (9.7)       |
| Eyes                      | 45 (3.3)        |
| Sight loss                | 2 (0.1)         |
| Visual disorder           | 37 (2.7)        |
| Upper limbs               | 238 (17.3)      |
| Pulselessness             | 67 (4.9)        |
| Systolic blood pressure difference (≥10 mmHg) | 53 (3.9) |
| Fatigue                   | 63 (4.6)        |
| Coldness                  | 23 (1.7)        |
| Numbness                  | 49 (3.6)        |
| Heart                     | 153 (11.1)      |
| Breathlessness            | 61 (4.4)        |
| Palpitation               | 29 (2.1)        |
| Feeling of chest tightness| 21 (1.5)        |
| Lung                      | 92 (6.7)        |
| Hemosputum                | 11 (0.8)        |
| Sensation of dyspnea      | 61 (4.4)        |
| Hypertension              | 54 (4.0)        |
| Lower limbs*              | 49 (3.6)        |
| Body pain*                | 218 (15.9)      |
| Systemic manifestation    | 562 (41.0)      |
| Fever                     | 476 (34.7)      |
| Malaise                   | 166 (12.1)      |
| Fatigue                   | 23 (1.7)        |

Data are expressed as n (% of 1,372 patients). *Leg claudication, fatigue, coldness, numbness, or pain. *Chest, back, or abdominal pain. (Cited from Watanabe Y, et al. Circulation. 2015, 12 (c) 2015 by American Heart Association, Inc.)

| Table 5. Clinical Features of Takayasu Arteritis |
|-----------------------------------------------|-----------------|
| Head and neck                                | 47.5            |
| Eyes                                         | 14.3            |
| Upper limbs                                  | 66.4            |
| Heart                                        | 37.8            |
| Lung                                         | 10.8            |
| Hypertension                                 | 38.0            |
| Intermittent claudication in the legs         | 9.5             |
| Systemic manifestation                        | 74.9            |

Data are expressed as % of 1,372 patients.

| Table 6. Complications of Takayasu Arteritis |
|---------------------------------------------|-----------------|
| Prevalence (%)                              |                 |
| Aortic valve regurgitation                  | 33.2            |
| Grade I*                                    | 14.1            |
| Grade II*                                   | 8.6             |
| Grade III*                                  | 9.8             |
| Grade IV*                                   | 6.2             |
| Ischemic heart disease                      | 10.6            |
| Eyes                                        | 14.0            |
| Cataract                                    | 7.6             |
| Funduscopic findings                       | 8.7             |
| Aortic aneurysm                             | 15.0            |
| Aortic dissection                           | 1.9             |
| Renal disorder                              | 11.2            |
| Hypertension                                | 39.4            |
| Renal artery stenosis                       | 13.1            |
| Brain ischemia                              | 13.2            |
| Thrombosis                                  | 3.7             |
| Hemorrhage                                  | 0.9             |

Data are expressed as % of 1,372 patients. *Regurgitation grade measured by color Doppler ultrasound. (Excerpts from Watanabe Y, et al. 2015)

Histologically, in an early stage, adventitial mononuclear cell infiltration accompanied by inflammatory cell infiltration to areas around the vasa vasorum is observed, and the media exhibits infarct lesions and granulomatous arteritis mixed with multinucleated giant cells that have phagocytosed fragmented elastic fibers (Figure 6). As a result of inflammation occurring on the adventitial side of the tunica media, elastic fibers of the media are lost in a moth-eaten pattern. While diffuse fibrosis is caused in the media and adventitia, the intima also develops marked thickening due to cell fibrosis, resulting in luminal stenosis (Figure 7).

In the scar stage, the adventitia is thickened due to marked fibrosis, and vasa vasorum with thickened wall is

Figure 4. Skin lesions observed in Takayasu arteritis (erythema nodosum). Skin lesions (erythema nodosum) often occurs in large numbers in the lower limbs, particularly, on the anterior aspect of the tibial region.
often observed. The arterial intima shows progressive fibrotic thickening, and major branches of the aorta often develop luminal stenosis. In addition, despite the presence of marked fibrotic lesions, active inflammation accompanied by multinucleated giant cells is often observed in the peripheries of the lesions.

With the recent increases in long-time survivors due to early detection and improvements in treatments, cases of Takayasu arteritis accompanied by atherosclerosis, aortic aneurysm, or aortic insufficiency are increasing.

4. Symptoms

Initial signs and symptoms include FUO, malaise, neck pain, pain in various regions, and dizziness, which resemble those of upper airway inflammation (Table 4). They are followed by signs and symptoms caused by vascular lesions.

When objective findings are included, signs of ischemia of the upper limbs such as a difference in blood pressure between the left and right arms and the absence of pulses in the upper limb are observed most frequently in about 66% of the patients, followed by dizziness and headache observed in about 48%. About 14% of the patients had visual disorders, and about 40% of the patients were hypertensive (Table 5). In Takayasu arteritis, many skin lesions (erythema nodosum) are often noted in the lower limbs, particularly, on the anterior aspect of the tibial region (Figure 8).

Complications include aortic insufficiency, aortic aneurysm, aortic dissection, ischemic attacks of the brain, pulmonary infarction, angina pectoris, subclavian steal syndrome, atypical coarctation of the aorta, and renovascular hypertension (Table 6). As observed in Table 6, complications vary widely including those caused by stenotic lesions and dilated lesions and tend to occur in large numbers. Symptoms are also diverse with some patients remaining asymptomatic and others developing various symptoms in an early stage. Moreover, Takayasu arteritis may be complicated by symptoms of autoimmune diseases such as inflammatory bowel disease, erythema nodosum, and arthritis.

5. Laboratory and Imaging Findings

5.1 Laboratory Findings

Currently, there are no specific findings on blood or biological tests for the diagnosis of Takayasu arteritis. Therefore, non-specific indices of inflammation including CRP and ESR are used as the biomarkers for the diagnosis of Takayasu arteritis. Increasing lines of evidence suggest that the presence of specific human leucocyte antigen (HLA) class I molecules, such as HLA-B*52 and HLA-B*67,23,24 are related to clinical manifestations and genetic predisposition of Takayasu arteritis. Thus, the presence of HLA-B*52 and HLA-B*67 are useful as adjunct to the diagnosis of Takayasu arteritis.

Laboratory findings useful for the evaluation of the activity of Takayasu arteritis include an increase in the number of leukocytes, exacerbation of anemia, and abnormalities of immunological indices such as immunoglobulin and complement levels as well as the elevation of CRP and ESR. Particularly, CRP is useful for the follow-up of patients who have received GC therapy,25,26 but it should be noted that CRP cannot be used for the evaluation of the activity of Takayasu arteritis in patients administered TCZ, a humanized antihuman IL-6 receptor monoclonal antibody.

Although serum amyloid A,27 Pentraxin-3,28-30 IL-6,31 IL-18,32 sRAGE,33 soluble ICAM-1,34 and matrix metalloproteinase35 have also been reported to be useful for the evaluation of the activity of Takayasu arteritis, these biomarkers have not been used for the actual clinical diagnosis of Takayasu arteritis and are not covered by health insurance.
in Japan as of 2018.

5.2 Imaging Findings
CT and MRI are recommended imaging modalities for the initial work-up of Takayasu arteritis (Figure 9).

5.2.1 Chest Radiography
Irregular contour of the descending aorta is noted in the margin of the descending aorta (Figure 9A, arrows).

5.2.2 CT
By CT, large vessels, coronary arteries, and various organs are evaluated (Figure 9B).
Dynamic CT angiography protocol consisted of a set of non-contrast, arterial-phase and late-phase scans is recommended for the initial examination, but a reduction of radiation exposure must be considered on follow-up examinations. On non-contrast images, the density of the arterial wall appears higher than the lumen (Figure 10A). Arterial phase images demonstrates clear contrast between the lumen and wall (Figure 10B). In the late-phase images, the “double ring-like pattern” is observed in the aortic wall in the early stage of Takayasu arteritis (Figure 10C).
In the chronic stage, stenosis or dilatation of the lumen, circumferential calcification of the wall (Figure 9B), and development of collaterals are noted.

5.2.3 MRI
By contrast-enhanced MR angiography, the vascular lumen, wall thickening, and contrast enhancement of the wall are evaluated (Figures 11 and 12). Morphological information of large vessels is also available by non-contrast MR angiography. For long-term follow-up, MRI is recommended because of no risk for radiation exposure.

5.2.4 Angiography
Angiography is indicated for endovascular treatment and evaluation of coronary and small arteries.

5.2.5 Ultrasonography
In Takayasu arteritis, a hyperechoic area is observed in the thickened wall of the common carotid artery (macaroni sign) (Figure 9C).

5.2.6 18F-FDG PET/PET-CT
Accumulation of 18F-FDG in the wall of large vessels is a finding useful for the diagnosis of Takayasu arteritis (Figure 13). Since April 2018, it has become possible to perform 18F-FDG PET/PET-CT under health insurance at some PET facilities in Japan for patients with large vessel vasculitis when the localization or activity of the lesion is difficult to determine by other examinations.

5.3 Ophthalmological Examinations
5.3.1 Manifestations Related to Ocular Ischemia
18–30% of patients with Takayasu arteritis have ocular symptoms such as blurred vision, transient visual loss, and eye pain, and most of these symptoms come from circulatory disturbance to the eye. Ophthalmological examinations can reveal manifestations related to ocular ischemia including Takayasu retinopathy (hypoperfusion retinopathy), ischemic optic neuropathy, and ruberosis iridis caused by type I, II, and V Takayasu arteritis (Numano’s classification by angiography) (Figure 3). In Takayasu retinopathy, tortuosity of retinal vessels, dilated retinal veins, retinal microaneurysms, hemorrhage, and cotton-wool spots can be seen in the fundus (Figure 14). Multiple microaneurysms scattered in the retina and wreath-like vascular anastomoses around the optic disc indicating prolonged retinal ischemia are characteristic findings (Figure 1). On fluorescein fundus angiography, prolonged arm-to-retina circulation time,

Figure 11. Gadolinium-contrast-enhanced MRA. Mild dilatation of the ascending aorta and occlusion of the brachiocephalic artery as well as proximal segments of the left common carotid and subclavian arteries are observed.

Figure 12. MR images of Takayasu arteritis. (A) Non-contrast T1-weighted image. (B) Gadolinium-contrast-enhanced T1-weighted image. Wall thickening with contrast enhancement are appreciated in the left common carotid artery.
occlusion of capillaries, microaneurysms, and arteriovenous anastomoses can be observed, and neovascularization in the retina and optic disc can be seen in the severe cases (Figure 15).

\subsection*{5.3.2 Ocular Manifestations Due to Systemic Hypertension}

In Type III, IV, or V Takayasu arteritis, which may be complicated by hypertension due to abdominal aorta/renal artery stenosis, hypertensive retinopathy may be observed. In this condition, narrowing of the retinal artery, retinal edema, white spots, hemorrhage, and optic disc edema develop. Although reports are few, hypertensive choroidopathy may also develop.

\section*{6. Diagnostic Methods and Criteria}

\subsection*{6.1 Diagnostic Criteria}

For the present revision of the guidelines, the Subcommittee of Large Vessel Vasculitis of the MHLW Research Committee for Intractable Vasculitis prepared new diagnostic criteria for Takayasu arteritis with partial modifications of those in the Guidelines 2008 reflecting progress in medicine without changing their basic principles (Table 7). The diagnosis is made primarily by imaging (CT, MRI, ultrasound, PET-CT, chest radiography, and angiography). According to the diagnostic criteria in Table 7, Takayasu arteritis is diagnosed when there is 1 or more of the symp-
Table 7. Diagnostic Criteria for Takayasu Arteritis

A. Signs and symptoms

1. Systemic signs and symptoms: Fever, generalized malaise, easy fatigability, lymphadenopathy (cervical), hypertension in younger patients (≥140/90 mmHg)
2. Pain: Carotidynia, chest pain, back pain, lower back pain, shoulder pain, upper limb pain, lower limb pain
3. Visual signs and symptoms: Transient or persistent visual impairment, precocious bright or dark sensation, loss of vision, fundus changes (hypotensive changes, hypertensive changes)
4. Head and neck signs and symptoms: Headache, toothache, jaw claudication, dizziness, hearing impairment, tinnitus, syncope, cervical vascular murmurs, hemiplegia
5. Upper limb signs and symptoms: Numbness, cold sensation, difficulty in arm raising, claudication, abnormal pulse and blood pressure (weakness or loss of radial artery pulse or left-right difference of ≥10 mmHg), increased pulse pressure (related to aortic insufficiency)
6. Lower limb signs and symptoms: Numbness, cold sensation, weakness, claudication, abnormal pulse and blood pressure (augmented or weakened pulse of lower limb arteries, reduced blood pressure, blood pressure difference between upper and lower limbs)
7. Chest symptoms: Shortness of breath, palpitation, dyspnea, bloody sputum, sensation of chest compression, anginal symptoms, arrhythmia, cardiac murmur, back vascular murmur
8. Abdominal signs and symptoms: Abdominal vascular murmur, complication by ulcerative colitis
9. Skin signs and symptoms: Erythema nodosum

*a* Intermittent mastication due to pain caused by mastication
*b* Intermittent exertion of the upper limbs due to pain and weakness caused by exertion
*c* Instances other than “10–30 mmHg higher in the lower limb than upper limb”

B. Examination findings

Imaging examination findings: In the aorta or its primary branches or both, multiple or diffuse hypertrophic lesions, stenotic lesions (including occlusions), or dilated lesions (including aneurysms) detected.

*a* The aorta and its primary branches correspond to the aorta (ascending, arch, thoracic descending, abdominal descending), primary branches of the aorta (including the coronary artery), and pulmonary artery.
*b* Multiple lesions are defined as those two or more of the above arteries or sites or two or more segments of the aorta.
*c* Hypertrophic lesions are detected by ultrasonography (macaroni sign of the common carotid artery), contrast-enhanced CT, contrast-enhanced MRI (circumferential contrast enhancement of the arterial wall), and PET-CT (circumferential FDG uptake of the arterial wall).
*d* Stenotic lesions and dilated lesions are detected by chest radiography (wave-like deformation of the descending aorta), CT angiography, MR angiography, echocardiography (aortic insufficiency), and angiography. They are accompanied by dilatation of the ascending aorta and frequently also by aortic insufficiency. In the chronic stage, circumferential calcification of the arterial wall is visualized by CT, and the development of collateral circulation is detected by CT angiography and MR angiography.

C. Conditions to be included in the differential diagnoses of Takayasu arteritis

Arteriosclerosis, congenital vascular anomaly, inflammatory abdominal aortic aneurysm, infectious aneurysm, syphilitic mesoaortitis, giant cell arteritis (temporal arteritis), vascular Behçet’s disease, IgG4-related diseases.

*Diagnostic categories*

Definite: At least 1 of the items in A + any of the conditions in B are observed, and conditions in C can be excluded.

(Suggestive findings)

1. Hematological/biological findings: Increased ESR or CRP, leukocytosis, anemia
2. Genetic examinations: Presence of HLA-B*52 or HLA-B*67

6.2 Differential Diagnosis

Takayasu arteritis should be differentially diagnosed from (1) arteriosclerosis, (2) congenital vascular anomalies, (3) inflammatory abdominal aortic aneurysm, (4) infectious aneurysm, (5) syphilitic mesoaortitis, (6) giant cell arteritis (temporal arteritis), (7) vascular Behçet’s disease, and (8) IgG4-related periaortitis. It can be differentiated from arteriosclerosis to an extent by the age of onset and distribution of the affected vessels. Mid-aortic syndrome is a possible congenital vascular anomaly that can be mistaken for Takayasu arteritis, but it can be differentiated, because the aortic wall is smooth despite stenosis. Inflammatory abdominal aortic aneurysm shows signs of inflammation, is often accompanied by hydronephrosis, and exhibits the characteristic mantle sign on CT. Infectious aneurysm often presents as a saccular aneurysm, can be multiple, but lacks...
other lesions, and it can be differentiated by checking other findings. Syphilitic mesoaortitis is rarely encountered recently and is differentiated serologically and bacteriologically. GCA frequently affects older individuals and is often complicated by myalgia (polymyalgia rheumatica). Vascular Behçet’s disease occasionally presents with saccular aneurysms but can be differentiated by checking other findings. IgG4-related periaortitis can be differentiated by the serum IgG4 concentration and IgG4-related lesions in other organs.

7. Policies and Guidelines of Treatment

Table 8 shows recommendations about treatment for Takayasu arteritis, and Figure 16 shows a flow chart of treatment for Takayasu arteritis.

7.1 Glucocorticoid/Immunosuppressant

7.1.1 Glucocorticoid

a. Indications

In previous cohort analyses, PSL was administered to 79–94% of the patients based on the disease activity (judged according to Kerr’s criteria). According to overseas reports, regimens such as PSL at 1 mg/kg/day ×1 month have been used. The Guidelines 2008 recommend a low dose regimen of PSL 20–30 mg/day ×2 weeks but has the additional statement, “increased to a maximum of 60 mg/day depending on the case”, and the efficacy rate of PSL alone by this regimen was about 50%. In a Japanese retrospective cohort of 106 cases, the initial dose of PSL was 38.9±14.6 mg/day and approximately corresponded to 0.5–1 mg/kg/day.
c. Steroid Pulse Therapy (recommendation class IIb, evidence level C)
This regimen is performed in emergent cases and at relapse of refractory cases.\(^{52,54,55}\)

**d. Dose-Reduction Rate and Maintenance Dose**
The dose of PSL should be reduced by confirming remission according to (1) symptoms, (2) blood inflammation markers, and (3) imaging findings. In a Japanese retrospective cohort study of 106 cases,\(^{49}\) the PSL dose-reduction speed was the most important factor that contributed to relapse, and the relapse rate differed significantly between dose-reduction speeds faster and slower than 1.2 mg/month. By the protocol of the Guidelines 2008,\(^{56}\) the dose was reduced by 5 mg every 2 weeks to 10 mg/day and by 2.5 mg every 2 weeks thereafter to the maintenance dose. However, considering that the PSL dose at relapse was 13.3 ± 6.9 mg/day, the dose should be reduced very carefully after it has been reduced to less than 20 mg/day. The maintenance dose is PSL 5–10 mg/day in many protocols.\(^{59,52,57}\)

**e. GC-Free Remission**
GC-free remission was maintained in 5 (17%) of the 30 patients by a protocol of the United States aimed to discontinue PSL.\(^{51}\) According to the surveillance of 150 cases in Japan reported in 1975, the GC discontinuation rate was 37.4%.\(^{56}\)

**f. Dose Increase at Relapse**
Whether the remission-inducing therapy is repeated or minor dose increases are attempted should be judged according to the severity.

### 7.1.2 Immunosuppressants

**a. MTX (recommendation class IIa, evidence level B) (Uncovered by Insurance in Japan)**
In a single-arm study in the United States, MTX (gradually increased from 0.3 mg/kg/week) and PSL (gradually reduced from 1 mg/kg/day) were administered to those in whom the effectiveness of PSL alone was insufficient or relapse was observed, resulting in remission attained in 81% and remission maintained after 7–18 months in 50%.\(^{58}\) MTX is the immunosuppressant that has been used most frequently for Takayasu arteritis. However, its problems are that the progression of vascular lesions may not be prevented and that it is often discontinued due to the lack of effect or adverse effects.\(^{6,50,59}\)

**b. AZA (recommendation class IIa, evidence level B) (Covered by Health Insurance in Japan Since February 23, 2011)**
In a single-arm study in India, AZA (2 mg/kg/day) and PSL (gradually reduced from 1 mg/kg/day) were administered to newly-onset patients. While remission was attained and maintained until after 12 months in all patients, CRP or ESR rose after 12 months in 40%, and progression of vascular lesions was observed in some.\(^{57}\) AZA is highly evaluated in protocols of various countries and is often administered to patients not responding to MTX.

**c. CY (recommendation class IIb, evidence level B) (Covered by Health Insurance in Japan Since February 23, 2011)**
In a prospective cohort of 20 cases in the United States, CY was added at 2 mg/kg/day (dose was modified to adjust the WBC to >3,000/µL) to 7 patients who responded insufficiently to PSL alone. The PSL dose-reduction effect was observed in all patients, and further progression was prevented in 4 of the 6 patients who had shown progression of vascular lesions.\(^{49}\) In many protocols, CY is substituted for MTX or AZA after 3 months in consideration of the possibility of adverse effects.

**d. MMF (recommendation class IIb, evidence level B) (Uncovered by Health Insurance in Japan)**
According to reports of 21 cases from India\(^{55}\) and 10 cases from Brazil,\(^{49}\) MMF (2 g/day) was administered to patients first treated for Takayasu arteritis or those who showed poor treatment responses, and reduced disease activity, decreases in CRP/ESR, and PSL-reducing effect were observed in most cases.

**e. Calcineurin inhibitors (recommendation class IIb, evidence level C) (Uncovered by Health Insurance in Japan)**
There have been case reports using tacrolimus at 1.5–4 mg/day\(^{61,62}\) and CyA at 150 mg/day or 4.3 mg/kg/day.\(^{53,64}\)

### 7.2 Biological Agents, Antiplatelets

#### 7.2.1 Biological Agents
The efficacy of biological agents for Takayasu arteritis has been evaluated primarily regarding two groups of biological agents, namely, TNF inhibitors and anti-IL-6 receptor antibody.

**a. TCZ (recommendation class I, evidence level B) (Covered by Health Insurance in Japan Since August 25, 2017)**
In the serum of patients with Takayasu arteritis, the IL-6 concentration has been reported to increase in association with the disease activity.\(^{31,32}\) Since Nishimoto et al. first reported TCZ treatment for patients with refractory Takayasu arteritis,\(^{65}\) similar reports have appeared in Japan, Europe, and the United States suggesting the efficacy of TCZ against Takayasu arteritis.\(^{56,70}\)

In a retrospective registry study of biological agents (TNF inhibitors and TCZ) in France, 49 patients with Takayasu arteritis were treated with biological agents (35 with a TNF-inhibitor, 14 with TCZ) with remission rates after 6 and 12 months of 75 and 83%, respectively. The 3-year relapse-free rate was 90.9% in those treated with biological agents and 58.7% in those treated with conventional synthetic DMARDs, showing a significant difference (\(P=0.0025\)).\(^{71}\)

In Japan, a clinical trial of TCZ was carried out in patients with refractory Takayasu arteritis (TAKT study).\(^{72}\) By the double-blind design, GC was forcibly tapered, and the time until relapse was evaluated as a primary endpoint. The hazard ratio in the TCZ group relative to the placebo group was 0.41 (decrease rate of relative risk: 59%) (\(P=0.0596\)).

**b. TNF Inhibitors (recommendation class IIa, evidence level B) (Uncovered by Health Insurance in Japan)**
Hoffman et al. reported that TNF inhibitor therapy was effective for Takayasu arteritis resisting GC therapy.\(^{73}\) However, according to the report by Schmidt et al. in 20 patients with refractory Takayasu arteritis, the remission induction rate was also satisfactory, but relapse was noted...
in 33% while TNF inhibitor therapy was continued, and the administration was discontinued due to adverse effects in 20%. No clear conclusion has been reached regarding the efficacy of TNF inhibitor therapy against Takayasu arteritis.

### 7.2.2 Antiplatelets (recommendation class IIa, evidence level B)

In patients with Takayasu arteritis, the occurrence of acute ischemic events such as acute myocardial infarction, unstable angina, transient ischemic attacks, stroke, acute lower limb ischemia, and acute intestinal ischemia has been reported to be significantly suppressed by oral administration of an antiplatelet (aspirin).

### 7.3 Surgical Treatment (Open Surgery and Endovascular Treatment)

#### 7.3.1 Principles of Surgical Treatment

In both open surgery and endovascular treatment (EVT) for patients with Takayasu arteritis, pre- and post-operative medical management of disease activity is crucial to obtain good surgical outcomes. The evaluation of indications for surgery, selection of strategies and the procedures, and postoperative management should be conducted by a multidisciplinary team. As for occlusive lesions, vascular restenosis occurs more frequently after EVT than after bypass surgery. Therefore, careful consideration is required to select EVT as the first-line treatment. After surgical treatment, all patients should have lifelong follow-up care.

#### 7.3.2 Disease Activity and Surgical Outcomes

The purpose of surgical treatment is to improve organ blood flow or to prevent rupture of aneurysms. Surgical treatment is best performed during a period of remission (non-active period) in which the patient needs neither GC nor immunosuppressants for maintaining the condition, if possible. However, even in patients in active phase, urgent surgery is often unavoidable to prevent aneurysm rupture or permanent ischemic organ damage, and performed under every effort to manage the inflammation. After surgery, maintaining remission leads to favorable long-term outcomes.

The selection of surgical treatment strategy, open surgery or EVT, is still based on experts' experiences. The strategy should be selected considering the long-term prognosis of the patient, since many patients with Takayasu arteritis have a potential of favorable life prognosis.

#### 7.3.3 Postoperative Management

If GC has been used preoperatively, GC therapy should be resumed immediately after surgery. Even in patients in remission phase, low dose GC therapy is recommended. The operated sites and residual lesions should be followed up routinely to prevent late complications including pseudoaneurysm at the anastomosis.

#### 7.3.4 Treatment for Vascular Lesions

**a. Surgical Revascularization**

While Numano's angiographic classification is appropriate for representing epidemiological case profiles, the following Ueno's clinical classification is useful to consider the target lesions of surgical treatment.

**i. Treatment for Type I Lesions (Occlusive Lesions of Aortic Arch Branches)**

The patient can be treated conservatively if they have few problems in their daily life. Concerning visual impairment, stage 2 and early stage 3 by Uyama's classification or a fundus blood pressure of around 50 mmHg are considered to be indications for revascularization. Bypass surgery is often selected. If there are severely diseased lesions in the bilateral carotid arteries, unilateral revascularization is recommended to avoid cerebral hyperperfusion syndrome.

**ii. Treatment for Type II Lesions (Occlusive Lesions of Thoracoabdominal Aorta)**

If the lesion does not involve the orifice of major branches of abdominal organs, extra-anatomical bypass surgeries such as aorto-aortic bypass grafting or replacement of the diseased aorta can be indicated. If there are symptoms of organ ischemia, surgical treatment is indispensable. Particularly the refractory renovascular hypertension should be managed for improving life prognosis by adopting renal artery bypass surgery, autologous renal transplantation, or even nephrectomy. For the patients with abdominal angina, mesenteric artery revascularization should be considered.

**iii. Treatment for Type III Lesions (Extensive Occlusive Lesions; Type I+Type II)**

In patients with both severe brain ischemia and severe hypertension, to prevent the brain from being exposed to high blood pressure after cerebral arterial reconstruction, simultaneous surgical treatment for renovascular hypertension should be considered. If brain ischemia is not severe, the initial target for surgery should be renovascular hypertension. Then, if hypoperfusion-associated brain disorders appear due to normalized blood pressure, carotid revascularization is performed in the second stage.

**iv. Treatment for Type IV Lesions (Aneurysmal Lesions)**

True aneurysms are the majority of the aneurysm. The Surgical indications for aneurysms in Takayasu arteritis are similar to those for common degenerative aortic and peripheral artery aneurysms.

Vascular occlusion and restenosis are may occur frequently after surgical revascularization. On the contrary, there is a report that the long-term patency and survival in Japan are relatively satisfactory.

### 7.3.5 Treatments for Cardiac Lesions

**a. Aortic Insufficiency**

Indications for aortic valve replacement should be evaluated based on patient’s condition and left ventricular function.
Biological valves are used for elderly patients and women who wish pregnancy. Reports that positively recommend aortic root replacement (Bentall procedure) have increased. In addition, if the patient seems difficult to achieve remission of the inflammation even after long-term medical treatment, aortic root replacement is recommended even without aortic root dilatation.\textsuperscript{93–95}

b. Aortic Root Dilatation
Composite graft replacement of aortic valve, aortic root, and ascending aorta, combined with re-implantation of the coronary arteries into the graft (Bentall procedure) is the most common procedure. Valve-sparing aortic root replacement is not recommended as the aortic valve tends to degenerate in many patients in a long period after surgery.\textsuperscript{96} The suture usually needs additional reinforcements in the surgical procedures.\textsuperscript{97}

c. Coronary Artery Stenosis
In coronary artery bypass surgery, appropriate graft selection is essential. If there are lesions in the aortic arch branches, the internal thoracic artery graft is inappropriate. The proximal end of a free graft should not be anastomosed to the diseased aorta. If coronary artery bypass grafting is performed simultaneously with procedures such as ascending aortic replacement, the proximal anastomosis should be made at the prosthetic aortic graft. Ostial endarterectomy and ostial patch angioplasty are effective in some patients.\textsuperscript{98}

\subsection*{7.3.6 Treatment for Pulmonary Artery Lesions}
A pressure overload of the right ventricle due to pulmonary hypertension is an indication for surgery and is treated by patch angioplasty using the pericardium or prosthetic graft replacement of the pulmonary artery. Favorable results of plain old balloon angioplasty (POBA) have also been reported.\textsuperscript{99}

\section*{8. Prognosis}
The 15-year survival rate of patients with Takayasu arteritis has been reported to be around 80%,\textsuperscript{100,101} but it can be modified by some poor prognostic factors, which include retinopathy, hypertension, aortic insufficiency, aortic aneurysm, progressive course, onset at a young age, and increased ESR.\textsuperscript{100} The disease activity may temporarily subside, but there have been many reports of high relapse rates.

The percentage of patients who require surgical treatment varies from 12 to 50%, but the percentage of those who receive early surgical intervention including percutaneous procedures is increasing.\textsuperscript{96} Heart failure is a more frequent cause of death than anastomotic complications, and heart failure is caused by aortic valve disease or ischemic heart disease.\textsuperscript{97} Late detachment of the aortic prosthetic valve and coronary bypass graft insufficiency are observed in about 10% of the patients who have undergone surgery,\textsuperscript{97} and the incidence of surgery-related late complication in Takayasu arteritis is high.

For the future, the cure rate is expected to be improved by the development of diagnostic techniques, particularly imaging modalities such as PET and MRI, and the use of biological agents.

\section*{9. Takayasu Arteritis in Children}
According to the database for national research of intractable diseases run by the MHLW of Japan, there were 140 patients with childhood-onset Takayasu arteritis in Japan in 2016. The list included patients who had survived to adulthood as well as 70 children who were <16 years of age. The male/female ratio was 1:7, and the median age at the onset was 10–11 years.

The initial symptoms of Takayasu arteritis are fever, malaise, abdominal pain, chest pain, arthralgia, and lymph node enlargement, with fever noted in about 80% of the patients.\textsuperscript{102,103} Children are now increasingly being diagnosed at an early stage of the disease because of improved diagnostic techniques and the spread of knowledge about Takayasu arteritis. In more than half the patients with childhood-onset Takayasu arteritis, the lesions are first seen in the abdominal aorta and its branches. In adult patients, the lesions occur more frequently in the head and neck arteries, ascending aorta, and aortic arch.\textsuperscript{102,103}

As there are no diagnostic criteria for childhood-onset Takayasu arteritis, the diagnosis depends on the criteria established for adults. Nevertheless, specific diagnostic criteria have been established for those applying for medical fee subsidies for children with specific chronic diseases.\textsuperscript{104} In such cases, inflammatory markers such as CRP and the ESR are generally elevated during the acute period. Imaging modalities, including ultrasonography, contrast-enhanced CT, CT angiography, MRI, and positron emission tomography (PET)-CT, are used for diagnosis. In addition, as lesions in children with Takayasu arteritis are more often located in the abdominal aorta and its branches than in adults, ultrasonography is a useful, convenient, non-invasive tool for diagnosis and follow-up. PET-CT is also a powerful emerging modality not only for the early diagnosis but for evaluating the distribution of lesions and monitoring disease activity. Since April 2018, PET-CT has become available under health insurance coverage at some PET facilities in Japan for patients with large-vessel vasculitis in whom the localization or activity of the lesions is difficult to determine by other modalities.

Treatment for children with Takayasu arteritis is commonly initiated with two to three courses of steroid pulse therapy followed by daily PSL (0.8–1.0 mg/kg), MTX (not covered by insurance in Japan) or AZA is generally used to prevent relapse and to accelerate GC tapering from the onset.\textsuperscript{98} IVCY and TCZ could be considered for those who have severe visceral lesions, who resist the initial treatment, who face difficulty reducing their GC dose, and/or who have repeated relapse. As children are less likely than adults to develop gonadal dysfunction from the CY, early treatment with IVCY may be positively considered.\textsuperscript{105} Because GCs — including pulsed therapy for patients whose status is complicated with renovascular hypertension — could increase the risk of reversible posterior leukoencephalopathy and hypertensive brain hemorrhage, the blood pressure should be tightly controlled according to the age-matched standard value. Growth impairment is also a serious adverse effect of GC in children. Therefore, if inflammatory markers have been negative for 6–12 months, the PSL dose should be reduced to a level that does not affect growth. As CY has exhibited both carcinogenicity and gonadal toxicity, excessive use should be avoided. Intravenous TCZ therapy has been reported effective for
treating childhood-onset Takayasu arteritis. The reports regarding subcutaneous TCZ therapy are limited, however, and future evaluation is awaited. Antiplatelets and anticoagulants are administered to patients who have vascular stenosis or marked vascular dilatation and are at high risk of thrombosis. More than half the children with Takayasu arteritis experience relapse and require treatment over a long period, although some can eventually discontinue all treatment.

III. Giant Cell Arteritis

1. Definition/Epidemiology/Subclassification

1.1 Definition
Giant cell arteritis (GCA) was defined by the 2012 CHCC as “arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries. Often involves the temporal artery. Onset usually in patients older than 50 years and often associated with polymyalgia rheumatica.” Since the temporal artery is not affected in all patients with GCA, and since temporal artery may be affected in other vasculitides, the term “giant cell arteritis” was adopted.

1.2 Epidemiology
The age at onset is usually 50 years or above, and the disease has a slight predilection for females. According to the nationwide epidemiological survey by the Ministry of Health and Welfare of Japan, the estimated number of treated patients was about 690 (0.65/100,000 persons), and the mean age at onset was 71.5 years.

1.3 Subclassification
GCA is subclassified into cranial GCA (C-GCA) localized in intracranial arteries and large-vessel GCA (LV-GCA), arteritis not localized intracranially but is present extracranially. However, the definition or clinical significance of LV-GCA has not been fully established.

2. Pathogenic Mechanism
Although the etiology of GCA is still unclear, it is known to be correlated with HLA-DRB1*0401, HLA-DRB1*0404, HLA-DQA1*0301, and HLA-DQB1*0302 as genetic factors. In addition, infection by microorganisms such as Mycoplasma pneumoniae, Chlamydia pneumoniae, and parvovirus 19 and environmental factors including smoking have also been reported to be involved in its pathogenesis.

In GCA, inflammatory cell infiltration in all layers is observed as in Takayasu arteritis. Especially, giant cells in the media and intima and occlusion of vascular lumen due to intimal thickening are characterized. CD83-positive dendritic cells and CD4-positive T cells in the adventitia play an important role for this process. Immature dendritic cells in the adventitia are matured through Toll-like receptor (TLR) and their matured dendritic cells activate CD4-
positive T cells. Moreover, cytokines secreted by these cells, IFN-α and IL-17, contribute to activation of macrophages and formation of giant cells. These macrophages and giant cells infiltrate into the intima, and secrete vascular endothelial growth factor, resulting in proliferation of vascular smooth muscle cells and remodeling of the vascular wall.

3. Pathological Findings

3.1 Affected Vessels
In GCA, middle-sized muscular arteries, particularly branches of the carotid artery and vertebral artery, are likely to be affected. Also, large elastic arteries such as the aorta, subclavian artery, and common iliac artery are often affected. Because the lesions are localized and occasionally segmented, temporal artery should be sampled over 2–4 cm and examined carefully.

3.2 Histological Findings
In muscular arteries such as the temporal artery, the lesions are formed primarily around the internal elastic lamina and the intimal side of the media (Figure 17).\textsuperscript{110} Inflammation is granulomatous; histiocyte proliferation, lymphocyte, plasma cell, and macrophage infiltration, and Langhans and foreign body giant cells are observed (Figure 18).\textsuperscript{110} The internal elastic lamina is ruptured and lost, multinucleated giant cells are likely to appear near it, and they occasionally seen to phagocytose the elastic lamina. Fibrinoid necrosis or neutrophil infiltration is rarely observed. The intima shows non-specific fibrotic thickening and may cause stenosis, but it is considered a secondary change associated with inflammation of the media.

In the aorta (elastic artery), granulomatous inflammation is formed primarily in the middle layer of the media. Elastic fibers are lost locally in a moth-eaten pattern (Figure 19).\textsuperscript{110} and histiocyte and lymphocyte infiltration and multinucleated giant cells are observed at such sites (Figure 20).\textsuperscript{110} Inflammation is also observed along the vasa vasorum that enters from the adventitia. In addition, loss of smooth muscle cells considered an ischemic change may develop at sites not affected by granulomatous inflammation, but elastic fibers remain at such sites. Thus, many infiltrating cells are observed with loss of elastic fibers at inflamed areas, whereas elastic fibers are observed without inflammatory cells at non-inflamed areas; these contrasting observations are mixed (Figure 19, inserted figure).\textsuperscript{110}

3.3 Differential Diagnoses and Similar Diseases
Takayasu arteritis: Since the frequent age at onset and sex difference in prevalence differ, age and sex are important information. In fact, differential diagnosis of GCA from Takayasu arteritis is considered difficult by pathological findings alone. However, inflammation occurs primarily in the inner and middle layers of the media in GCA, but the outer layer of the media to the adventitia are affected in Takayasu arteritis. Giant cells and granulomatous change are more notable in GCA than in Takayasu arteritis.

Buerger disease-like arteritis: Cases in which marked intimal thickening is observed in the temporal artery not accompanied by destruction of the internal elastic lamina or the media have been reported as Buerger disease.

Localized GCA: Granulomatous arteritis with giant cell infiltration occasionally occurs locally in small arteries of the urogenital organs including the uterus, ovary, and ureter and mammary glands, but their sites and the size of the affected arteries differ from those in GCA.
4. Symptoms

Generalized symptoms of GCA include fever associated with inflammation (often mild fever, occasionally remittent fever), malaise, easy fatigability, body weight loss, polymyalgia, and polyarthralgia. Local symptoms vary according to the site of the affected vessel. In the nationwide survey of 66 cases of GCA in Japan, symptoms including headache of the temporal region (80.3%), scalp pain (63.3%), tenderness of the temporal artery (52.6%), weakened pulse of the temporal artery (40.0%), visual impairment (43.9%), and ischemic optic neuropathy (21.2%) were observed.

External carotid artery lesions may cause temporal pain, swelling/tenderness of the temporal artery, jaw claudication, tongue claudication, and mandibular pain. These symptoms may occur both bilaterally and unilaterally. Scalp pain is often complained of when the patient combs or brushes hair, and jaw claudication is characterized by jaw pain during mastication.

If the ophthalmic artery is affected, symptoms including impairment of visual acuity, loss of vision, misty vision, and diplopia may occur. Abnormalities of visual acuity/visual field appear early after the onset, and caution is necessary, because about 23–44% of the patients show reduced visual acuity, and 4.4–6.5% show complete loss of vision. Sudden loss of vision is often first noted on awakening in the morning.

As mentioned in the definition of CHCC2012, lesions of GCA appear in the aorta and/or its major branches. The presence of subclavian artery lesions is considered a characteristic of LV-GCA. Common carotid artery lesions cause headache, dizziness, syncopal attacks, and hemiplegia. Subclavian artery lesions cause pain, cold sensation, and easy fatigability of the upper extremities and present attenuation or loss of the pulse of the radial artery and a difference in the blood pressure between the left and right limbs (≥10 mmHg). Aortic lesions cause disorders including chest pain, back pain, aortic aneurysm/dissecting aortic aneurysm, and aortic insufficiency.

Polymyalgia rheumatic (PMR) is observed in 30–60% of the patients with GCA, and as PMR is complicated by GCA in 16–21% of the patients.

5. Laboratory/Imaging Findings

5.1 Laboratory Findings

There are no laboratory findings specific to GCA. On blood tests, high ESR, increased CRP, chronic inflammatory anemia, and hypoalbuminemia are observed. An ESR of ≥50 mm/h is included in criteria for the classification of GCA, and GCA with normal CRP and ESR is rare. CRP and ESR are also used as markers of the flare of disease activity, and elevations of CRP and ESR may be the only findings at the relapse.

The IL-6 concentration in peripheral blood has been reported to change with the disease activity.

5.2 Imaging Findings

Diagnostic imaging modalities for GCA include CT, MRI, ultrasonography, and FDG-PET.

On MRI, thickening and contrast enhancement of the wall of the superficial temporal artery (arrow), which are findings specific to active GCA, are observed (arrow).

On CT, wall thickening and contrast enhancement are observed in 45% of the patients, and the modality is superior to MRI in that a broader area can be imaged more quickly and that image quality is relatively high.

On ultrasonography, the “dark halo” is detected around the superficial temporal artery due to edema of the arterial wall. It may not be observed early after the onset, and the sensitivity is reported to be about 40%.

The diagnostic ability of FDG-PET is high as abnormal accumulation has been reported to be observed in the blood vessel in 80% of the patients. It has become possible to perform FDG-PET under health insurance at some PET facilities in Japan for patients with large vessel
arteritis in whom the localization or activity of lesions is difficult to determine by other examinations since April 2018. However, there are limitations such as that it is expensive and that it can be performed at relatively few facilities.

## 5.3 Ophthalmological Examinations

20–30% of the GCA patients have blurred vision or visual deterioration,\textsuperscript{111,123,124} and some patients with GCA have diplopia, transient visual impairment, and the visual field defects. Blurred vision, visual deterioration and visual field defects can be caused by anterior ischemic optic neuropathy, occlusion of the central retinal artery, or occlusion of the cilioretinal artery,\textsuperscript{111,125} and they can be revealed by fundus examination. Diplopia is caused by restriction of ocular movements associated with ischemic external ophthalmoplegia. In anterior ischemic ocular neuropathy, which is the most frequent cause of visual impairment in GCA, pale edema of the optic disc is observed (Figure 23).\textsuperscript{126}

In silent GCA, which presents with systemic symptoms such as fever, easy fatigability, and loss of body weight rather than conventionally known symptoms (headache, tenderness of the temporal artery, weakened pulse, blindness), visual disorders are rare, but fundus lesions such as cotton-wool spots may be observed.\textsuperscript{124,127,128}

### Table 9. ACR Criteria for the Classification of Giant Cell Arteritis (Proposed by the ACR in 1990)

| Criterion | Definition |
|-----------|------------|
| 1. Age at disease onset ≥50 years | Development of initial symptoms or 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, un-related to arteriosclerosis of cervical arteries |
| 4. Elevated erythrocyte sedimentation rate | 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 |

(From Hunder GG, Bloch DA, Michel BA, et al., *Arthritis Rheum* 1990,\textsuperscript{129} John Wiley and Sons. (c) 1990, American College of Rheumatology.)

GCA is diagnosed if at least 3 of these 5 criteria are present (sensitivity: 93.5%, specificity: 91.2%)

### 5.3 Ophthalmological Examinations

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In silent GCA, which presents with systemic symptoms such as fever, easy fatigability, and loss of body weight rather than conventionally known symptoms (headache, tenderness of the temporal artery, weakened pulse, blindness), visual disorders are rare, but fundus lesions such as cotton-wool spots may be observed.\textsuperscript{124,127,128}

### 6. Diagnostic Methods and Criteria

#### 6.1 Diagnostic Criteria

The classification criteria by ACR of 1990 (Table 9),\textsuperscript{129} which are widely used for the diagnosis of GCA, are also adopted as the criteria of the MHLW of Japan. Tenderness or reduced pulse along the temporal artery is evaluated by palpation. While conditions can be classified as GCA even without pathological demonstration of GCA, biopsy of the unilateral temporal artery is recommended for the diagnosis. Vascular ultrasonography for wall thickening of the temporal artery is useful as an adjuvant diagnostic method.\textsuperscript{130,131}

Jaw claudication has low diagnostic sensitivity but is a clinical feature highly suggestive of vasculitis, which can be confirmed by temporal artery biopsy.\textsuperscript{132} Ischemic optic neuropathy is poorly sensitive but highly specific to GCA,\textsuperscript{129} and prompt diagnosis in cooperation with an ophthalmologist is recommended if the patient is aware of reduced visual acuity.

#### 6.2 Points of Attention in Diagnosing GCA

Since the 1990 ACR classification criteria are not prepared as diagnostic criteria, diagnosis by exclusion is necessary concerning unidentified fever, chronic inflammatory disease, and headache. Special attention to differential diagnoses must be paid if GCA cannot be pathologically demon-
Aortic lesions are considered to complicate GCA in about 20–30% of the patients. Aortic lesions such as stenosis of branches of the aorta and aortic aneurysm appear at the diagnosis of GCA in some patients, but they appear 5 or more years after the diagnosis in others. The relationship between aortic lesions and disease activity is unclear, but, epidemiologically, the risk of the occurrence of aortic aneurysm is higher than in those with non-GCA. Aortic lesions are related to the prognosis of GCA. Therefore, aortic lesions should be evaluated at the diagnosis or relapse of GCA by the same method as in Takayasu arteritis. FDG-PET is useful (it has become possible to perform the examination under health insurance at some PET facilities in Japan since April 2018 for patients with large vessel arteritis in which the localization or activity of the lesion is difficult to determine by other examinations).

Table 10. Recommendations and Evidence Level of Treatments for GCA

| Treatment                      | Recommendations | Levels of evidence |
|--------------------------------|-----------------|--------------------|
| Glucocorticoid (GC)            | I               | B                  |
| Steroid pulse therapy          | I               | B                  |
| Methotrexate (MTX)*            | IIa             | A                  |
| Cyclophosphamide (CY)          | IIb             | B                  |
| Azathioprine (AZA)             | IIb             | B                  |
| Cyclosporine (CyA)*            | III             | B                  |
| Tocilizumab (TCZ)              | I               | A                  |
| Infliximab (IFX)*              | III             | B                  |
| Adalimumab (ADA)*              | III             | B                  |
| Etanercept (ETN)*              | IIb             | B                  |
| Antiplatelets                  | IIa             | B                  |

*Uninsured in Japan.

7. Policies of Treatment

Recommendation classes and evidence levels of treatments for GCA are shown in Table 10. Figure 24 shows a flow chart of treatments for GCA.

7.1 Glucocorticoid/Immunosuppressants

7.1.1 Glucocorticoid

GC is effective and is the first-line treatment for GCA (recommendation class: I, evidence level: B). Since a delay in the initiation of treatment increases the risk of blindness and irreversible neurological damage, a high dose of GC should be initiated promptly if GCA is suspected.

- **Initial Treatment**
  1) In patients without ophthalmic or neurological symptoms, PSL at 0.5–1 mg/kg/day (60 mg/day at the maximum) is recommended (recommendation class: I, evidence level: B).
  2) In patients with rapidly developed ophthalmic or neurological symptoms, steroid pulse therapy (mPSL at 0.5–1 g/day, 3 days) is recommended to be initiated and followed by PSL at 1 mg/kg/day (60 mg/day at the maximum) (recommendation class: I, evidence level: B). GC reduction should be considered only in the absence of clinical symptoms and normalized inflammatory markers such as CRP and ESR after sustaining the initial dose for 2–4 weeks. Most patients can be weaned from GC in 1–2 years, but GCA recurs in about half the patients.

- **Treatment of Relapse**
  1) An increase of 5–10 mg/day of PSL is usually sufficient to treat a relapse in the absence of ophthalmic or neurological symptoms.
  2) An increase to the initial dose of PSL should be considered in the presence of ophthalmic or neurological symptoms.

7.1.2 Immunosuppressants

Immunosuppressants are administered with GC to those who resist GC, those who have developed relapse with gradual reduction of GC, and those in whom rapid reductions of GC are needed due to adverse reactions. However, the therapeutic effect of the concomitant use of immunosuppressants on GCA is considered limited. GCA is not treated with immunosuppressants alone. MTX (uninsured) (recommendation class: IIa, evidence level: A), CY (recommendation class: IIb, evidence level: B), and AZA (recommendation class: IIb, evidence level: B) have been reported to be effective as concomitant immunosuppressants.

7.2 Biological Preparations/Antiplatelets

7.2.1 Biological Preparations

GCA responds well to moderate or high dose of GC therapy. While early tapering of its dosage is necessary to reduce adverse events, GCA often relapses during tapering. To examine whether the concomitant use of biologics prevents flare-up of the disease, and reduce cumulative dose of GC, RCTs concerning the efficacy of the concomitant use of TCZ, ADA, or IFX were carried out in Europe and the United States.

7.2.2 TCZ

The efficacy of a protocol of initiating the administration of TCZ, which is an anti-IL-6 receptor antibody, with GC therapy has been confirmed by phase II and phase III trials.
The phase II trial showed that the remission rate at week 12 was significantly higher, and the relapse rate until after week 52 was significantly lower, when TCZ was used concomitantly with early tapering schedule of PSL. In the phase III trial, the remission maintenance rates at weeks 12–52 were significantly higher in the TCZ group even when PSL was discontinued at week 26, and cumulative dose of GC was significantly decreased in the TCZ group. Concerning refractory cases with a history of treatment using immunosuppressants and TNF inhibitors, there have been case reports and small case series reporting that PSL could be reduced to a low dose or discontinued by the concomitant use of TCZ. The evidence level of TCZ is higher than those of immunosuppressants or TNF inhibitors. It should be administered to cases that flare during tapering of GCs or require early tapering of GC, with attention to the safety and in consideration of the risk-benefit balance (recommendation class: I, evidence level: A, covered by health insurance in Japan).

### 7.2.3 TNF Inhibitors

Since the efficacy of ADA and IFX, among the TNF inhibitors (uncovered by health insurance in Japan), has not been demonstrated by the results of clinical trials, the concomitant use of TNF inhibitors with GC from an early stage of treatment is not recommended (recommendation class: III, evidence level: B) despite the problem that the evaluation method for the activity of GCA has not been sufficiently established. The efficacy of TNF inhibitors against relapse during GC therapy or the use of immunosuppressants is unclear. Etanercept (ETN) is expected to have a GC-sparing effect, and its reevaluation is awaited (recommendation class: IIb, evidence level: B).

### 7.2.4 Antiplatelets (recommendation class: IIa, evidence level: B)

GCA is occasionally complicated by cerebrovascular disorders and cardiovascular events, although vasculitis rarely develops in intracranial arteries except for the ophthalmic artery. The concomitant use of low-dose aspirin (81–100mg/day) has been reported to reduce the risk of cerebrovascular disorders by retrospective observational studies. EULAR recommends the concomitant use of a small dose of aspirin without contraindications.

### 7.3 Invasive Treatments

The evidence concerning surgical/endovascular treatments for large vessel lesions associated with GCA is meager. Please refer to Chapter II 7-3 (Invasive Treatments for Takayasu Arteritis).
8. Prognosis

Factors that affect the prognosis include (1) sequelae of vascular ischemia (blindness, cerebral infarction, myocardial infarction), (2) aneurysm (dissecting/ruptured), and (3) treatment-related complications (infections, and morbid fracture due to immunosuppressive therapy such as long-term GC therapy). According to the national epidemiological survey by the Ministry of Health and Welfare of Japan in 1998, cure/recovery was reported in 81.8%, cerebral infarction in 12.1%, blindness in 6.5%, and death in 4.5% as short-term outcomes. GCA as well as PMR is a disease that recurs repeatedly, and GC therapy was continued in 43% and 25% of the patients 5 and 9 years, respectively, after its initiation according to a report from Sweden. Analysis of causes of death in a cohort study in Minnesota showed that the mortality rate due to ischemic enteritis was 4.9 times higher in patients with GCA, and 5.1 times higher in those with GCA complicated by aortic aneurysm or dissection, compared with the general population. In a single facility cohort in northwestern Spain, aortic aneurysm occurred secondarily in 9.5% of the patients with GCA, and hypertension and marked acute inflammatory reaction at the time of first diagnosis were risk factors.

IV. Buerger Disease

1. Definition and Epidemiology

1.1 Definition

Buerger disease causes segmental lesions in arteries and veins of the extremities and is frequently observed in males in their 20-40s. It is closely related to smoking and is occasionally complicated by migrating thrombophlebitis. Lesions mainly affect the arteries of the forearm to the hand and the infrapopliteal artery to arteries of the foot. The life prognosis is favorable, but the quality of life (QOL) is sometimes impaired by ischemic pain at rest or ulcer/gangrene which leads to minor limb amputation. The incidence of major amputation increases if the patient fails to stop smoking.

1.2 Epidemiology

As of 2014, about 7,000 patients were certified to have Buerger disease, one of the specific diseases (Figure 25). Recently, the number of female patients has been increased to 11–23% of the whole patients, presumably due to an increase in smoking rates in female. In Japan, the majority of patients are elderly patients who have grown old after the onset in young age. The disease is prevalent in South Asia, East Asia, and Turkey. In Japan, Buerger disease used to be reported to account for 16% of patients treated for occlusive arterial disease but is presently estimated to account for 1% or less due to the decrease in the number of patients with this disease and the increase in that with atherosclerotic diseases.

Figure 25. Annual changes in the numbers of patients with refractory vasculitides estimated from the numbers of certificates of patients with specific diseases issued. (Cited from the Japan Intractable Diseases Information Center)
2. Pathogenesis

It has been suggested that pathogenesis of Buerger disease are related to smoking, infection, activated condition of vascular endothelial cells, and the occurrence of microcirculation disorder. The involvement of racial/ethnic factors has also been suspected.

Many of the patients are heavy smokers. The disease has been reported to be induced by exposure to cold, trauma, and sympathetic nerve stimulating drugs, but patients are considered to have some history of smoking including passive smoking. Many patients have dental root inflammation, and the same periodontal pathogens have
been detected in the arterial wall and oral cavity.\textsuperscript{180}
Attenuation of electric signals of the sympathetic nerve to the muscles and skin,\textsuperscript{181} reduced blood catecholamine level due to change in peripheral sympathetic nerve responses to smoking,\textsuperscript{182} impairment of endothelium-dependent vasodilation of peripheral arteries, and increased expression of adhesion factors in endothelial cells and inflammatory cells\textsuperscript{183} have been reported, and activation of platelets via serotonin receptors is speculated.\textsuperscript{184}

### 3. Pathological Findings

Figure 26 shows pathological images, and Figure 27 shows a diagram of characteristic features of Buerger disease. In Buerger disease, middle-sized vessels of the lower or upper extremities are affected, and as thrombi cause segmental occlusion of arteries, gangrene is observed in peripheries. The following pathogenic features characteristic of occluded arteries are observed: (1) In the acute period, microabscesses in which neutrophils aggregate and multinucleated giant cells are occasionally observed in the vascular wall, particularly, intima.\textsuperscript{172,185} (2) The internal elastic lamina is not displaced, remains flexed, and may even be overflexed.\textsuperscript{186} This contrast with displacement of the internal elastic lamina by the intima observed in occlusive atherosclerosis and thrombosis, which are major differential diagnoses. (3) Fibrosis of the adventitia with no fibrosis of the media,\textsuperscript{187} (4) edema immediately inside the external elastic lamina,\textsuperscript{187} (5) onion-like multi-layering of endothelial cells of recanalized vessels,\textsuperscript{187} and (6) thickening of the endothelial cells of vasa vasorum\textsuperscript{187} are also observed frequently. These are features caused by inflammation within the vascular wall or from outside the blood vessel and impairment of microvessels. (7) Immunohistochemically, macrophage/lymphocyte infiltration tightly attached to the internal elastic lamina may be demonstrated.\textsuperscript{188}

### 4. Symptoms

#### 4.1 Ischemic Signs/Symptoms in the Upper and Lower Limbs

##### 4.1.1 Ischemic Signs/Symptoms in the Lower Limbs

**a. Coldness**
Patients feel coldness mainly in their toes.

**b. Paresthesia**
Numbness often occurs commonly in the fingers, toes, feet, and hands, particularly after exercising or walking.

**c. Skin Color Change**
The skin color of affected digits turns red (rubor) even when the limbs are located at the same level with the heart. Cyanosis indicates critical digit ischemia.

**d. Intermittent Claudication**
Ischemic intermittent claudication develops in the foot in an early stage, in the calf when the above-knee arteries are involved, and in the thigh and buttock when the iliac arteries are involved.

**e. Rest Pain**
Severe and stinging rest pain often disturbs patient’s sleep.

**f. Ulcer/Gangrene**
Ulcer and gangrene often occur in the fingers and toes, particularly around the nails. Ulcer and gangrene can develop beginning from small injury and extend rapidly.

#### 4.1.2 Ischemic Signs/Symptoms in the Upper Limbs

Ischemic signs/symptoms in the upper limbs are milder than those in the lower limbs and are reported to be primary chief complaints in about 5–14% of the patients.\textsuperscript{180,190}

#### 4.2 Involvement of Visceral Arteries

Although rare, lesions in the cerebral artery,\textsuperscript{191} coronary artery,\textsuperscript{192,193} renal artery,\textsuperscript{194} mesenteric artery,\textsuperscript{195,196} and internal thoracic artery\textsuperscript{193} have been reported.

#### 4.3 Migratory Superficial Thrombophlebitis

Recurrent and migratory superficial thrombophlebitis (phlebitis migrans/migrating thrombophlebitis) occurs in the limbs.

#### 4.4 Incidences of Signs/Symptoms

According to a survey in Japan in 1993, signs/symptoms were observed in the upper limbs alone in 5.1% of patients, lower limbs alone in 74.7%, and both upper and lower limbs in 20.2%. The affected arteries were the anterior tibial artery in 41.4%, posterior tibial artery in 40.4%, and ulnar artery in 11.5%.\textsuperscript{197}

According to the analysis conducted at the Department of Vascular Surgery of Nagoya University from 1977 to 1988, the initial symptoms were paresthesia, coldness, and cyanosis in 37% of patients, foot or calf claudication in about 30%, and severe ischemic symptoms such as rest pain and ulcer/gangrene in about 30%. Through the entire course, ulcer/gangrene was observed in 72%, migratory phlebitis in 45%, and upper limb lesions in 90%.\textsuperscript{198}

### 5. Clinical Features and Laboratory Findings

#### 5.1 Physical Findings (Table 11)

#### 5.2 Examination Items (Table 12)

Thermographic evaluation with cold-water stress is useful for the diagnosis of Raynaud’s phenomenon. For patients with intermittent claudication, maximum walking distance as well as recovery time of the ankle-brachial index, which is reduced after walking, can evaluate circulatory reserve of the lower limb. Angiography is indispensable in patients considered to have indication for bypass surgery of the lower leg.

#### 5.3 Findings of Vascular Imaging (Table 13,\textsuperscript{198} Figures 28–30\textsuperscript{198–200})

Differentiation from collagen diseases such as SLE, scleroderma, and vascular Behçet’s disease is particularly important. However, the differentiation is difficult by imaging findings alone.\textsuperscript{201,202}

#### 5.4 Hematological Examinations

There is no specific hematological abnormality. ESR and...
CRP values are usually normal.

6. Diagnostic Methods and Criteria

6.1 Diagnosis

There are various diagnostic criteria. When patients fulfill all of the 5 criteria of Shionoya’s clinical diagnostic criteria (Table 14), the clinical features are typical. However, even without fulfillment of all criteria, Buerger disease can be diagnosed if clinical findings including vascular images or pathological findings are consistent, and differential diagnoses can be excluded. Since young people with hypertension or dyslipidemia have increased, the careful diagnosis based on imaging and histological examinations is necessary, including differentiation from arteriosclerosis obliterans.

6.2 Conditions to Be Differentiated From Buerger Disease

Conditions to be differentiated from Buerger disease include arteriosclerosis obliterans, traumatic arterial thrombosis, popliteal artery entrapment syndrome, popliteal artery adventitial cyst, SLE, scleroderma, vascular Behçet’s disease, thoracic outlet syndrome, and atrial fibrillation.
7. Policies and Guidelines of Treatment

Table 15 shows recommendations about treatment for Buerger disease.

7.1 Conservative Treatment

7.1.1 Smoking Cessation/Lifestyle Guidance

Patients should avoid even passive smoking, keep the affected limbs warm and clean, and avoid injury. Smoking after the initial visit correlates with increased limb amputation rate. Symptoms can be resolved in many patients by conservative therapy centering on smoking cessation.

7.1.2 Drug Treatment

For coldness and numbness, drug treatment should be attempted first. As oral antiplatelet agents, Cilostazol, beraprost, sarpogrelate, limaprost alfadex, ticlopidine, and clopidogrel are used. Alprostadil (a complex of prostaglandin E1 [PGE1]-α-cyclodextrin [CD] complex, lipo-PGE1) is an injection drug used for the treatment.

7.1.3 Exercise Therapy

Supervised exercise therapy is useful for the treatment of intermittent claudication. The effects should be evaluated...
after the program has been carried out for 3–6 months.

### 7.1.4 Pain Control
In addition to oral medications, fentanyl tape is also available. Continuous epidural anesthesia or toe amputation can be an option.

### 7.2 Surgical Treatment

#### 7.2.1 Revascularization
Revascularization is indicated particularly in patients with rest pain or ulcer when no improvement has been observed in symptoms by conservative treatment. Using autogenous vein grafts is recommended for bypass surgery. The potency of infrapopliteal bypass in Buerger disease is generally lower than that in arteriosclerosis obliterans. However, major amputation is required in only small number of patients even if the graft occlusion has occurred.

#### 7.2.2 Sympathectomy
Sympathectomy should be considered for painful ulcers of the toes and fingers when revascularization is impossible. Pharmacological sympathetic blockade can also be a choice.

#### 7.2.3 Others
Angiogenesis therapy (gene therapy, autologous bone marrow (monocyte) transplantation, peripheral blood monocyte transplantation), remains in the experimental stage.

### 8. Prognosis

#### 8.1 Prognosis of Ischemic Limbs
It is estimated that 70% of the patient will experience ischemic ulcer or necrosis at least once during the course. Patients tend to repeat exacerbation and remission of symptoms, therefore, not all the patients with Fontaine stage III/IV disease need limb amputation.

On long-term follow-up studies, major limb amputation was performed in 2.7–10.5% of the patients. According to questionnaire surveys by the MHLW Group Conference, 8.8% resulted in major limb amputation, and 16.7–20.5% of the patients required toe amputation. Patients who need revascularization of the upper limb are few. While some patients require finger amputation, very few patients need major amputation of the upper limb.

#### 8.2 Factors Contributing to Exacerbation and Improvement
Smoking is considered to shorten the remission period and invite exacerbation. Patients who continue smoking after the appearance of symptoms resist various treatments and often come to need major amputation consequently. If patients can avoid foot injury by hospitalization, their symptoms may be alleviated. Hospitalization also leads patients to strict smoking cessation.

#### 8.3 Prognosis of Non-Critical Ischemic Limbs
Almost all patients have two or more affected limbs. The disease rarely progresses in non-critical or non-dominant ischemic limbs if patients can continue smoking cessation but may progress if patients continue smoking.

#### 8.4 Concomitant Diseases and Life Prognosis
The life expectancy of patients is considered favorable. The most common cause of death is malignant neoplasm, followed by heart failure, cerebral infraction, and liver cirrhosis. Concomitant diseases include diabetes, hypertension, dyslipidemia, cerebrovascular disorders, ischemic heart disease, and arteriosclerosis obliterans. Therefore, the disease management including atherosclerotic risk factors is required according to the patients’ age.

### V. Polyarteritis Nodosa

#### 1. Definition and Epidemiology
Polyarteritis nodosa (PAN) is defined as “Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with ANCA”.

Presently, the number of patients is estimated to be about 600, but 3,442 patients held certificates for medical benefits for specific diseases in 2015. The male/female ratio of the patients is 1:1 to 1:2, and the average age at onset is 55 years.

#### 2. Pathogenic Mechanism
The etiology is unknown, but secondary PAN that follows HBV infection has been recognized.

#### 3. Pathological Findings
In the acute period, severe inflammation and necrosis are observed in the vascular wall of muscular arteries, and lesions are present as segments. In the affected blood vessels, fibrinoid necrosis and rupture of the internal/external elastic laminae are observed, often causing aneurysms (Figure 31).

#### 4. Symptoms

Patients with PAN present systemic symptoms and organ symptoms due to ischemia (Table 16). PAN in which lesions are localized in the skin is called cutaneous PAN or cutaneous arteritis.

#### 5. Laboratory and Imaging Findings
There is no laboratory finding specific to PAN. ANCA must be confirmed to be negative. Examinations including skin biopsy, angiography, and sural nerve biopsy are performed.
Necrotizing arteritis in the bladder muscle layer. Fibrinoid necrosis of the arterial wall and inflammatory cell infiltration to the arterial wall and surrounding tissue are observed. (HE stain) (Provided by Prof. Akihiro Ishizu, Hokkaido University)

Table 16. Clinical Symptoms of Polyarteritis Nodosa

| Clinical signs/symptoms       | Prevalence (%) |
|-------------------------------|---------------|
| General symptoms              | 80            |
| Neurologic manifestations     | 75            |
| Arthralgia, Myalgia           | 60            |
| Cutaneous signs/symptoms      | 50            |
| Renal manifestations          | 50            |
| Gastrointestinal manifestations| 40            |
| Hypertension                  | 35            |
| Pulmonary manifestations       | 25            |
| Central nervous system...     | 20            |
| Testicular manifestations     | 20            |
| Cardiac manifestations        | 10            |
| Peripheral vascular...        | 10            |

(Reproduced with modification from Pagnoux C, et al. 2010)

Table 17. MHLW Diagnostic Criteria for Polyarteritis Nodosa

For Definite and Probable Diagnoses

| 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 obstruction |
| 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) Differential diagnosis                  |
| 1) Microscopic polyangiitis                 |
| 2) Granulomatosis with polyangiitis (formerly known as Wegener’s granulomatosis) |
| 3) Eosinophilic granulomatosis with polyangiitis (formerly known as allergic granulomatous angitis) |
| 4) Kawasaki disease                         |
| 5) Connective tissue disease (SLE, RA)      |
| 6) IgA vasculitis (formerly known as Henoch Schönlein purpura) |

[Notes]

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

(Report of the Intractable Vasculitis Study Group of the MHLW, 2005 Revised)
6. Diagnosis and Diagnostic Criteria

Table 17 shows the diagnostic criteria for PAN by the MHLW of Japan.219

7. Policies and Guidelines of Treatment

Table 18 shows recommendations about treatments for PAN.

7.1 Remission Induction Therapy

7.1.1 Moderate/Severe PAN With Lesions in Vital Organs

Four-week initial treatment is performed using PSL at 1 mg/kg/day with IVCY or daily oral CY administration from the beginning of treatment (recommendation class: I, evidence level: B). If symptoms are extremely severe, steroid pulse therapy is performed simultaneously (recommendation class: IIa, evidence level: C). If severe renal disorder is noted, plasma exchange (uninsured) should also be considered (recommendation class: IIb, evidence level: C).

7.1.2 Mild PAN Not Accompanied by Vital Organ Lesions

Treatment is initiated with PSL alone (0.5–1.0 mg/kg/day) (recommendation level: I, evidence level: B). If symptoms are not improved, CY or MTX is used concomitantly.

7.1.3 Symptomatic Treatments/Management of Adverse Reactions

Antihypertensive drugs, circulation improving medications, and treatments for neurological disorders should be used in combination with prophylaxis for infection.

7.2 Remission Maintenance Therapy

PSL is reduced and continued at a maintenance dose of 5–10 mg/day. CY is replaced with AZA at 1–2 mg/kg/day or MTX at 7.5–15 mg/week (uninsured) (recommendation class: IIb, evidence level: B).

8. Prognosis

The 5-year survival rate of patients with PAN is 75–93%.223,224 As prognostic factors, proteinuria of ≥1 g/day, renal insufficiency, cardiomyopathy, severe gastrointestinal manifestation and central nervous system involvement were extracted in 1996,225 and an age of ≥65 years, cardiac symptoms, renal insufficiency, and gastrointestinal involvement were reported in 2011.226

VI. Microscopic Polyangiitis

1. Definition and Epidemiology

1.1 Definition

Microscopic polyangiitis (MPA) is classified as small-vessel angitis related to ANCA and defined as “a necrotizing vasculitis that primarily affects small vessels (capillaries, venules, arterioles) and shows only little or no immune deposits. Necrotizing arteritis may affect not only small vessels but also middle-sized vessel. Necrotizing glomerulonephritis is observed in most patients, pulmonary capillary angitis is often observed, and granulomatous inflammation is not observed.”1

1.2 Epidemiology

According to the summary of the number of certificates for recipients of medical care for specific diseases issued at the end of the fiscal year 2015, the number of MPA patients was 8,511 (Figure 25).11 The male/female ratio is 1:1.1 slightly in favor of women, and the mean age of the patients was 70.5 years.227 The annual incidence of MPA per 1 million people has been reported to be 18 in Japan,228 7 in the UK, 8 in Spain, and 3 in Germany.229 Among subtypes of ANCA, myeloperoxidase (MPO) ANCA (MPO-ANCA) is predominant in Japan, accounting for 97.4%, and proteinase 3 (PR3) ANCA (PR3-ANCA) accounts for 2.6%.227 In Western countries, MPO-ANCA and PR3-ANCA occupy 40–58% and 26–50%, respectively, and the PR3-ANCA is more prevalent than in Japan. Also, interstitial pneumonia is prevalent at 45% in Japan.227

2. Pathogenic Mechanism

An autoimmune mechanism, i.e., genetic and environmental factors interact to produce ANCA, which is an autoantibody, and it induces vascular endothelial damage, is suspected to be involved.

2.1 Genetic Factors

HLA haplotype analysis: In Japanese patients with MPA, 50% are reported to be positive for HLA-DRB1*0901, and the percentage is significantly higher than in healthy...
controls. According to the results of GWAS (comprehensive analysis of genetic polymorphisms in whole genome) concerning ANCA-associated vasculitis based on multicenter collaborative research in Europe, MPA and ANCA-associated vasculitis positive for MPO-ANCA were suggested to be significantly related to SNP in the HLA-DQ region.

In addition, gene polymorphism of ANCA-associated vasculitis is estimated to be more closely related to the specificity of ANCA such as MPO-ANCA and PR3-ANCA than clinical classification of MPA and GPA.

### 2.2 Environmental Factors

Agents including silica, drugs, and infection (viruses, Gram-negative rods) are suspected to be involved in MPA. Among drugs, propylthiouracil (anti-thyroid drug) has been reported most frequently, and minocycline (antibiotic) and hydralazine (antihypertensive) have also been reported.

### 2.3 Pathology

Inflammatory cytokines such as TNF-α, ANCA, MPO, and neutrophil activation have been suggested to be involved (ANCA-cytokine sequence theory). ANCA produced by an autoimmune mechanism excessively activates neutrophils alone with inflammatory cytokines is estimated to release a network of fine fibers (chromatin fibers) called neutrophil extra-cellular traps and damage the vascular endothelium.

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**Table 19. Diagnostic Criteria for Microscopic Polyangiitis**

| <Diagnostic Criteria> For definite and probable diagnoses |
|----------------------------------------------------------|
| **(1) 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. |
| **(2) Major histological findings** |
| Necrosis of arterioles, capillaries and postcapillary venules, and infiltration of inflammatory cells into tissues surrounding vessels |
| **(3) 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 pneumonia |
| **(4) Diagnosis** |
| 1. Definite |
| (a) Patients with ≥2 major clinical findings and positive histological finding |
| (b) Patients with ≥2 major clinical findings including Items 1and 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 |
| **(5) Differential diagnosis** |
| 1. Polyarteritis nodosa |
| 2. Granulomatosis with polyangiitis (formerly known as Wegener’s granulomatosis) |
| 3. Eosinophilic granulomatosis with polyangiitis (formerly known as allergic granulomatous angiitis/Churg Strauss syndrome) |
| 4. Arteritis of Kawasaki disease |
| 5. Collagen disease (SLE, RA, etc.) |
| 6. IgA vasculitis (formerly known as Henoch Schönlein purpura) |

**[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 relapse of disease.
5. Various diseases to be differentiated exhibit necrotizing vasculitis but can be differentiated according to characteristic signs and symptoms and laboratory findings.

(Report of the Intractable Vasculitis Study Group of the MHLW)
3. Pathological Findings

In MPA, necrotizing vasculitis is observed primarily in small vessels (capillaries, venules, arterioles) distributed to various organs including the kidney, lung, skin, and nervous system (Figure 32). On immunoglobulin staining by the fluorescent antibody method, little or no immune deposits are observed (pauci-immune).

Typical small-vessel vasculitides due to MPA are focal/segmented necrotizing glomerulonephritis and crescentic glomerulonephritis in the kidney and alveolar hemorrhage due to pulmonary capillaritis in the lungs.

4. Signs and Symptoms

As systemic symptoms, there are fever, malaise, anorexia, and body weight loss. As local lesions/symptoms, there are a wide variety of symptoms due to organ disorders shown below.

Kidney symptoms: Various symptoms due to necrotizing glomerulonephritis (edema, glomerular hematuria, RPGN).

Lung lesions: Bloody sputum, hemoptysis, melanoptysis, cough, and dyspnea due to alveolar hemorrhage and dry cough and dyspnea due to interstitial pneumonia.

Skin symptoms: Purpura, livedo reticularis, subcutaneous nodules
Ophthalmic lesions: Conjunctival congestion, diplopia, reduced visual acuity, ophthalmalgia.
ENT symptoms: Hearing impairment due to otitis media
Peripheral nerve lesions: Paresthesia of the limbs, motor disorders
Central nervous system disorders: Symptoms due to lesions of the hemiplegia, headache, and disturbance of consciousness due to cerebral infarction or cerebral hemorrhage, symptoms due to lesions of the cranial nerves such as facial nerve palsy, and headache and disturbance of consciousness due to hypertrophic pachymeningitis.
Gastrointestinal lesions: Abdominal pain, melena

5. Laboratory and Imaging Findings

As findings indicating inflammatory reaction, there are increases in CRP/gammaglobulin, ESR, peripheral blood leukocyte count, and platelet count. Laboratory/imaging findings in typical organ disorders are presented.

In patients with kidney lesions, abnormal urinalysis findings (proteinuria, glomerular hematuria, red blood cell cast, and granular cast) indicating nephritis and a decrease in eGFR or increase in BUN/serum creatinine indicating the reduction of renal function may be observed. RPGN is often noted, and serial measurements of eGFR are important.

Concerning lung lesions, non-segmental infiltrative shadow indicating alveolar hemorrhage is a typical finding. Interstitial pneumonia often presents reticular or annular shadows primarily in the bilateral lower lung fields on chest radiography and reticular shadow, honeycomb lung, and infiltrative shadow immediately below the pleura on CT, showing a usual interstitial pneumonia (UIP) pattern.

Ophthalmic lesions (episcleritis) and ENT lesions (neural deafness) are observed, and there are peripheral nerve lesions (findings of mononeuropathy multiplex), central nervous system disorders (headache, disturbance of consciousness due to cerebral infarction, cerebral hemorrhage, or hypertrophic pachymeningitis), and gastrointestinal lesions (abdominal pain, melena).
6. Diagnosis/Diagnostic Criteria

6.1 Diagnosis

Table 19 shows the diagnostic criteria for MPA by the MHLW Research Committee of Intractable Vasculitides.\textsuperscript{236}

6.2 Procedure of Differential Diagnosis

First, vasculitides due to infection, malignant neoplasm, drugs, and other collagen diseases must be excluded. ANCA may also be positive in infectious endocarditis and collagen diseases such as SLE. For the differentiation of MPA from infectious endocarditis, the history of dental treatment, blood culturing, and echocardiography findings are important.

After the above condition have been excluded, and primary middle-sized/small-vessel vasculitis is considered possible, ANCA-associated vasculitides are classified by following the 3 steps shown in Figure 33.\textsuperscript{237} EGPA is excluded first, and GPA is excluded next. If these two diseases have been excluded, urinalysis findings characteristic of glomerulonephritis and findings of small-vessel vasculitis such as purpura are present, and ANCA is positive, the possibility of MPA is high. Even if MPA is initially diagnosed, the diagnosis is changed if lesions due to granulomatous inflammation such as pulmonary nodules are confirmed during the course, and the diagnosis of GPA or EGPA are fulfilled.

In MPA, caution is necessary as impairment of only one organ may be observed at the facility that diagnoses the disease initially, but disorders of various organs may appear successively.

7. Policies and Guidelines of Treatment

The basic treatments for MPA are GC and immunosuppressants (including RTX) (Figure 34).\textsuperscript{238,239} Plasma exchange therapy may also be included (uncovered by insurance in Japan).

By the Guidelines for the Management of ANCA-associated vasculitis 2017 (jointly prepared by the MHLW Study Groups on Intractable Vasculitides, Intractable Kidney Diseases, and Diffuse Lung Diseases), the following treatments are recommended (the strength of recommendation and reliability of the evidence are presented according to the GRADE system).\textsuperscript{238} See the recommendations and comments in Part 1 of the same Guidelines. See the section, VIII Treatments in Part 2 of the same Guidelines for the dosage and dose regimen of each drug.

7.1 Remission Induction Therapy

The following CQs and the answers to them are the same for MPA and GPA.

CQ1

What regimens are effective as remission induction therapies for ANCA-associated vasculitis?

(1)-(i) As a remission induction therapy for ANCA-associated vasculitis, GC+IVCY or oral CY is proposed instead of GC alone.

CQ2

Is plasma exchange useful as a remission induction therapy for ANCA-associated vasculitis with severe kidney disorder?

(1)-(i) As a remission induction therapy for ANCA-associated vasculitis with severe kidney disorder, GC+oral CY+plasma exchange* is proposed instead of GC+oral CY+steroid pulse therapy.

Concerning the recommendations in CQ1 and CQ2, there are the following points of attention. Drugs/treatments indicated by * cannot be recommended in general, because they are uncovered by insurance in Japan. Consultation with nephrologists is recommended concerning patients with severe kidney disorders including RPGN. Plasma exchange should be performed by a physician with sufficient experience.
7.2 Remission Maintenance Therapies

CQ3
What regimens are useful as remission maintenance therapies for ANCA-associated vasculitis?

As a remission maintenance therapy for ANCA-associated vasculitis, the concomitant use of AZA in addition to GC is proposed.

Strength of recommendation: Weak
Reliability of evidence: Very low
RTX, MTX*, and MMF* can be alternative drugs to be used for remission maintenance therapy. The drugs/treatments indicated by * cannot be recommended in general, because they are uncovered by insurance in Japan.

8. Prognosis

The prognosis of MPA has been markedly improved due to early detection as a result of the increased prevalence of ANCA measurement and knowledge about the disease, modifications of immunosuppressive therapy, improvements in anti-infection measures.

In 2008, EULAR reported that the remission rate of MPA except the renal-limited type was 81–91% and that the 5-year survival rate was 45–76%. However, in 2011, the European Vasculitis Study Group evaluated the long-term survival rate of patients with ANCA-associated vasculitis including MPA (mean follow-up period: 5.2 years) and reported a mortality rate of 25%. The report mentioned a eGFR of <15 mL/min/1.73 m², old age, and high disease activity (BVAS) as factors that increased the mortality rate.

According to the Prospective Study of the Severity-Based Treatment Protocol for Japanese Patients with MPO-ANCA-associated Vasculitis (JMAAV), a prospective clinical study to clarify the usefulness of severity-based treatment protocols for MPO-ANCA-associated vasculitis carried out in Japan, the remission induction rate was 89.4%, mortality rate was 10.6%, rate of progression to end-stage renal disease was 2.1%, and relapse rate was 19.0%. The mortality rate by the severity of the disease was 50% for severest, 13% for severe, and 4% for mild cases, and the causes of death included vasculitis and infection.

The RemiT-JAV-RPGN, a prospective study of 321 cases of ANCA-associated vasculitis by the Study Group on Intractable Vasculitis and Study Group on Progressive Kidney Diseases of the MHLW of Japan, which included 197 cases of MPA, reported that the survival rate was 92.5%, and the remission induction rate was 76%, half a year after the initiation of remission induction therapy. In addition, the condition progressed to end-stage renal disease in 12.7% during the observation period.

VII. Granulomatosis With Polyangiitis

1. Disease Concept, Definition, and Epidemiology

Granulomatosis with polyangiitis (GPA), first reported in 1939 by Wegener, a German pathologist, is an intractable vasculitis with the following 3 clinicopathological characteristics: (1) Necrotizing granulomatous inflammation in the upper airway (E: ear and nose) and the lung (L: lung), (2) focal segmental necrotizing glomerulonephritis in the kidney (K: kidney), and (3) generalized necrotizing vasculitis of middle-sized/small vessels. According to a recent clinical research, the disease has a slight predilection to women, and often affects people in their 40s–60s, but may also occur in children and older people.

2. Pathogenic Mechanism

Concerning the action mechanism of ANCA in GPA, the ANCA-cytokine sequence theory was proposed, neutrophil extracellular traps released by neutrophils at cell death are considered to be involved in the formation of pathological features.

3. Pathological Findings

In E and L, parenchymal necrosis and granulomatous inflammation are noted (Figure 35), and necrotizing vasculitis is observed from middle-sized to small arteries, veins and capillaries. Histological findings in K are consistent with focal segmental or crescentic nephritis and are pauci-immune.

4. Signs and Symptoms

In addition to systemic symptoms such as fever and body
5. Laboratory and Imaging Findings

Typical chest radiography findings are nodular lesions accompanied by multiple or single cavities (Figure 36), and differentiation from malignant neoplasm and tuberculosis is necessary. In Western countries, cytoplasmic ANCA (c-ANCA) (PR3-ANCA) is positive in 80–96% of the patients with previously untreated active GPA, but patients positive for perinuclear ANCA (p-ANCA) (MPO-ANCA) and those positive for c-ANCA (PR3-ANCA) are observed at a ratio of approximately 1:1 in Japan.227

6. Diagnosis and Diagnostic Criteria

A revised version of the diagnostic criteria proposed by the MHLW study group in 1998 is used for the diagnosis of GPA (Table 20).247

7. Policies and Guidelines of Treatment

Treatments for GPA can be divided into remission induction therapy and remission maintenance therapy. The Guidelines for the Management of ANCA-associated vasculitis 2017 recommends the following based on the GRADE system.238

In ANCA-associated vasculitis, it is difficult to induce remission by inadequate immunosuppressive therapy, and the exacerbation rate is high even if remission has been achieved. However, excessive immunosuppressive therapy increases the risk of severe infection, and treatments dependent on GC is likely to induce complications such as osteoporosis and diabetes, which affects the patient QOL.

The following CQs and related recommendations apply both to MPA (Chapter VI) and GPA. (See Figure 34 in Chapter VI.)

### 7.1 Remission Induction Therapy

**CQ1**

What regimens are useful for remission induction therapy for ANCA-associated vasculitis?

(1)-(i) As a remission induction therapy for ANCA-associated vasculitis, GC+IVCY or oral CY is proposed instead of GC alone.

Strength of recommendation: Weak
Reliability of evidence: Very low

(1)-(ii) As a remission induction therapy for ANCA-associated vasculitis, GC+IVCY is proposed instead of GC+oral CY.

Strength of recommendation: Weak
Reliability of evidence: Very low

Oral CY may be used as an alternative of IVCY.

(2) As a remission induction therapy for ANCA-associated vasculitis, GC+CY is proposed instead of GC+RTX.

Strength of recommendation: Weak
Reliability of evidence: Very low*/low**

For patients in whom the use of RTX is judged to be appropriate, GC+oral CY.

(3) If neither CY nor RTX can be used, GC+MTX* is proposed as a remission induction therapy for patients with ANCA-associated vasculitis with no severe organ disorders and mild impairment of renal function.

Strength of recommendation: Weak
Reliability of evidence: Very low

*Uncovered by insurance in Japan

(4) If neither CY nor RTX can be used, GC+MMF* is proposed when the above recommendation (3) cannot be applied.

Strength of recommendation: Weak
Reliability of evidence: Very low

*Uncovered by insurance in Japan

**CQ2**

Is plasma exchange useful in remission induction therapy for ANCA-associated vasculitis with severe renal disorder?
(1) GC+oral CY+plasma exchange* is proposed instead of GC+oral CY+steroid pulse therapy for remission induction therapy for ANCA-associated vasculitis with severe renal disorder.

Strength of recommendation: Weak
Reliability of evidence: Very low

(1) GC+oral CY+plasma exchange is proposed instead of GC+oral CY for remission induction therapy for ANCA-associated vasculitis with severe renal disorder.

Strength of recommendation: Weak
Reliability of evidence: Very low

*Covered by insurance in Japan from April 2018

Points of attention concerning the recommendations for CQ1 and CQ2 are as follows: Since the drugs/treatments indicated by * are uncovered by health insurance in Japan, they cannot be recommended in general. It is recommended to consult a nephrologist concerning patients with severe renal disorders including RPGN. Plasma exchange should be performed by a physician with sufficient experience.

7.2 Remission Maintenance Therapy

CQ3
What regimens are useful as remission maintenance therapy for ANCA-associated vasculitis?

The concomitant use of AZA in addition to GC is proposed in remission maintenance therapy for ANCA-associated vasculitis.

Strength of recommendation: Weak
Reliability of evidence: Very low
RTX, MTX*, and MMF* can be alternative drugs to be used in maintenance remission therapy.

*Since the drugs/treatments indicated by * are uncovered by health insurance in Japan, they cannot be recommended in general.

8. Prognosis

In GPA, induction of remission has become possible in many patients by GC+CY therapy. However, relapse during maintenance therapy is often observed. In addition, severe infection is the most frequent cause of death. The prognosis of GPA is expected to be improved by measures to prevent complications including infection and the development of new maintenance therapies.

VIII. Eosinophilic Granulomatosis With Polyangiitis

1. Definition and Epidemiology

Eosinophilic granulomatosis with polyangiitis (EGPA) is a disease separated from polyarteritis nodosa (conventionally periarteritis nodosa) due to 3 characteristics: (1) Bronchial asthma, (2) peripheral blood eosinophilia, and (3) histological findings of eosinophil infiltration around middle/small-sized vessels (primarily arterioles) and necrotizing and/or necrotizing granulomatous vasculitis or the presence of extravascular granuloma. The disease used to be called Churg-Strauss syndrome, but was renamed to EGPA in 2012 and defined as “Eosinophil-rich and necrotizing granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and clinically associated with asthma and eosinophilia.” The number of patients being treated is estimated to be about 1,900, the mean age at onset is about 55 years, and the male/female ratio is 1:1.7 slightly in favor of females. In Europe, 0.5–6.8 new patients/year/1 million people contract the disease, and the prevalence is reported to be 10.7–13/1 million people.

2. Pathogenesis

The cause of the disease is unknown. Its relationship with the leukotriene receptor antagonist (LTRA) is dubious, and a reduction in GC after the use of LTRA has been suggested to be a possible cause. Genetically, relationships with HLA-DRB1*04, *07, and HLA-DRB4 have been reported. The pathological features include tissue damage due to eosinophil infiltration and immunological mechanisms such as IL-4, IL-5, and IL-13. Recently, a relationship with IgG4-related disease has also been suggested.

3. Pathological Findings

Major histopathological findings of EGPA are infiltration of cells primarily eosinophils around middle/small vessels, fibrinoid necrosis, and the presence of extravascular granuloma.

4. Signs and Symptoms

Typically, bronchial asthma occurs first, and after repeated relapses of asthma attack, eosinophilia, systemic signs and symptoms such as fever, and vasculitic lesions such as mononeuritis multiplex, ischemic enteritis, cutaneous vasculitis appear (Figure 37). Vasculitis often develops within 3 years after the onset of bronchial asthma. Mononeuritis multiplex is observed in more than 90% of the patients.

5. Laboratory and Imaging Findings

Eosinophilia should be more than 10% of leukocytes or 1,500/μL. The percentage of patients positive for MPO-
ANCA is about 40–50%, and PR3-ANCA (c-ANCA) is rare. Chest radiography often presents bilateral infiltrative shadows with non-segmental distribution, occasionally exhibits ground-glass appearance, and may show thickening of the bronchial wall or interlobular septa.

### 6. Diagnosis and Diagnostic Criteria

Patients are classified as EGPA by Lanham’s criteria (Table 21) or ACR criteria (Table 22). However, in Japan, the diagnostic criteria by the Ministry of Health and Welfare of Japan proposed in 1998 are used. (Table 23)

Table 24 shows recommendations concerning treatments for EGPA. Treatments for ANCA-associated vasculitides vary with the severity and disease type.
7.1 Acute Phase

For patients with mild EGPA, oral PSL at 0.3–0.6 mg/kg/day (15–30 CY (1–2 mg/kg/day)) or oral AZA (0.5–1.5 mg/kg/day) is used concomitantly as appropriate (recommendation class: IIa, evidence level: C). For patients with severe EGPA, oral PSL at 0.6–1.0 mg/kg/day (40–60 mg/day) or steroid pulse therapy is administered with concomitant administration of CY within 4 weeks (recommendation class: IIa, evidence level: B). CY is administered orally (2 mg/kg/day) or intravenously (0.5–0.75 g/m²/3–4 weeks, total of 3–6 times). For patients with severest EGPA showing conditions such as diffuse alveolar hemorrhage, plasma exchange (2.0–3.0 L for 3 days) should be performed simultaneously. Overseas, RTX, an anti-CD20 antibody preparation, is used for patients with ANCA-positive treatment-resistant cases (recommendation class: IIb, evidence level: B).

7.2 Chronic Phase

After induction of remission, PSL is reduced gradually to 10 mg/day or less in 6–18 months. High-dose intravenous γ-globulin (IVIG) therapy for residual peripheral neuropathy has been covered by health insurance in Japan from January 2010 (recommendation class: IIa, evidence level: B).

7.3 Remission Phase

PSL is maintained at 5–10 mg/day. CY should be discontinued after about 6 months and replaced by drugs such as MTX or AZA (recommendation class: IIa, evidence level: C).

7.4 Exacerbation Phase (at the Time of Relapse)

In principle, treatments should be similar to those in the acute phase. A total dose of CY must be no more than 10–15 g by checking the past doses. Biological agents such as anti-IL-5 antibody mepolizumab and anti-IgE antibody omalizumab (omalizumab is uncovered by health insurance in Japan).

8. Prognosis

By the above treatments, remission can be achieved within 6 months in 90% or more patients, and the 5-year survival rate is 97%. In rare instances, intestinal perforation, heart failure, renal dysfunction, cerebrovascular disorders may occur. Dysesthesia due to mononeuritis multiplex often persists and irreversible impairment remains in about two-thirds of the patients.

IX. Anti-Glomerular Basement Membrane Disease

1. Definitions and Epidemiology

Anti-glomerular basement membrane disease means poor-prognosis kidney/lung lesions caused by antibody to glomerular basement membrane (GBM). By the CHCC classification revised in 2012, it is classified as an immune complex small vessel vasculitis and is subclassified into 3 disease types: (1) renal-limited anti-GBM antibody nephritis, (2) Lung-limited anti-GBM antibody alveolar hemorrhage, and (3) the type with both kidney and lung involvements.

Of these disease types, anti-GBM antibody glomerulonephritis is a disease with poor prognosis that clinically develops RPGN or, occasionally, acute kidney injury and histologically exhibits crescentic necrotizing glomerulonephritis and linear IgG staining (linear pattern) in the loop wall by immunofluorescence study. If complicated by lung hemorrhage, it is called Goodpasture’s disease.

It is a relatively rare disease with a reported incidence of 0.5–1.0 persons/year/1 million people. According to the survey by the MHLW of Japan, of the 1,772 patients with RPGN accumulated until 2006, 81 (4.6%) had anti-GBM antibody nephritis, 27 (1.5%) had Goodpasture’s disease with lung hemorrhage, and a total of 61.1% had anti-GBM disease. The mean ages of the patients with anti-GBM nephritis and Goodpasture’s disease, which used to be observed frequently in middle-aged individuals, are 61.6 (11–77) and 70.9 (57–93) years, respectively, indicating advanced aging of the patients.

2. Pathogenesis

The antigen for anti-GBM antibody is present in the noncollagenous domain 1 (NC1 domain) in the C-terminal of the α3 chain of type IV collagen distributed in the glomerular and pulmonary capillary basement membrane, and the amino acid residues at positions 17–31 on the N-terminal side (epitope A; EA) and those at positions 127–141 on the C-terminal side (epitope B; EB) have been identified. Usually, these epitopes are buried in the basement membrane, but, if the basement membrane of the lung or kidney is damaged due to infection such as influenza, smoking, or inhaled toxic substances, the α-chain hexamer is disassociated to expose the epitopes in the α3 and 5 chains, and anti-GBM antibody is produced. When it binds with the basement membrane antigen of the renal glomeruli or pulmonary capillaries, T-lymphocyte-mediated immune responses are induced, and disruption of the basement membrane and vasculitis occur due to local infiltration of inflammatory cells and subsequent inflammatory reactions.

3. Pathological Findings

By light microscopy, pathological features of severe crescentic necrotizing glomerulonephritis are observed. Immunofluorescence shows linear GBM staining for IgG is observed along the capillary walls.

4. Signs and Symptoms

In addition to symptoms due to nephritis and lung hemorrhage, systemic symptoms such as malaise, fever, body weight loss, and arthralgia are observed frequently. The symptoms observed at the onset are most frequently
non-specific ones such as malaise and fever. Macroscopic hematuria is also a relatively frequent finding. It is also important to check a history of smoking and recent infection.

5. Laboratory Findings

In nearly all patients, hematuria, nephritic urinalysis findings, an elevated serum Cr level, and signs of marked inflammation are observed. Proteinuria of varying degrees is also observed, and it occasionally reaches nephrotic ranges. Anemia is also severe in many patients. Checking of anti-GBM antibody, which becomes positive, is essential for the definitive diagnosis. The anti-GBM antibody level is parallel to the disease activity and often becomes negative as the disease is treated.

Patients in whom both anti-GBM antibody and ANCA are positive (double positive) have been known, and ANCA (typically MPO-ANCA) is positive in about 20–30% of the patients with anti-GBM-antibody glomerulonephritis. Conversely, anti-GBM antibody is positive in about 5–10% of the patients with ANCA-associated vasculitis.

6. Diagnosis and Diagnostic Criteria

Table 25 shows the diagnostic criteria for anti-GBM antibody glomerulonephritis as a designated intractable disease in Japan.

7. Policies and Guidelines of Treatment

Table 26 shows recommendations about treatments for anti-GBM disease.

7.1 Initial Treatment

The treatment for anti-GBM disease is determined in consideration of the presence or absence of organ lesions (kidney, lung lesions) and the disease severities.

7.1.1 When Non-Dialysis-Dependent RPGN or Lung Hemorrhage Is Noted

Usually, PSL is administered at 1mg/kg/day (started by steroid pulse therapy using mPSL), and triplet combination therapy consisting of PSL, IVCY (500–750mg/m²/month) or oral CY (1–2mg/kg/day), and plasma exchange is carried out (recommendation class: I, evidence level: B). The dose of IVCY is adjusted according to the age and serum Cr level.

7.1.2 When Severe Renal Impairment Requiring Dialysis Is Present, and Recovery From Renal Failure Cannot Be Expected

The treatments are decided in consideration of the general conditions including the presence or absence of lung lesions.

7.2 Maintenance Therapy

After the initial treatment, PSL and CY are gradually reduced, and immunosuppressive therapy is usually continued for 6–12 months. Long-term maintenance therapy is usually unnecessary without relapse of the disease.

7.3 Comments About Treatments

The objective of treatment is to control the progression of nephritis and lung hemorrhage as soon as possible and to remove anti-GBM antibody that causes the disease immediately. Intensive anti-inflammatory therapy (GC including steroid pulse therapy), elimination of anti-GBM antibody (plasma exchange), and suppression of anti-GBM antibody production (GC and immunosuppressive therapy) are carried out simultaneously as soon as possible. Plasma exchange has recently been covered by health insurance in Japan, up to 2 courses of 7 sessions within two weeks each.

8. Prognosis

Once anti-GBM antibody becomes negative, and clinical remission is obtained, relapse of the disease is rare thereafter. Therefore, maintenance therapy is usually unnecessary. However, as cases of relapse after a long interval from the onset have also been reported, follow-up is essential. In patients who are also positive for ANCA, relapse tends to be observed more frequently than in those positive for anti-GBM antibody alone.
X. Urticarial Vasculitis

1. Definition and Epidemiology

Long-persisting urticarial and cutaneous leukocytoclastic angiitis are observed. There is a report that about 20% of patients diagnosed with urticarial had urticarial vasculitis.\(^2\)

The disease is classified into primary and secondary as well as hypocomplementememic and normocomplementememic types. Hypocomplementememic urticarial vasculitis was newly adopted by CHCC 2012 along with anti-C1q vasculitis as its another name.\(^1\)

2. Pathogenesis

The disease, in which immunoglobulin and complement are deposited in the wall of the affected vessels, belongs to immune complex vasculitis. Viral infections (hepatitis B, hepatitis C) and collagen are known to be included as causative disorders of secondary urticarial vasculitis. The collagen-like region of C1q, which is the antigen for anti-C1q antibody, hepatitis virus, and drugs have been suggested as causes of the disease.\(^2\)

3. Pathological Findings

Neutrophil-dominant perivascular infiltration, red blood cell extravasation, and fibrinoid deposits are observed in small arteries and veins in the upper and middle layers of the dermis. Deposits of immunoglobulin and complement are also observed. Mehregan et al. reported that immunoglobulin and complement deposits are observed in the cutaneous basement membrane in 69.6% and in the dermal capillary wall in 86.9% of the patients in hypocomplementememic cases but in 17.8% and 28.9%, respectively in those with normocomplementememic cases.\(^2\)
Sanchez et al. showed that the positive rate increases even in the normocomplementemic type if systemic symptoms are present.\(^2\)

4. Signs and Symptoms

Persisting (often for 24 hours or longer) urticarial is accompanied by signs and symptoms such as purpura, livedo reticularis, erythema, bullae, mixed presence of bloody bullae, burning sensation, and pain. Some patients exhibit ring-shaped or wood grain-like urticarial (Figure 38).

While 54% of the hypocomplementememic patients were diagnosed with SLE during the course of the disease,\(^2\) only 3% of the normocomplementememic patients were reported to have developed SLE.\(^2\)

Hypocomplementememic urticarial vasculitis with characteristic systemic symptoms such as arthritis, renal symptoms, gastrointestinal symptoms, and ophthalmic symptoms is called hypocomplementememic urticarial vasculitis syndrome (HUVS). Kidney impairment is more likely to follow a serious course in children.\(^2\)

Ophthalmic symptoms are observed in 15% of patients with SLE, but symptoms including episcleritis and uveitis are noted in 61% of patients with HUVS.\(^2\)

5. Laboratory and Imaging Findings

5.1 Histopathological Examinations

Necrotizing vasculitis is detected, but fibrinoid degeneration is unlikely to occur, because the capillary wall is primarily affected (called leukocytoclastic vasculitis). Neutrophil infiltration is unclear because of edema due to urticarial. Deposits of immunoglobulin and complement are noted in the vascular wall.

5.2 Seriimmunological Examinations

Measurement of complements. Since there is the possibility of systemic vasculitis, ANCA and cryoglobulin are measured. With secondary pathogenesis in mind, anti-nuclear antibody (ANA), and dsDNA antibody, anti-SSA antibody, and anti-SSB antibody are examined.

ANA is positive in 95% of SLE patients and 61–71% of HUVS patients\(^2\) and negative in 5% and 66%, respectively.\(^2\)

There are reports that anti-dsDNA antibody is positive in ≥70% of the SLE patients and 17% of HUVS patients\(^2\) but negative in 5–30% and 85%, respectively.\(^2\)

and that anti-C1q antibody is observed in 38–61% of SLE patients\(^2\) and 100% of HUVS patients.\(^2\)

6. Diagnosis and Diagnostic Criteria

Urticarial vasculitis is definitively diagnosed based on persisting urticarial and necrotizing vasculitis demonstrated by skin biopsy (Evidence level: C). Schwartz et al. required fulfillment of the presence of urticarial and hypocomplementemia and at least 2 of cutaneous vasculitis, arthritis, glomerulonephritis, episcleritis or uveitis, recurrent abdominal pain, and anti-C1q antibody in blood for the diagnosis of HUVS.
7. Policies and Guidelines of Treatment

Table 27 shows recommendations concerning treatments for urticarial vasculitis. Treatment is initiated with anti-histamine and anti-allergic agents (recommendation class: IIb, evidence level: C). However, anti-histamine/anti-allergic drugs are reported to be ineffective. For patients with severe skin symptoms or organ disorders, GC is selected (recommendation class: IIa, evidence level: C). A dose of 20–30 mg/day is necessary, and steroid pulse therapy was reportedly necessary for conditions complicated by SLE. For patients who show serious systemic symptoms or GC resistance, the concomitant use of CyA, AZA or CY can be an option (recommendation class: IIb, evidence level: C). In addition, plasma exchange, IVIG, and RTX, an anti-CD20 antibody preparation, have also been reported (recommendation class: IIb, evidence level: C).

Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported by Millns et al. and Mehregan to be effective (recommendation class: IIb, evidence level: C). Colchicine and hydroxychloroquine have been selected as first-line treatments based on the results of retrospective studies (recommendation level: IIb, evidence level: C). Rectisol is considered effective in patients who secondarily develop SLE (recommendation class: IIb, evidence level: C).

8. Prognosis

Systemic symptoms are absent or mild in normocomplementemic urticarial vasculitis but severer in the hypocomplementemic type.

XI. IgA Vasculitis (Henoch-Schönlein Purpura)

1. Definition and Epidemiology

Henoch-Schönlein purpura (HSP) was renamed as IgA vasculitis. The disease is classified as a small vessel vasculitis based on the size of the affected vessels. It may occur in people of all ages but most frequently affects those aged 3–10 years and appears to have a slight predilection for boys. It is a common vasculitis in children. It is reportedly complicated by glomerulonephritis in about 50–80% of adults and 20–50% of children.

2. Pathogenesis

The pathogenesis remains unclear.

3. Pathological Findings

Histologically, the disease is characterized by infiltration of inflammatory cells, which are primarily multinuclear leukocytes, around small vessels and IgA deposits in vessel walls. In the skin, histological features of leukocytoclastic necrotizing small-vessel vasculitis accompanied by dermal hemorrhage are observed. In the renal glomeruli, deposits of IgA and C3 are observed primarily in the mesangial region by immunofluorescent staining similarly to IgA nephropathy.

4. Signs and Symptoms

4.1 Skin Signs and Symptoms

Symmetric palpable purpura with punctate distribution are observed in the lower limbs and back in nearly all patients (Figure 39).

4.2 Joint Symptoms

Pain and swelling of joints are observed in 70–80% of the patients.
4.3 Gastrointestinal Symptoms
Symptoms including abdominal pain, vomiting, bloody stools, and melena are observed in 50–70% of the patients.

4.4 Renal Symptoms
Abnormal urinalysis findings often appear within a few days to 1 month after the onset of vasculitis. The onset is with hematuria alone in 15%, hematuria+proteinuria in 38%, acute nephritic syndrome in 15%, nephritis+nephrotic syndrome in 23%, and nephrotic syndrome in 8%.

5. Laboratory and Imaging Findings
The platelet count is normal, and indices of the clotting system such as the prothrombin time and partial thromboplastin time are also normal. The plasma factor XIII activity is reduced in about 3/4 of the patients and decreases with exacerbation of the clinical condition. The serum IgA level increases in about 40–60% of the patients in an early stage of the disease. Rumpel-Leede test is positive, which indicates weakening of the capillary resistance, in about 30% of the patients.

Patients with IgA vasculitis complicated by glomerulonephritis show hematuria (microscopic, macroscopic), erythrocyte deformation in urine sediment, granular cast and red blood cell cast, and proteinuria of varying degrees depending on the severity of nephritis.

6. Diagnosis and Diagnostic Criteria
In children, IgA vasculitis can be diagnosed if 2 or more of the 4 classification criteria of the American College of Rheumatology are met: [(1) palpable purpura, (2) acute abdominal colic, (3) presence of granulocytes in the walls of small arteries and veins on biopsy, and (4) age of ≤20 years]. Histopathological examinations by biopsy show features of leukocytoclastic vasculitis with infiltration of multinuclear leukocytes and monocytes around small vessels and deposits of IgA, C3, and IgG in vascular walls. Adult purpura nephritis was designated as an intractable disease in July 2015 and is classified according to the criteria by the American College of Rheumatism.

The renal tissue classification of purpura nephritis by the International Study of Kidney Disease in Children (ISKDC) is shown below.

Grade I: Minimal changes
Grade II: Mesangial proliferation alone
Grade III: a) focal, b) diffuse mesangial proliferation; crescents<50% of glomeruli
Grade IV: a) focal, b) diffuse mesangial proliferation; crescents 50–75% of glomeruli
Grade V: a) focal, b) diffuse mesangial proliferation; crescents >75% of glomeruli
Grade VI: Membranoproliferative glomerulonephritis

7. Policies and Guidelines of Treatment
Table 28 shows recommendations about treatment for IgA vasculitis.
7.1 Treatment for Extrarenal Manifestations

Rest is maintained, and symptomatic treatments are performed depending on the symptoms.
1) Anti-histamine drugs are administered for painful edema and itching of the skin (recommendation class: IIb, evidence level: C)
2) Non-steroidal anti-inflammatory drugs (NSAIDs) are administered for joint symptoms (recommendation class: IIa, evidence level: C)
3) If severe abdominal symptoms cannot be controlled even by the administration of analgesics, glucocorticoid (GC) is administered, tapered, and discontinued after 1–2 weeks.301,302 (recommendation class: IIa, evidence level: C)
4) If a decrease in the plasma factor XIII level to 90% or less is accompanied by abdominal symptoms and joint symptoms, the administration of dried human clotting factor XIII concentrate should be considered (recommendation class: IIa, evidence level: B)
5) In children, the administration of GC at the onset does not contribute to a decrease in the rate of subsequent occurrence of nephritis or abdominal symptoms.303,305

The KDIGO guidelines recommend no use of GC to prevent the occurrence of nephritis306 (recommendation class: III, evidence level: B)

7.2 When Complicated by Nephritis

ISKDC class I–II: Antiplatelets are often administered (recommendation class: IIb, evidence level: C).
ISKDC class III–VI: The following treatments are considered.
1) GC (PSL 1 mg/kg/day)301 (recommendation class: IIa, evidence level: C)
2) Steroid pulse therapy+iv urokinase*+oral CY307 (recommendation class: IIa, evidence level: C)
3) AZA+GC combination therapy308,309 (recommendation class: IIa, evidence level: C)
4) MMF alone310 or MMF*+GC combination therapy311 (recommendation class: IIb, evidence level: C)
5) CyA* alone312 or CyA*+GC combination therapy313 (recommendation class: IIb, evidence level: C)
6) Plasma exchange therapy* (recommendation class: IIb, evidence level: C) There are reports that plasma exchange was effective in children.314,315
7) CY alone316 or IVCY+GC combination therapy317 is not effective (recommendation class: III, evidence level: B)
8) There is a report suggesting the effectiveness of tonsillectomy*+steroid pulse therapy also for purpura nephritis318 (recommendation class: IIa, evidence level: C)

*Not covered by health insurance in Japan

The above recommendations are based primarily on reports concerning children, but the KDIGO guidelines suggest treating adults with nephritis complicating adult IgA vasculitis similarly to children.306

8. Prognosis

The prognosis of IgA vasculitis is basically favorable, and the disease often follows a monophasic course and is remitted spontaneously in several weeks. Relapse is observed in 10–20% of the patients and the episode occasionally persists for more than a year.

In children, nephritis is observed in about half the patients, but exacerbation to end-stage renal disease is rare. In adults, 85% of the patients suffer nephritis, which often develops into end-stage renal disease, and the prognosis is poorer than in children.

XII. Cryoglobulinemic Vasculitis

1. Definition and Epidemiology

Cryoglobulin (CG) is protein that precipitates in serum or plasma at a low temperature and dissolves when heated to 37°C. Since cryoglobulinemia is asymptomatic in some patients, a condition that exhibits clinical features of immune complex-mediated vasculitis is called cryoglobulinemic vasculitis (CV).245,319

CV may be a primary disorder without an underlying disorder, or a secondary disorder. Cryoglobulinemia occurs secondarily to HCV infection in 40–65% and collagen disease in 15–25% of the patients.320,323

2. Pathogenesis

Cryoglobulinemia is classified into 3 types (Table 29).324,325 Recently, essential CV has decreased to about 10% or less with accumulation of anti-HCV antibody-positive cases.326,327

3. Pathological Findings

Type I shows microthrombi due to non-inflammatory eosinophilic amorphous substances can be detected in the kidney and skin-biopsy specimens. In Types II and III, necrotizing vasculitis in small vessels of the upper and middle layers of the dermis is observed. Histological findings of membranoproliferative glomerulonephritis are characteristic in the kidney.

4. Clinical Features

See Table 30.325

5. Laboratory and Imaging Findings

If vasculitic lesions associated with cold exposure are noted, examinations for serum CG and causative disorders (lymphoproliferative disease, hepatitis virus infection, collagen disease, etc.) should be performed.
### Table 29. Cryoglobulin Classification

| Components | Type I | Type II | Type III |
|------------|--------|---------|----------|
| Simple     | Monoclonal immunoglobulins (IgG, IgM, or IgA) or Bence Jones protein/monoclonal free light chains | Monoclonal immunoglobulins (IgM, IgG, or IgA) and polyclonal immunoglobulin (mostly IgG) | Polyclonal immunoglobulins of all isotypes |
| Pathological features | Microthrombosis | Immune complex-mediated vasculitis | Immune complex-mediated vasculitis |

- **Type I**
  - Components: Simple
  - Pathological features: Microthrombosis
  - Disease association: Waldenstrom's macroglobulinemia, Multiple myeloma, Monoclonal gammopathy associated with lymphoproliferative disorder, Light chain disease

- **Type II**
  - Components: Mixed
  - Pathological features: Immune complex-mediated vasculitis
  - Disease association: Hepatitis C, Essential cryoglobulinemia, Sjogren's syndrome, Systemic lupus erythematosus, Viral infections (Hepatitis B and C, CMV, EBV, HIV), Endocarditis, other bacterial infections, Biliary cirrhosis

- **Type III**
  - Components: Mixed
  - Pathological features: Immune complex-mediated vasculitis
  - Disease association: Essential cryoglobulinemia, Sjogren's syndrome, Systemic lupus erythematosus, Viral infections (Hepatitis B and C, CMV, EBV, HIV), Endocarditis, other bacterial infections, Biliary cirrhosis

(Reproduced from Brouet JC, et al. 1974 and Motyckova G, et al. 2011 with modification, John Wiley and Sons. (c) 2011, Wiley-Liss, Inc.)

### Table 30. Clinical and Laboratory Features of Cryoglobulinemia

| Clinical manifestations | Type I | Type II | Type III |
|-------------------------|--------|---------|----------|
| Arthralgia > arthritis  | +      | ++      | +++      |
| Purpura                 | +      | +++     | +++      |
| Gangrene/acrocyanosis   | +++    | +       | ±        |
| Hyperviscosity          | +++    | ±       | −        |
| Hematologic             | ++     | ±       | ±        |
| Renal                   | +      | ++      | +        |
| Neurologic              | +      | ++      | ++       |
| Liver                   | ±      | ++      | +++      |
| Lung                    | −      | +       | +        |
| C3                      | Normal | Decreased| Decreased|
| C4                      | Normal | Decreased| Decreased|
| CH50                    | Normal | Decreased| Decreased|
| RF                      | +      | ++      | ++       |
| Autoantibodies (ANA, etc.) | −     | ++      | ++       |
| Hepatitis B             | −      | +       | +        |
| Hepatitis C             | −      | +++     | +++      |

ANa, antinuclear antibodies; RF, rheumatoid factor; Hematologic features include thrombosis and bleeding and spurious/artifact thrombocytosis. (Reproduced from Motyckova G, Murali M., Am J Hematol 2011 with modification, John Wiley and Sons. (c) 2011, Wiley-Liss, Inc.)

### Table 31. Preliminary Criteria for Classification of Cryoglobulinemic Vasculitis

Satisfied if at least two of the three items (questionnaire, clinical, laboratory) are positive the patient must be positive for serum cryos in at least 2 determinations at ≥12 week interval

(i) **Questionnaire item: at least two out of the following**
- Do you remember one or more episodes of small red spots on your skin particularly involving the lower limbs?
- Have you ever had red spots on your lower extremities which leave a brownish color after their disappearance?
- Has a doctor ever told you that you have viral hepatitis?

(ii) **Clinical item: at least three out of the following four (present or past)**
- Constitutional symptoms: Fatigue, Low grade fever (37–37.9°C, >10 days, no cause), Fever (>38°C, no cause), Fibromyalgia
- Articular involvement: Arthralgias, Arthritis
- Vascular involvement: Purpura, Skin ulcers, Necrotizing vasculitis, Hyperviscosity syndrome, Raynaud’s phenomenon
- Neurological involvement: Peripheral neuropathy, Cranial nerve involvement, Vasculitic CNS involvement

(iii) **Laboratory item: At least 2 out of the 3 questions. (present)**
- Reduced serum C4
- Positive serum rheumatoid factor
- Positive serum M component

CG, cryoglobulin; CV, cryoglobulinemic vasculitis. (Cited from Ann Rheum Dis De Vita S, Soldano F, Isola M, et al. 2011 with permission from BMJ Publishing Group Ltd.)
Diagnosis and Diagnostic Criteria

As a result of a multicenter collaborative study in Europe, preliminary classification criteria for CV have been proposed (Table 31).\(^{328}\)

Policies and Guidelines for Treatment

Table 32 shows recommendations about treatments for CV. In addition to avoiding cold exposure and keeping warm, analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) are used. If there are rapidly progressive organ disorders, the use of glucocorticoid (GC) (including pulse therapy)+RTX (often 375mg/m\(^2/\)week×4 times) or CY (2mg/kg/day) (recommendation class: IIa, evidence level: B) is recommended. If RTX cannot be used, treatment using CY is recommended.\(^{329-331}\)

In secondary cryoglobulinemia, treatments for the primary disorder are performed in addition to immunosuppressants (recommendation class: IIa, evidence level: B).\(^{331-333}\) For essential cryoglobulinemia, combination therapy of GC and RTX is recommended (recommendation class: IIa, evidence level: B). Plasma exchange therapy should be considered in cases with (1) hyperviscosity syndrome, (2) acute respiratory insufficiency, alveolar hemorrhage, and acute mesenteric vasculitis,\(^{334}\) and (3) RPGN requiring dialysis\(^{330}\) (recommendation class: IIb, evidence level: C). RTX and plasma exchange therapy are not covered by health insurance in Japan.

Prognosis

Regarding the prognosis of mixed cryoglobulinemia without the involvement of HCV infection, the 5-year survival rate is 79%. Age (≥65 years or older), sex (male), complication by respiratory and gastrointestinal lesions, and renal failure are important prognostic factors.\(^{327}\)

XIII. Behçet’s Disease

1. Definition and Epidemiology

1.1 Definition

Behçet’s disease is an inflammatory disorder characterized by oral apthha, skin symptoms, ophthalmic lesions, and genital ulcers.\(^{335}\) Vascular involvement is one of serious manifestations which appear in some patients.\(^{336,337}\)

1.2 Epidemiology

There are about 20,000 patients with Behçet’s disease in Japan. The frequency of vascular involvement has been reported 6.3–15.3%.\(^{336}\)

2. Signs and Symptoms

2.1 Deep-Vein Thrombosis

Deep-vein thrombosis is the most common vascular lesion and prevalent in the lower extremities.\(^{336,337}\) More serious venous lesions such as superior vena cava syndrome, Budd-Chiari syndrome, and cerebral venous sinus thrombosis can occur.\(^{336,338}\)

2.2 Aneurysms and Arterial Occlusion

Aneurysms and arterial occlusions develop in the large and medium-sized arteries. Aortic insufficiency cause by aneurysm is associated with poor prognosis.\(^{336,337,339}\) Peripheral aneurysms, which are often at risk of rupture and bleeding, are multiple in the one-third of the patients.\(^{336,340}\) An arterial occlusion causes the local ischemic symptoms.

2.3 Pulmonary Artery Involvement

Rupture of pulmonary artery aneurysm causes fatal hemoptysis.\(^{336,341}\) The pulmonary lesions are commonly complicated with pre-existing deep-vein thrombosis. Frequency of the lesions is low in Japanese patients compared with the other regions.

3. Laboratory and Imaging Findings

3.1 Laboratory Findings

There is no specific data for Behçet’s disease. A pathergy test, HLA-B*51, A*26, and inflammatory responses on blood tests are listed as suggestive findings in the diagnostic criteria of the MHLW of Japan.

3.2 Imaging Findings

3.2.1 Venous Lesions

Venous thrombotic lesions are illustrated by ultrasonography and contrast-enhanced CT.\(^{336,337}\)

3.2.2 Arterial Lesions

Contrast-enhanced CT is a standard modality to detect arterial lesions.\(^{336,337}\) PET-CT (not approved),\(^{336}\) which simultaneously assesses the morphological changes and

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Table 32. Recommendations and Evidence Levels About Treatments for CV

| Recommendations | Levels of evidence |
|-----------------|--------------------|
| Glucocorticoid (GC) | IIa | B |
| Cyclophosphamide (CY) | IIa | B |
| Rituximab (RTX)* | IIa | B |
| Plasma exchange therapy* | IIb | C |

*Uncovered by health insurance in Japan.
3.2.3 Pulmonary Lesions

Pulmonary artery aneurysms are examined by chest CT scan after screening of chest radiography. Lung perfusion scintigraphy is helpful to detect occlusive lesions in the pulmonary vessels.\(^{336,341}\)

### 4. Diagnosis and Diagnostic Criteria

#### 4.1 Diagnosis

The diagnosis of Behçet's disease is made based on combinations of symptoms, according to the diagnostic criteria of the MHLW, Japan. Table 33 compares the MHLW criteria with other sets of representative international criteria.\(^{342,343}\) In addition, local assessment of the vascular lesions is essential.\(^{337}\)

#### Table 33. Comparison of Diagnostic Criteria for Behçet's Disease

|                  | MHLW\(^{337}\) | ISG\(^{342}\) | ITR-ICBD\(^{343}\) |
|------------------|---------------|--------------|-------------------|
| Oral aphtha      | Major symptom | Essential    | 2                 |
| Skin symptoms    | Major symptom | ✓            | 1                 |
| Ophthalmic lesions | Major symptom | ✓            | 2                 |
| Ulcer of the vulva | Major symptom | ✓            | 2                 |
| Arthritis        | Minor symptom |              |                   |
| Epididymitis     | Minor symptom |              |                   |
| Intestinal lesions | Minor symptom |              |                   |
| Vascular lesions | Minor symptom |              | 1                 |
| Nerve lesions    | Minor symptom |              | 1                 |
| Pathergy test    | Suggestive finding | ✓ | (1) |
| HLA-B51 A26      | Suggestive finding |              |                   |

Diagnoses according to the MHLW criteria.

(1) Complete form: Appearance of the 4 Major symptoms during the course.

(2) Incomplete type: 3 Major symptoms, 2 Major symptoms+2 Minor symptoms, typical ophthalmic symptoms+1 other Major symptom or 2 Minor symptoms.

(3) Suspected: Appearance of some Major symptoms, typical Minor symptoms recurring or exacerbated.

(4) Variant types: (a) Intestinal type, (b) Vascular type, (c) Neurological type.

Behçet's disease can be diagnosed or classified by the ISG criteria, which require oral aphtha plus 2 or more symptoms out of four symptoms indicated by (√), or by the ITR-ICBD criteria in which the total score is more than 4.

ISG: International Study Group for Behçet's Disease; ITR-ICBD: International Team for the Revision of the International Criteria for Behçet's Disease (from Japan Intractable Diseases Information Center, Behçet’s disease,\(^{337}\) International Study Group for Behçet's Disease. 1990,\(^{342}\) International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). 2014\(^{343}\)).

#### 4.2 Differential Diagnosis

##### 4.2.1 Venous Lesions

Major differential diagnoses include idiopathic venous thrombosis, congenital thrombotic tendency (protein C deficiency, protein S deficiency, antithrombin III deficiency, etc.), antiphospholipid antibody syndrome, surgical invasion, malignant neoplasm, and local compression.

##### 4.2.2 Arterial Lesions

Arterial lesions that should be differentiated from Behçet’s disease include Takayasu arteritis, GCA, PAN, infectious aneurysm, and Buerger disease and arteriosclerosis obliterans.

##### 4.2.3 Pulmonary Lesions

Hughes-Stovin syndrome is characterized by pulmonary artery aneurysms and venous thrombosis without the mucocutaneous and ocular symptoms.

#### 5. Policies and Guidelines of Treatment

Table 34 summarizes recommendations for treatments of Behçet’s disease, according to the guidelines from Behçet’s Disease Research Committee (BDRC), MHLW, Japan.

##### Table 34. Recommendations and Evidence Levels About Treatments for Behçet’s Disease

| Treatment                        | Recommendations | Levels of evidence |
|----------------------------------|-----------------|--------------------|
| Glucocorticoid (GC)              | IIA             | B                  |
| Azathioprine (AZA)               | IIA             | B                  |
| Cyclophosphamide (CY)            | IIA             | B                  |
| Cyclosporine (CyA)               | IIB             | C                  |
| Methotrexate (MTX)*              | IIB             | C                  |
| TNF inhibitors                   | IIB             | B                  |
| Anticoagulants                   | IIA             | C                  |
| Vascular reconstruction          | IIB             | B                  |
| Endovascular treatment           | IIB             | B                  |
| Perioperative immunosuppressive therapy | IIA | B                  |

*Uncovered by health insurance in Japan.
b. Combination of GC and CY (recommendation class: IIa, evidence level: B)
For severe venous lesions and aneurysms, high-dose GC including steroid pulse therapy and IV CY (1,000 mg/month) are conducted as the remission induction therapy followed by maintenance therapy using oral PSL and AZA.

c. TNF Inhibitors (recommendation class: IIb, evidence level: B)
Sporadic case reports have shown efficacy of anti-TNF monoclonal antibody for serious forms of vascular involvement in Behçet’s disease. IFX has been approved since 2015 in Japan.

5.1.2 Anticoagulant Therapy (recommendation class: IIa, evidence level: C)
Anticoagulant therapy is not recommended by EULAR, though retrospective studies have shown warfarin is used frequently in Japan and other countries.337,345–347 The guidelines by BDRC, MHLW, Japan recommends the use of anticoagulants or antiplatelet drugs in patients having risk of bleeding.337

5.2 Surgery and Endovascular Treatment
5.2.1 Operative Indication (recommendation class: IIb, evidence level: B)
Rupture or impending rupture of aneurysm and arterial occlusion are indications for surgery. Postoperative complications such as suture failure, occlusion, and anastomotic aneurysm are frequent.336,348

5.2.2 Perioperative Immunosuppressive Therapy (recommendation class: IIa, evidence level: B)
The perioperative concomitant use of immunosuppressive therapy has been shown to prevent post-operative complications and relapses.336,349

5.2.3 Catheterization and Endovascular Treatment (recommendation class: IIb, evidence level: B)
Endovascular treatment is optional for some patients.350–352

6. Prognosis
Several studies have shown that vascular lesions, particularly arterial lesions, are critical prognostic factors of Behçet’s disease.353 The vascular involvement such as pulmonary artery aneurysm, aortic aneurysm, and Budd-Chiari syndrome can be fatal.

XIV. Malignant Rheumatoid Arthritis

1. Definition and Epidemiology
Vasculitis of small and medium-sized vessels associated with rheumatoid arthritis (RA) is called rheumatoid vasculitis (RV). Malignant RA (MRA) is Japan’s original concept defined as “RA that has a severe clinical condition due to extra-articular symptoms including vasculitis”.354 and is not synonymous with RV. A clinical profile of MRA is shown in Figure 40.

![Figure 40. Clinical features of malignant rheumatoid arthritis. RA (Progressive and destructive synovitis/RF positive/ACPA positive)](Advance Publication)
MRA is observed in 0.6–1.0% of the patients with RA, the peak age at the diagnosis is 60–69 years, and the male/female ratio is 1:2 (Figure 25). The incidence of RV has been decreasing recently. Risk factors for RV include HLA-C*03, male sex, a long duration of illness, severe RA, and the presence of peripheral/cerebral vascular lesions.

2. Pathogenesis

The pathogenesis of MRA is unclear, but mechanisms including an involvement of auto-antibody targeted to blood vessels, induction of inflammation due to deposition of immune complexes, and local activation of cellular immunity have been suggested.

3. Pathological Findings

Infiltration of mononuclear cells and neutrophils into the vascular wall are observed, and it is accompanied by necrosis, leukocytoclast, and features of destruction of the vascular wall including rupture of the elastic lamina. MRA is classified into the systemic vasculitis type characterized by necrotizing vasculitis of muscular arteries and peripheral arteritis type characterized by fibrous proliferation of the intima and endarteritis obliterans. Generally, the pathological findings are primarily those of leukocytoclastic vasculitis accompanied by deposits of immune complex in lesions of small arteries, capillaries, and small vessels, and pauci-immune type in lesions of medium-sized arteries and glomeruli.

4. Signs and Symptoms

MRA is more frequent in long-standing RA with advanced joint destruction, and rheumatoid nodules are often observed. Systemic type of MRA follows an acute course and causes symptoms such as a fever of ≥38°C, body weight loss, purpura, episcleritis, myalgia, interstitial pneumonia, pleurisy, mononeuritis multiplex, and gastrointestinal bleeding. Interstitial lesions of the lung often progress chronically but occasionally show an acute or subacute course.

5. Laboratory and Imaging Findings

Findings including inflammatory reaction, hypergammaglobulinemia, anti-citrullinated peptide antibody (ACPA), immune complexes, and a decrease in complement are observed. The rheumatoid factor (RF) level is high.
6. Diagnosis and Diagnostic Criteria

The diagnostic criteria shown in Table 35 are used.

7. Policies and Guidelines of Treatment

Table 36 shows recommendations about treatments for MRA. The dosage/ regimen of MTX and bDMARDs are the same as those for the treatment of usual RA.

MTX is administered for active RA without contraindication.

| Recommendation | Levels of evidence |
|----------------|--------------------|
| Glucocorticoid (GC) | IIa  C |
| Steroid pulse therapy | IIb  C |
| Methotrexate (MTX) | IIa  C |
| Azathioprine (AZA) | IIa  C |
| Cyclophosphamide (CY) | IIa  B |
| TNF inhibitors | IIa  B |
| Tocilizumab (TCZ) | IIa  C |
| Rituximab (RTX)* | IIb  B |
| Abatacept | IIb  C |

*Uncovered by health insurance in Japan. Note: MTX and biological drugs are covered by health insurance for rheumatoid arthritis.

8. Prognosis

The 1-, 5-, and 10-year survival rates of patients with systemic RV are 89.6, 47.7, and 26%, respectively, and no improvement is observed compared with the past. According to a domestic epidemiological survey, the outcome was alleviation in 21%, no change in 26%, exacerbation in 31%, death in 14%, and unknown/others in 8%, and the most frequent cause of death was respiratory failure.

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Appendix 2. Disclosure of Potential Conflicts of Interest (COI): JCS 2017 Guideline on Management of Vasculitis Syndrome

| Author | Employment or supervisory position (private firm) | Shareholder | Patent royalty | Reward | Manuscript fee | Research fund offered | Scholarship donation/endowed chair | Other rewards | Declaration concerning sponsor/relatives concerning the first degree or those who share the income/property |
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