Chapter 2
Aortitis

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One Definition for Multiple Diseases: Classification, Epidemiology, Etiopathogenesis

"Aortitis" is a pathological term literally indicating inflammation of the aorta. It is used in nosography as a comprehensive term, encompassing the multiple etiologies possibly causing aortic wall inflammation [1]. A suggested classification of those etiologies distinguishes between two groups, i.e. infectious or non-infectious: within non-infectious aortitides, it discriminates different diseases following the current classification criteria for vasculitides (Table 2.1).

Infectious aortitis is a life-threatening disease, with high inherent risk of acute complications such as aortic aneurysm rupture; non-infectious forms however are often characterized by an indolent and insidious course, with progressive

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Table 2.1 Classification of aortitis

Non-infectious[a]
Associated with vasculitides
With large-vessel vasculitis
Giant cell arteritis[b]
Takayasu arteritis[b]
With variable vessel vasculitis
Cogan's syndrome[b]
Behçet's disease[c]
With medium- and small-vessel vasculitis
Polyarteritis nodosa[d]
Wegener arteritis[d]
Microscopic polyangiitis[d]
Associated with systemic rheumatic disorders
HLA-B27 associated spondyloarthropathies
Ankylosing spondylitis[b]
Reiter syndrome[c]
Replapsing polychondritis[c]
Systemic lupus erythematosus[d]
Rheumatoid arthritis[d]
Sarcoidosis[d]
"Single organ" vasculitis
Isolated idiopathic aortitis (thoracic)
Isolated idiopathic periaortitis (abdominal)
Idiopathic retroperitoneal fibrosis (Ormond disease)
Inflammatory abdominal aortic aneurysm
Radiation-induced aortitis

(continued)

Table 2.1 (continued)

Infectious
Luetic (syphilis)
Mycobacterial (tubercolosis)
Bacterial
Salmonella spp.
Staphylococcus spp.
Streptococcus pneumonia

[a]Non-infective forms of aortitis (except radiation-induced aortitis) are here classified following the 2012 Chapel Hill Consensus Conference Classification of vasculitides [2]: "large-vessel", "medium-vessel" and "small-vessel" indicate the arteries preferentially involved; variable-vessel = large, medium and small arteries are evenly involved
[b]Vasculitis with common involvement of the aorta (>10 %)
[c]With less common involvement of the aorta (<10 %)
[d]Only case reports of aortic involvement or very small series reported

worsening, leading to significant quality-of-life limitations and potentially lethal evolutions. As a result of the different pathophysiological processes underlying the various forms of aortitis, it can in turn assume the phenotypes of dilative or obstructive disease of the aorta and its main branches, and present either isolated or within one of the several possible associated systemic syndromes, with or without involvement of other organs, eventually resulting in a myriad of diverse clinical pictures. A high index of diagnostic suspicion is necessary to avoid the complications and a correct differential diagnosis among the different etiologies is required to timely set the correct therapeutic strategy [1]. Diagnosis and differentiation can take advantage today of well-codified clinical criteria, at least for the most frequent forms of aortitis, multiple imaging modalities, laboratory tests and, to some extent, histology. In this chapter, we will address the description of aortitis and its treatment, emphasizing the above multiplicity

of etiologies, involved mechanisms and clinical pictures, and focusing on the pharmacotherapy of the most common and notable forms of aortitis.

Non-infectious Aortitis

Non-infectious aortitis is more frequently encountered than infectious aortitis: inflammation is secondary to an autoimmune reaction in most of the non-infectious diseases, idiopathic in a minority of cases. The association between autoimmune ("rheumatic") diseases and aortic involvement is well known, but the prevalence of aortic involvement in the different rheumatic diseases is quite variable: in some of them, namely large-vessel vasculitides, aortic involvement is, by definition, part of the canonical clinical picture (e.g. Takayasu arteritis, giant cell arteritis); in others (e.g. spondyloarthropathies or anti-neutrophil cytoplasmic antibody-related diseases) an arterial inflammation, possibly but not regularly involving also the aorta, can be observed as a part of a systemic or multiorgan involvement. In fact, according to the 2012 Chapel Hill Consensus Conference Nomenclature [2], vasculitides that affect large arteries more often than the others are named "large-vessel vasculitis", those affecting predominantly medium caliber arteries are referred to as "medium-vessel vasculitis" and those affecting predominantly small size vessels are named "small-vessel vasculitis" (Table 2.1). Consistently, in 2006 a review on aortic involvement in rheumatic disorders listed Takayasu arteritis and giant cell arteritis among those most frequently affecting the aorta (>10 % patients), along with long-standing ankylosing spondylitis and Cogan syndrome; rheumatic diseases in which aortic involvement is an uncommon (<10 %) but well-documented complication include rheumatoid arthritis, seronegative spondyloarthropathies, Behçet disease and relapsing polychondritis; rheumatic diseases with isolated case reports of aortic involvement or uncertain involvement include

sarcoidosis, antineutrophil cytoplasmic antibody-associated aortitis (Wegener granulomatosis and *polyarteritis nodosa*), and systemic lupus eryhematosus [3].

Giant-cell arteritis (GCA), also known as Horton's (temporal) arteritis, is a chronic inflammatory large- and medium-vessel vasculitis that affects persons older than 50 years of age (reported male to female ratio ranges 1:2 to 2:3). GCA is much more common than Takayasu arteritis in the general population, with an estimated incidence of about 19 cases/million/year among patients over 50 years of age [4]. Although there is a markedly increased incidence of GCA in northern Europe and in populations with similar ethnic background [5], the disease can occur in all populations. The rate of aortic involvement in GCA is classically reported around 15–18 % (with a predominance of the ascending aorta, but possible involvement of the abdominal), however subclinical inflammation of the aorta may be present in a notably larger proportion of GCA patients. Branches most commonly involved are those arising from the external carotid artery, especially the superficial temporal artery, but ophthalmic, vertebral, coronary, and mesenteric arteries may also be involved.

The etiology of GCA is not well established. Polymorphisms of genes such as tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase (eNOS), intercellular adhesion molecule (ICAM)-1, IL-6, and others appear to be more frequent in patients with GCA, although their pathogenetic role is still to be determined. It has been also postulated that a still unknown infectious pathogen may trigger the aberrant immune response [6].

The characteristic pathology feature of GCA is the presence of granulomatous inflammatory reaction in the vessel wall, with mostly macrophages, $CD4^+$ T-cells and giant multinucleated cells constituting the granulomas, particularly located at the intima-media border, but also B-cells. Giant cells can actually be absent in 30–40 % cases. The $CD4^+$ lymphocytes differentiate into T-helpers and produce interferon-gamma (IFN-γ), which activates macrophages, in turn

producing reactive oxygen species and proteolytic enzymes, including matrix metalloproteases, the effectors of arterial wall elastic matrix degradation [7]. Lymphocytes and macrophages' products, including TNF-α and IL-6, also enter the blood and are responsible for the systemic clinical syndrome in GCA (see next section). Alternatively or adjunctively, a systemic inflammatory response may stimulate pattern recognition receptors at vascular level thereby activating vascular dendritic cells, in turn initiating T-cell response. The intima may be thickened and the medial elastic *laminae* fragmented, whereas in the late stages intimal changes may be minimal and medial changes are largely constituted by fibrosis.

Also known as pulseless disease or Martorell syndrome, Takayasu arteritis (TKA) is a necrotizing and obliterative segmental, large-vessel panarteritis of unknown cause with a predilection for young women (>80 % of cases). Epidemiology varies in the different geographic areas: in the United States, incidence estimates from Olmstead County, Minnesota, are 2.6 cases/million/year, whereas in Sweden and Germany they are 1–1.2 cases/million/year [8] Autopsy studies in Japan document a much higher prevalence, with evidence of TKA in 1 every 3,000 individuals. Also, the age of disease onset differs: it is earlier (15–25 years) in Asians compared to European women (40 years) [9]. Involvement of the aorta is frequent, reported between 80 and >90 %. The most commonly affected aortic segment is the abdominal aorta, however ascending aorta involvement has been described as more typical in Japanese women [3].

Although the exact etiology of TKA is not well known, a prior tubercular or streptococcal infection, genetic factors, and autoimmune mechanisms (possible association with rheumatoid arthritis) have been implicated as etiological factors [9]. The pathogenetic mechanisms are unknown as well, although it is considered to be antigen-driven cell-mediated autoimmune processes, although the specific antigenic stimuli have not been identified [10]. Vessel injury occurs as a result of invasion by leukocytes (including T-lymphocytes, NK-cells, B-lymphocytes, macrophages and others) deriving from the *vasa vasorum*, migrating to the intimal layer and producing a number of cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha

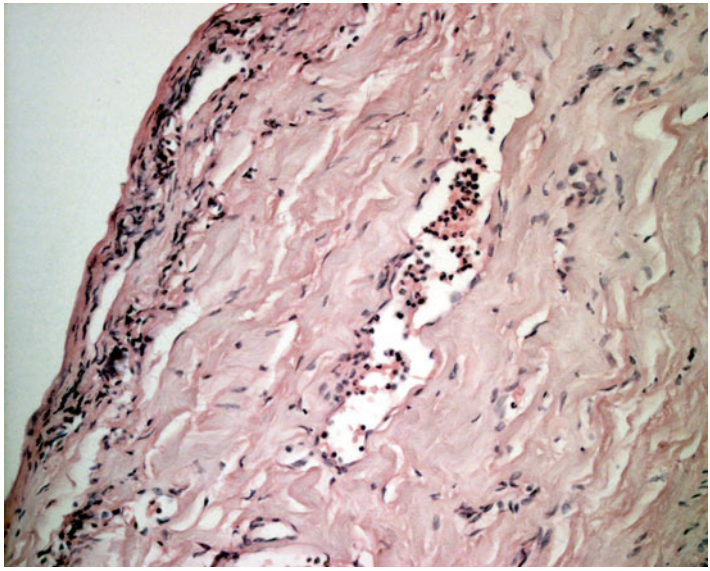

FIGURE 2.1 Histology findings of early stage non-infectious aortitis. Hematoxylin-eosin coloration shows multiple infiltrates of lymphocytes in the adventitia and sub-adventitial media, particularly surrounding the *vasa vasorum*, along with areas of initial focal medial elastic fibers disruption

(TNF-α), B-cell activating factor (BAFF) and others. Myointimal proliferation most commonly results, leading to stenosis of the vessel (most commonly the abdominal aorta) or its branches (especially supra-aortic vessels, iliac arteries and renal arteries), however medial smooth muscle cell necrosis and derangement of the extracellular matrix is another possible evolution, leading to aneurysm formation in 45 % cases (more common at the aortic root and ascending tract) [8]. Aside from the presence of granulomas, possibly including giant cells, in the aortic wall (particularly in the adventitia) and of perivascular cuffing of the *vasa vasorum*, histopathology usually reveals lymphoplasmacytic infiltrate of adventitia and media (Fig. 2.1), a non-specific finding present in a number of rheumatic disorders, such as relapsing polychondritis, systemic lupus erythematosus (SLE),

ankylosing spondylitis, as well as in aortitis of infectious or toxic etiology. At late stages (at least >5 years of disease), unspecific wall calcification is observed, especially in the case of stenotic evolution.

Indeed, the pathology pictures of the different forms of aortitis show substantial overlap, and contribute to make differential diagnosis quite challenging. In this perspective, the stenotic lesions, with thickened intima and media, have been reported as pathognomonic of TKA [8].

Ankylosing Spondylitis (AS) is an HLA-B27 disease classified as a seronegative spondyloarthritis, since it is not characterized by circulating rheumatoid factor. Risk of aortic involvement (predominantly aortic valve, root, ascending aorta) increases with disease duration. Pathology studies of the sacroiliac joints in patients with AS have shown a prominent role of synovitis and subchondral myxoid bone marrow changes, processes mediated by activated T-lymphocyte-derived TNF-α and TGF-β, in initiating intra-articular joint destruction; a *Klebsiella pneumoniae* infection may participate in providing an antigen that reaches the synovia and initiates T-cell responses in genetically susceptible individuals [11]. Similar mechanisms could induce the typical fibrosis changes of AS-associated valvulitis and aortitis: in particular at the level of the proximal aorta, *vasa vasorum* narrowing, fibrotic changes in the adventitia, medial matrix disruption and fibrosis and myointimal proliferation ensue [12].

Cogan's syndrome (CS) is a rare disease of young adults, with a mean age of 29 years at disease onset, defined by the presence of both ocular (keratitis) and inner ear inflammation [13]. Aortitis with valvulitis and aortic insufficiency has been documented as occurring from 2 weeks to 12 years after the initial diagnosis of the syndrome and has an estimated prevalence of up to 10 % [1, 3]. Etiopathogenesis is unknown: formerly believed to derive from a *Clamydia spp*. infection, today, after the finding of autoantibodies and lymphocyte activation against corneal and endothelial antigens, it is considered an autoimmune disorder [14]. Histologic analysis of the aortic wall reveals inflammation with prominent

lymphocytic infiltration, destruction of medial elastic tissue, fibrosis, and neovascularization, which finally result in aneurysm formation [15].

Behçet disease (BD) is a rare, multisystemic, and chronic inflammatory disease of unknown etiology, characterized by mucocutaneous manifestations (aphtous ulcers), especially including genital and oral ulcers and often-severe sight-threatening inflammatory eye disease. It can be associated (up to 30–40 % cases) with vasculitic manifestations in arteries and veins of variable size [2]. The frequency of aortic involvement in BD varies according to different studies, ranging from 50 % of patients in reports from Turkey and Italy [16], to <1 % in other studies including only clinically significant aortic aneurysms [17]. Macroscopically, saccular aneurysms affecting the abdominal and/or thoracic aorta and their branches are typical of BD. Histopathology of the involved aorta shows lymphocytic infiltration mixed with histiocytes and eosinophils with giant cells around vasa vasorum of media and adventitia. Destruction of media leads to aneurysm formation and may proceed to pseudoaneurysm formation and rupture [18]. Aortitis derives not from direct large-vessel inflammation but rather due to vasculitis of the *vasa vasorum* that supply the vessel wall.

Apart from AS, other HLA-27-associated seronegative spondyloarthropathies can present with vascular involvement and potentially, but more rarely compared to the other abovementioned syndromes, with aortitis. These include Reiter's syndrome, an arthritic disease of the lower limbs associated with typical cutaneous lesions and relapsing polychondritis, affecting proteoglycan rich tissues, such as cartilages and vessels. Less frequently, some of the anti-neutrophil cytoplasmic antibody- (ANCA-) related diseases, namely Wegener's granulomatosis, microscopic polyangiitis and polyarteritis nodosa, which more typically involve small-size vessels, can be associated with large-vessel involvement and therefore aortitis. Whether aortitis in such cases is initiated by *vasa vasorum* involvement or by primitive inflammation of the intimal layer ("intimitis") has not been clarified yet [19].

Following the 2012 Chapell Hill Consensus Conference Nomenclature [2], isolated idiopathic aortitis (more frequently observed at the abdominal level) should be classified within the group of "single organ" vasculitides. Idiopathic aortitis is characterized by aortic wall inflammation in absence of any systemic disease or infection, and it usually involves the ascending aorta and arch. This condition affects women more often than men (3:2 ratio) and is asymptomatic until it is discovered incidentally or by post-surgical histological analysis [20]. In those latter cases, macroscopic appearance can already suggest inflammatory etiology, i.e. by the typical diffuse irregular scarring of the intima, referred to as "tree-barking" sign [1]. Histology can vary, however overlapping with the spectrum of lesions already mentioned above for specific etiologies. Infiltrates can include macrophages, T-cells, B-cells and also giant multinuclear cells. Idiopathic inflammatory aneurysms of the abdominal aorta, constituting 5–25 % of all abdominal aneurysms [21], are characterized by thickening of the aortic wall, associated with a considerable peri-aortic reaction and dense adhesions. They are more frequently observed in young males with familiar history of aneurysm, and use of tobacco smoke. Retroperitoneal fibrosis is characterized by a chronic inflammation with fibrous tissue deposition in the retroperitoneum surrounding the aorta, the stem of its main abdominal branches and the ureters. Complications include hydronephrosis, aortic-enteric fistula, and secondary bacterial infections [1].

It has been recently discovered that some cases of idiopathic aortitis, idiopathic aneurysm and retroperitoneal fibrosis are actually secondary to a so-called "IgG4-related systemic disease", in which multiple organs are involved by inflammatory infiltrates constituted by IgG4-expressing plasmacells, and abnormally high levels of IgG4 are found in the serum. This syndrome was first described in patients with autoimmune forms of pancreatitis, but other glands (e.g. salivary glands and thyroid) can be involved, as well as lungs, kidneys, heart, retroperitoneum, mediastinum and aorta [22].

Infectious Aortitis

Infectious aortitis is an infectious and inflammatory process of the aortic wall directly induced by micro-organisms. In the preantibiotic era, it was most likely a complication of bacterial endocarditis secondary to *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Staphylococcus*. Nowadays, the most common pathogens, which account for almost 40 % of infections, include *Staphylococcus aureus* and *Salmonella spp*. Other pathogens involved include *Treponema pallidum*, *Mycobacterium tuberculosis* (less common today in developed countries), and other bacteria such as *Listeria*, *Bacteroides fragilis*, *Clostridium septicum*, and *Campylobacter jejuni* [23]. The aorta is normally very resistant to infection; however, an abnormal aortic wall, like that associated with atherosclerotic disease, preexisting aneurysm, medial degeneration, diabetes, vascular/valvular malformation, medical devices, or surgery, makes it more susceptible to infection, if a bacteriaemia occurs [24]. Mechanisms of infection include hematogenous spread (e.g. in non-typhoid *Salmonella spp*. Gastroenteritis), contiguous seeding from adjacent infection, septic emboli of the aortic *vasa vasorum* and traumatic or iatrogenic inoculation. Infected (or "mycotic") aortic aneurysms are part of the spectrum of infectious aortitis and account for <3 % cases of aortic aneurysms. Men are affected more often than women, with most cases seen in adults after the fifth decade of life: elderly or immunocompromised patients are more susceptible to bacterial seeding at the level of preexisting aortic lesions. Both host leukocytes and responsible bacteria can induce aortic wall lesions, namely extracellular matrix degradation, by producing a variety of proteases including matrix metalloprotease-1, –2, –8 and –9 [25]. The collagenase activity may be relatively localized, leading to formation of a saccular abdominal aortic aneurysm or pseudoaneurysm in an otherwise normal appearing vessel. Collagenase activity may also be intensive, which may explain the rapid course associated with infected abdominal aortic aneurysms. Typical pathology findings include aortic

atherosclerosis, acute suppurative inflammation, neutrophil infiltration, and bacterial clumps. About two-thirds of patients can show acute inflammation superimposed on severe chronic atherosclerosis; the remainder show atherosclerosis with chronic inflammation or pseudoaneurysms [25].

A Challenging Diagnosis

Clinical Pictures

Since symptoms and signs associated with aortitis during the initial phase of the disease are unspecific, a high level of diagnostic suspicion is required for an early diagnosis and a timely treatment.

Giant cell arteritis usually develops later in life compared to TKA, with only few cases reported at an age younger than 50, and is twice more frequent in women than in men. The clinical onset is quite abrupt so that patients are often able to tell a certain date for the appearance of symptoms. The frequent involvement of the temporal artery leads to the most evident symptoms, i.e. localized headache, scalp tenderness, jaw claudication. Either in association with those symptoms or isolately, the involvement of other vessels, also including the aorta, may cause impairment of vision (anterior ischemic optic neuropathy, *amaurosis fugax* or diplopia) together with signs of inflammation, fever of unknown origin with night sweats, claudication of the upper limbs, rarely hearing impairment and dizziness, stroke, symptoms of aortic insufficiency and myocardial ischemia [26].

Clinical examination evidences alterations of the temporal artery region, which appears tender, swollen, firm, beaded or reddened with a reduction of the artery pulse. Similar signs can be found in the occipital region as well. At the level of the upper limbs there may be an asymmetry of radial pulses and blood pressure or bruits of the subclavian and axillary region. Symptoms and signs of an associated *polymyalgia reumatica* can also be present, including reduced range of motion of

shoulders, particularly with impaired arm abduction, a reduced internal and external rotation of the hip, tenderness of the upper arms and thighs. When the suspicion of GCA arise, fundoscopy by an experienced investigator may be appropriate, even in patients showing no eye impairment [26].

The diagnosis of GCA relies on clinical, laboratory, and histological criteria as described in the 1990 American College of Rheumatology classification scheme [27] (Table 2.3).

The existence of an atypical pattern of GCA has been described, in which the temporal artery is spared and the disease more consistently affects large arteries, such as aorta. In this case the clinical scenario may be completely different, mostly dominated by systemic symptoms as fever, decline in general wellbeing, laboratory evidence of inflammation and rarely pain in the lower back or abdomen. This makes reaching the clinical diagnosis of GCA with large vessel involvement even later that for temporal arteritis, sometimes only after histology of the intraoperative specimen [28].

Early published data on aortic involvement in patients with GCA were based on the rate of aortic aneurysms diagnosed fortuitously or after acute events (aortic dissection and rupture of an aortic aneurysm). Thus, in retrospective studies, the prevalence of aortitis ranged from 3 to 18 % [29]. Owing to the introduction of new imaging techniques, capable to show aortic involvement before the development of structural abnormalities, rates of aortic involvement ranging between 33 and 45 % have been disclosed.

Aortic involvement is most often localized at the ascending aorta, and occurs quite late during the natural history of GCA (median time from diagnosis 11 years for the thoracic location) most often manifesting as annuloaortic ectasia, determining aortic valve insufficiency or ascending aortic aneurysm. Acute aortic dissection is a possible complication and occasionally represents the first evidence of disease (within 1 year median time of diagnosis). Abdominal aortic aneurysm can also develop and aneurysms are usually present in the thoracic descending segment in the late phase of the disease [30].

Diagnosis of *Takayasu arteritis* is usually delayed, as a result of the vague nature of the symptoms in its initial phase (often referred to as "pre-pulseless phase"). Mirroring the general systemic inflammation, symptoms of this stage may include fever, malaise, weight loss, night sweat, arthralgia and myalgia [31]. In the late phase the chronic inflammatory process leads to vascular lesions such as aneurismal dilatation, as a consequence of disruption of the connective scaffold in the arterial wall. During the late ("pulseless") phase, systemic manifestations usually remit significantly and symptoms are mainly related to organ ischemia: arm claudication, dizziness, headache, stroke, visual impairment, renal arterial hypertension, angina, myocardial infarction, pulmonary hypertension [26].

The involvement of the aorta and its main branches is common in this disease, most frequently in the abdominal segment, followed by the descending thoracic aorta and the aortic arch. A 53 % prevalence of aorta stenosis has been reported, in 70 % cases affecting the abdominal aorta [32]. Rapid expansion of aortic aneurysms (45 % cases), aortic rupture (33 %) and (more rarely) intramural hematoma and acute aortic dissection, constitute possible severe complications reported to occur in TKA aortitis [33, 34].

Clinical examination should focus on vascular and neurologic systems: a check of the arterial pulses and auscultation of the subclavian, carotid, abdominal and femoral region may evidence asymmetry of pulses and bruits; a bilateral check of blood pressure in the arms and in the legs should always be performed, as it may show significant pressure differences; a neurological examination may detect signs of an ischemic neurological damage [26].

The onset of specific symptoms and signs of TKA is usually early, i.e. during the third or fourth decade of life. Classification criteria have been developed in 1990 by the American College of Rheumatology for TKA [35] (Table 2.2). The most recently issued classification of TKA, based on the vessels involved, distinguishes: type I, involvement of the main branches from the aortic arch; type IIa, involvement of the ascending aorta, aortic arch and its branches; type IIb,

Table 2.2 Diagnostic criteria for Takayasu's arteritis (according to the American College of Rheumatology)

Age of 40 years or less at disease onset
Claudication of the extremities
Decreased pulsation at one or both brachial arteries (compared to pulses at lower limbs)
Systolic blood pressure difference of >10 mmHg between the two arms
Bruit over the subclavean artery or the aorta
Angiography evidence of focal or segmental occlusion or narrowing of large arteries (including the aorta), not resulting from arteriosclerosis or fibromuscular dysplasia

If at least three criteria are present, the diagnosis is made, with sensitivity and specificity of 90 and 98 % respectively

involvement of the ascending aorta, aortic arch and its branches, and thoracic descending aorta; type III, involvement of the thoracic descending aorta, abdominal aorta and/or renal arteries; type IV, involvement of the abdominal aorta and/or renal arteries; and type V, the combined features of type IIb and IV [8].

Non infectious aortitis may be secondary to rheumatic disease, usually driven by aberrant immune responses, giving rise to clinical pictures in which the specific manifestations of the aortic involvement may be confounded by the systemic clinical scenario dominated by the underlying disease or may initially be overlooked by both patients and physicians.

Ankylosing spondylitis (AS) is part of a group of diseases called spondyloarthropaties, associated with HLA-B27 antigen, characterized by sacroilitis, enthesitis, inflammatory bowel disease or psoriasis. It begins with back pain and stiffness during the second or third decade of life, affecting men two to three times more than women. Diagnosis requires at least four of the following criteria: age younger than 40 at onset, insidious onset of arthropathy, back pain for more than 3 months, morning stiffness, improvement with exercise.

Aortitis is present in 80 % of patients with long-standing AS, usually affecting the aortic root and the aortic valve, with insufficiency. AS may also affect the myocardium with impairment of the conduction system [36].

Cogan's syndrome is a rare disease, characterized by ocular, inner ear, and vascular inflammation. Cardiovascular manifestations include aortitis and necrotizing vasculitis, which may induce coronary, renal, and iliac artery stenosis. About 10 % of patients may have aortitis with aortic aneurysm, and valvulitis with aortic insufficiency. Young male patients are predominantly affected, usually presenting with eye redness, photophobia, or eye pain from interstitial keratitis, audiovestibular manifestations similar to those in Ménière syndrome, neural deafness, and possibly symptoms of aortic insufficiency with or without associated ischemic syndromes due to coronary or iliac stenosis, or hypertension related to renal artery stenosis [37].

Relapsing polychondritis is a paroxysmal and progressive inflammatory disease of the cartilaginous structures, affecting the ear, nose, and hyaline cartilage of the tracheobronchial tree. It is caused by autoimmune response against proteoglycan rich tissues. Aortic involvement may be observed in 5 % of patients, resulting in aneurysm formation in the thoracic and abdominal aorta and obliterans vasculitis in other medium-sized and large arteries. Typical of the acute phases is the histological picture of vasa vasorum extending also through both the media and the edematous intima [38].

Aortitis may be associated also with *Behçet's disease*, a systemic chronic disease with typically relapsing course affecting predominantly males of the Mediterranean area and Eastern countries. Its diagnosis is made upon the criteria established by the International Study Group for Behçet's Disease: presence of oral ulceration and at least two between genital ulceration, eye lesions, skin lesions or a positive pathergy test. In one-fifth of patients affected by aortitic complication, multiple pseudoaneurysms can develop, also involving the iliac, femoral, popliteal, and subclavian arteries.

Less frequently, aortitis may be associated with other rheumatologic diseases including rheumatoid arthritis (5 %), Reiter disease (<1 %) and systemic lupus erythematosus (few cases reported).

No specific clinical picture is associated with *idiopathic aortitis* of the thoracic segment, which can indeed be asymptomatic and detected incidentally: diagnosis is made in such cases at the time of histopathology review after thoracic aortic aneurysm surgery. In some cases unspecific thoracic pain can occur, but in most instances no systemic inflammatory symptoms are present. An idiopathic inflammatory aneurysm of the abdominal aorta can present with back or abdominal pain and constitutional symptoms, similarly to other non-infectious etiologies, and differentiation can be suggested by laboratory results and by histological analysis after surgical excision. Clinical onset of retroperitoneal fibrosis can be accompanied by renal function impairment, due to ureteral obstruction and in some cases by intestinal symptoms (e.g. abdominal pain and/or mass with or without sickness and vomit, related to duodenal obstruction) [39].

Infectious aortitis is a severe clinical entity, insidious insofar as it can be virtually undistinguished from non-infectious forms in terms of clinical presentation, and associated with a high inherent risk of acute and life-threatening complications. *Salmonella spp*. are reported to be the commonest pathogens involved in infective aortitis, accounting for almost 40 % of infective aortitis together with *Staphylococcus aureus*, mostly involving the abdominal aorta. The more frequent route of infection is a bacteremia following an ingestion of contaminated food, and a subsequent colonization of a pre-existing aortic atherosclerotic lesion. Aortic infection from a contiguous site, such as a paravertebral abscess complicating a spondylodiscitis is less common. Rare complications are aorto-enteric fistula and endo-myocardial abscess. The natural history of infectious aortitis is characterized by the progressive expansion of the aneurysm, with a greater tendency to rupture, compared to other etiologies, if not diagnosed

and treated promptly. The majority of patients affected by infective aortitis are symptomatic, especially in the aneurysmal stage of the disease. Fever and back pain are the most common symptoms, being present respectively in the 77 % and 65 % of patients with infected aortic aneurysm. Chills, sweats, abdominal symptoms as nausea and vomiting are other possible symptoms [40].

Pneumoccoccal aortitis is rare and is usually due to bacteriemic spread from distant infection foci, such as pneumonia, urinary tract infections, endocarditis, osteomyelitis, cellulitis. Abdominal aorta is the segment most often involved by pneumococcal aortitis, followed by descending thoracic aorta [41].

Aortitis may be a clinical consequence of *Treponema pallidum* determining obliterative vasculitis of aortic *vasa vasorum*, during the third (late) phase of syphilis. After a progressive decrease in its epidemiological importance over the last century, primary syphilis has doubled its incidence during the first decade of the new century, with a majority of cases among homosexual men. This probably heralds a new resurgence of tertiary syphilis, in the next years, with a new epidemiological pattern of infective aortitis. Luetic aortitis typically involves the tubular portion of the ascending aorta, aortic arch and descending thoracic aorta, sparing the sinuses of Valsalva. Consequently, aortic insufficiency associated to aortic root dilatation has been only seldom reported. Clinical diagnosis is most often made based upon serologic confirmation of syphilis and a characteristic pattern of vascular involvement [42].

Other microorganisms, such as *Enterococcus spp*., *Listeria monocytogenes*, *Bacteroides fragilis*, *Clostridium septicum*, human immunodeficiency virus (HIV), *Mycobacterium tuberculosis* may less frequently cause infectious aortitis. A positive history for signs and symptoms of the primary infection should guide the diagnosis towards infectious etiology, if an aortitis has been detected, importantly distinguishing it from autoimmune etiology. The warning has been issued that tuberculous aortitis, possibly evolving towards vessel stenosis

or occlusion, might be misdiagnosed as Takayasu arteritis and erroneously treated by glucocorticoids, which may obviously worsen the infection course.

Imaging and Laboratory

The relevant, though complementary role played by imaging in the diagnosis of aortitis was officially recognized in the 2010 American College of Cardiology / American Heart Association Guidelines for the diagnosis and management of patients with thoracic aortic disease (Class I, level C), as it was in the American College of Rheumatology criteria for the diagnosis of Takayasu arteritis [35, 43].

Imaging provides important information for establishing the diagnosis, contributing in the differentiation between aortitis and other causes of aortic dilatation or large vessel stenosis, estimating the extent of disease, helping to monitor disease activity and response to therapy, and guiding biopsies (in GCA-associated temporal arteritis). The different available imaging methods are used to describe, with different specificity, the two elements of (1) the aortic lumen and (2) aortic wall changes. In large-vessel vasculitis, imaging studies document the anatomic distribution of the lesion, characterized by homogeneous artery wall swelling and aortic dilatation or peculiar large vessel stenoses with smoothly tapered luminal narrowing.

Giant cell arteritis typically involves the branches of the external carotid arteries. The aorta and its main branches are usually unaffected but the possible occurrence of an atypical pattern of large-vessel GCA with negative temporal artery biopsy is reported in up to 25 % of patients [26] and often unsuspected until life-threatening complications occur. Large-vessel form of GCA usually involves the axillary arteries bilaterally and less frequently the subclavian, brachial, femoro-popliteal axis or the aorta itself. However, because aortitis-related complications may be a source of both severe morbidity and mortality, routine

screening for aortic involvement is mandatory in patients with any form of GCA [28].

The peripheral aortic branches are easily accessible to ultrasonography (US) that shows a perivascular hypoechoic halo similar to the finding at the temporal artery (the "halo sign"), which reflects wall edema. Soon after pharmacologic treatment initiation, wall edema decreases and US reveals an increase of the wall echogenicity because fibrosis occurs, being still visible in more than a half of patients even after 1 year of treatment [44]. When GCA affects arteries in the lower limbs, special attention must be paid for a differential diagnosis with atherosclerosis that often occurs at these sites but with different characteristics (atherosclerotic plaques are usually calcified, asymmetric and inhomogeneous) [45].

Computed tomography (CT) angiography is commonly the initial imaging study performed because it is diffusely available. It has an excellent spatial resolution and multidetector scanners allow multiplanar reformation and three-dimensional reconstruction. Actually, CT is less sensitive than other techniques, as magnetic resonance imaging (MRI) or positron-emission tomography (PET), for identifying early wall changes but in an advanced phase it is useful to reveal luminal changes such as stenosis, occlusion, dilatation, aneurysm, calcification and mural thrombi. Contrast-enhanced CT scan may help diagnosis of aortitis showing a concentric thickening (>3 mm) of the arterial wall with post-contrast enhancement [28].

MRI can provide accurate information on involvement of the aorta and its branches, moreover high resolution MRI can investigate temporal arteries. MRI is able to detect the earliest vascular inflammation in the vessel wall and also the luminal changes of the mature phase: findings in GCA include circumferential thickening of the vessel-wall in T1-weighted images, producing a high signal on T2-weighted images (wall edema), and post-gadolinium enhancement in the affected segment [28].

18-Fluorodeoxyglucose (18FDG) – PET-CT is a useful imaging modality in the assessment of active inflammation in

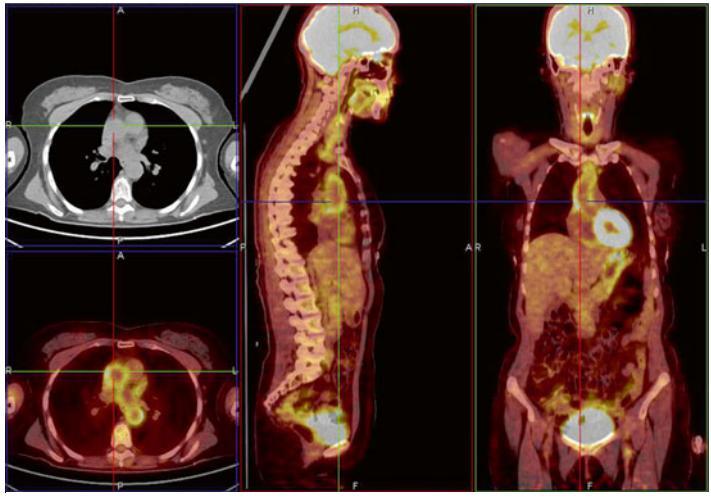

FIGURE 2.2 18FDG-PET-CT showing hyper-uptake at the level of the ascending aorta. Such levels of uptake are highly indicative of aortitis; lower levels may be associated with atherosclerotic lesions, whereas the normal has no detectable uptake (Courtesy of Drs M. Bifulco and F. Porcaro, Nuclear Medicine Diagnostics Unit of the Monaldi Hospital, Naples, Italy)

cardiovascular diseases including aortitis, atherosclerosis and acute dissection. Normally there is no radiotracer accumulation in the arterial wall, thus any 18FDG up-take can be consider a sign of inflammatory infiltrates or infection (Fig. 2.2). Large-vessel FDG uptake is usually graded on a 4-point scale: none (grade 0), lower than liver uptake (grade 1), similar to liver uptake (grade 2) and higher than liver uptake (grade 3). Grades 2–3 are relatively specific for vasculitis, while grade 1, or rarely 2, has been observed in atherosclerotic vessels [46]. Moreover, to exclude false positivity due to atherosclerosis (especially in lower limb lesions), some authors suggest relying only on the upper-body sites of 18-FDG uptake for the diagnosis of GCA [47]. In GCA 18FDG-PET may reveal early inflammation sites even in the absence of detectable structural changes at CT: abnormal

uptake in the aortic arch or large thoracic arteries is found in more than 50 % of affected patients. This is of particular importance for establishing the diagnosis in atypical clinical scenarios with predominance of systemic signs of inflammation, with negative temporal artery biopsy [28]. Since inflammatory cell infiltration is likely to happen prior to the development of wall edema, PET can be even more sensitive for early aortitis than MRI. Contrary to MRI, PET cannot investigate cranial arteries because of its low spatial resolution and the background noise derived from the brain (high FDG uptake of the neuronal cells). PET may also be useful for monitoring the response to treatment: the persistence of 18FDG uptake in the arterial wall at follow-up despite an adequate therapy has been described to have a predictive role for vascular remodeling and aneurismal dilatation [48].

No specific laboratory tests exist for the diagnosis of GCA. Erythrocyte Sedimentation Rate (ESR) and also C Reactive Protein (CRP) readings are high in most patients, and ESR elevation is included between the diagnostic criteria, although up to 10 % of patients with documented GCA have normal sedimentation rates at the time of diagnosis. On the contrary, an elevated ESR can be seen in most of the disorders usually considered in the differential diagnosis of patients with possible vasculitis, notably infections and malignancies, thus limiting the diagnostic usefulness of this test. Acute phase reactants may serve as simple tools for monitoring disease activity during therapy. Many patients have mild to moderate anemia, thrombocytosis and slightly elevated transaminases [26, 43].

While large vessel GCA typically involves the axillary arteries, in *Takayasu's arteritis* the most commonly involved sites are the subclavian arteries (93 %), followed by the aorta (65 %), and the common carotid arteries (58 %) [26]. Other possible sites described for TKA are renal, vertebral, innominate, axillary, superior mesenteric, common iliac, and pulmonary arteries.

Differently from GCA, CT angiography is essential in the early steps of the diagnostic process for TKA, being the

imaging technique with the highest predictive power for demonstrating the abnormalities of the affected vessels. The typical finding in the early stage of the disease is the wall thickening that has been described as the "double ring" sign. This is due to edema in the intimal layer which gives a low-density signal next to a high-density signal from the infiltrated media and adventitia. In the chronic phase of the disease (≥5 years) CT scan may show calcifications of the previous inflamed sites: these are commonly linear and tend to spare the ascending aorta [21].

MRI may also help in the diagnosis of TKA because of its intrinsic ability to investigate the early wall changes occurring before lumen stenosis develops, with findings similar to those in large-vessel GCA. Phase-contrast (PC) – MRI and magnetic resonance angiography (MRA) can also document multiple stenoses, mural thrombi, thickening of aortic valve cusps, and pericardial effusions [21, 49]. For the absence of ionizing radiations, MRI is recommended for serial imaging follow-up especially in young patients.

In a normal carotid wall, US shows an hypoechoic space known as the intima-media complex (IMC), in between two hyperechogenic layers. When edema occurs in the arterial wall, there is an increased and diffuse thickening of the IMC that has been referred to as "macaroni sign", unique of TKA [50]. This diffuse thickening, together with the arterial segments involved, help to differentiate vasculitis from atherosclerosis. The stenosing lesions evolve quite slowly, which explains the common presence of collaterals, with reported cases of reverse flow in vertebral arteries with or without the subclavian steal phenomenon in patients with Takayasu disease [51]. US is useful in TKA also for the investigation of the aortic valve, ascending aorta and pulmonary artery [52].

18FDG-PET represents a promising, yet not definitively established, method to help in the diagnosis of TKA in patients with constitutional symptoms and fever of unknown origin. Hybrid imaging with 18FDG-PET (detecting circumferential increased metabolic activity) and CT or MRI (allowing more precise anatomic localization of the disease)

has emerged as a valuable tool in diagnosing and monitoring treatment response in TKA aortitis. The European League Against Rheumatism (EULAR) recommends PET, together with MRI, for diagnosing large-vessel vasculitis, most notably in patients with TKA, as histological documentation is difficult to obtain in the large-vessel forms of the disease [53].

In TKA laboratory test findings are similar to those of GCA. The ESR and CRP are in most cases highly elevated in active disease, although a smaller number of patients have normal ESR or CRP values [26].

When non-infectious aortitis is ascertained, in the absence of an identifiable vasculitis or rheumatic systemic syndrome with possible secondary aortic involvement, *idiopathic aortitis* is diagnosed. Usually the diagnosis is made post-operatively on the basis of the histological findings on the aortic specimen (giant cells or lymphoplasmacytic inflammation). Patients with idiopathic aortitis have more diffuse and more often extensive (also thoracic descending and thoracoabdominal) dilatation of the aorta compared with those with non-inflammatory dilatations [54]. Idiopathic aortitis patients are generally older at presentation and have greater diameters than those with large vessel vasculitis-associated aortitis, probably related to the silently progressing nature of the disease [55]. CT-scan identifies the inflammatory aneurysm as a hypo-dense mass with thickening of the periaortic tissues that show delayed contrast enhancement in CT angiography following the rapid intra-luminal enhancement.

In idiopathic inflammatory abdominal aneurysms the thickening of the aortic wall/periaortic tissues typically spares the posterior aspect of the vessel [56]. CT is also important to asses possible adhesions of the mass with the abdominal organs in order to plan the surgical strategy (i.e. transperitoneal versus retroperitoneal approach). In the pre-operative phase, MRI helps detailing aneurysm localization (suprarenal versus infrarenal) and demonstrates the presence of periaortic inflammation, adventitial thickening and turbulent flow inside the aneurysm. Diffusion-weighted MR imaging shows a hyperintense halo surrounding the aneurysm.

FDG-PET helps to evaluate the grade of inflammation and also the extent of adhesions if combined to CT/MRI. US shows a periaortic hypoechoic mass that represents the inflammatory process surrounding a thickened aortic wall.

On CT-scan *retroperitoneal fibrosis* appears as a retroperitoneal paraspinal mass with soft-tissue density (isoattenuating compared to adjacent ileo-psoas muscles), surrounding the abdominal aorta and often encircling the ureters and the inferior vena cava, with a variable involvement of the abdominal organs including duodenum and pancreas. Usually this mass is not displacing the aorta form the anterior surface of the spine [57].

Clinical diagnosis of *infectious aortitis* is not simple given the unspecific nature of signs and symptoms, that are usually more evident only in an advanced stages of the disease (aneurysm expansion) or when acute complications occur (rupture of the aneurysm). The definitive etiology is determined only by blood cultures, which can be positive in 50–80 % of the patients, but imaging supports clinical examination and concur to discriminate among alternative diagnoses [57].

Contrast-enhanced CT is the imaging modality of choice in most medical centers because of its widespread availability and multiplanar capability. The association of imaging evidence of a saccular aortic aneurysm, positive blood cultures and typical symptoms of the original infectious focus is diagnostic of the full-blown clinical picture of infective aortitis. In the early stage, aneurysm may not be present but other signs can be evident, including aortic wall thickening with or without contrast enhancement, periaortic nodularity, periaortic soft tissue mass, fluid collections, fat stranding, increasing aortic diameters, and air within the aortic wall. Fluid collection and gas bubbles within the periaortic tissue are signs of impending rupture even in absence of an aneurysm. CT scan helps to discriminate alternative diagnoses such as intramural hematoma, aortic dissection, penetrating aortic ulcer, pseudoaneurysm [1]. MRI with gadolinium contrast can obtain a better imaging definition of earlier alterations of the aortic wall. Segments affected may appear thickened, enhanced and

edematous in the edema-weighted sequences [58]. PET-CT can be a useful adjunct in infectious aortitis, depicting the activity phase of the infectious process.

A strict association between infective aortitis (particularly of the ascending tract) and infective valve endocarditis has been reported, especially in the pre-antibiotic era. Transoesophageal echocardiography is the gold standard method in the diagnosis of infective valve endocarditis, and at the same time it allows for thorough investigation of the proximal tract of the aorta to rule out signs of aortitis [59].

Without appropriate treatment, natural progression of infectious aortitis is rapid with the development of mycotic aneurysms and high propensity to rupture. The term mycotic aortic aneurysm was coined by Wilson in 1984 to describe an aneurysm developed on a previous unaffected aorta following an infective embolus originating from a valve endocarditis [60]; today it encompasses all aneurysms that develop as a complication of infective aortitis. Its incidence is rare, representing only 0.7–2.6 % of all aortic aneurysms, most frequently localized at the abdominal segment, followed by the descending thoracic aorta [61, 62]. At CT/MRI, a mycotic aneurysm (Fig. 2.3) appears as a saccular aneurysm with lobulated contours and possible additional features as periaortic soft tissue density mass, edema, fat stranding, and/or fluid collections. Rapid increase in size and/or change in shape of an aneurysm should increase the diagnostic suspicion for an infectious etiology [63].

Typically Enterococcus infections cause thoracic aortitis, whereas Salmonella spp. mostly affect the abdominal aorta, like in the pneumococcal aortitis [64]. Tubercular aortitis normally involves the aortic arch and the descending thoracic aorta as a focal pseudo-aneurysm with multiple out-pouching and wall thickening. This kind of lesion can be combined with caseous necrosis of periaortic lymph nodes, bones or paraspinal abscesses from which the infection has extended to the aorta for contiguity [65]. In the third phase of syphilis, cardiovascular system may be affected with manifestations as luetic aortitis, aortic aneurysm, aortic valvulitis with regurgitation

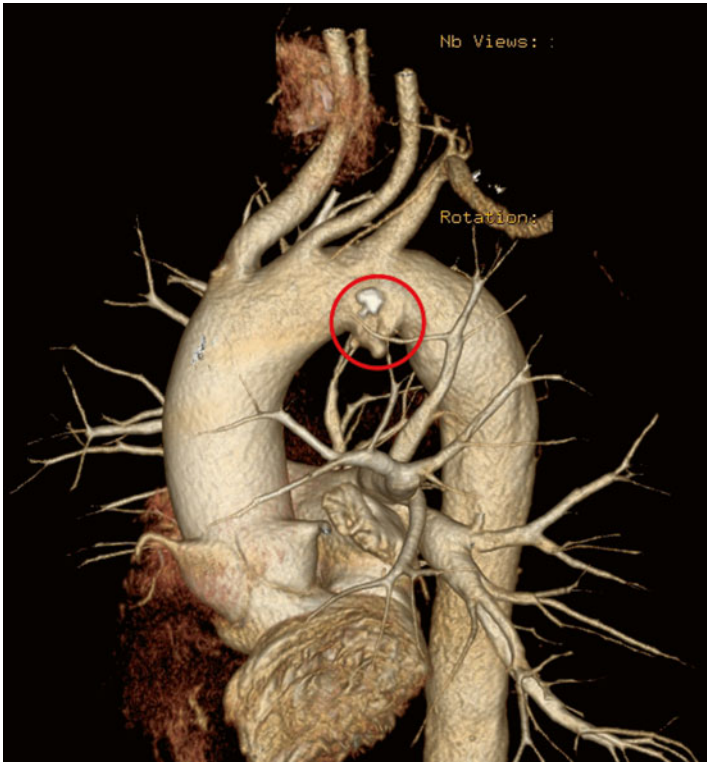

FIGURE 2.3 Multi-slice CT scan reconstruction in a patient with mycotic aneurysm of the aortic arch (*encircled in red*). The typical appearance of a small saccular aneurysm due to infectious aortitis (from *Escherichia spp*. in this patient) is evidenced, with its irregular profile due to multiple out-pouches. Location of the lesion is also typical, i.e. opposite the origin of aortic branches

and coronary stenosis. The most commonly involved site is the ascending aorta, followed by aortic arch and descending thoracic aorta. The infectious process normally evolves in aneurysmal disease with diffuse wall thickening and typical "tree-barking" appearance of the luminal surface at gross examination. On delayed enhancement CT scan the affected

aortic wall may have a double-ring appearance mimicking Takayasu aortitis [66]. Giant syphilitic aneurysms involving the thoracic aorta and determining sternum erosion or rightward displacement of the mediastinum have been described [67, 68].

As for non-infectious aortitis, laboratory tests are complementary to imaging in the diagnosis of infectious aortitis. Leukocytosis and neutrophilia are present in 65–83 % of cases. ESR and CRP are elevated in most of the patients. Microbiology is of paramount importance to identify etiology in infectious aortitis. Blood cultures are positive in 50–85 % of the patients and a microorganism can be isolated from the excised aortic tissue in up to 76 % of the patients [24]. The diagnosis of syphilitic aortitis has to be confirmed by serologic tests. Serology include sensitive non-treponemal serologic tests (rapid plasma reagin test, Venereal Disease Research Laboratory test) and specific treponemal serologic tests (fluorescent treponemal antibody-absorption test, microhemagglutination-T pallidum test).

The Role of Pharmacotherapy in Aortitis

First-Line Pharmacotherapy of Non-infectious Aortitis

The vast majority of non-infectious forms of aortitis is represented by auto-immune disorders, namely vasculitis (e.g. GCA and TKA) and systemic diseases (e.g. Rheumatoid Arthritis and SA). Therefore, the mainstay of the pharmacotherapy for non-infectious aortitis is immunosuppressive therapy. While guidelines and official professional societies recommendations have been issued for the most epidemiologically relevant large-vessel vasculitides (although with quite low levels of supporting evidence) [53, 69], no specific pharmacologic protocols exist for the aortitis that occurs with variable frequencies in patients affected by vasculitides.

Glucocorticoids are the cornerstone of drug therapy for large-vessel vasculitides. Given the inherent risks of severe

morbidities (e.g. ocular impairment in GCA, renal or coronary stenosis in TKA, etc.), a timely diagnosis, preferably before the onset of such organ complications, is crucial, so that glucocorticoids can be administered early and at high initial doses. According to the EULAR (European League Against Rheumatism) 2009 recommendations, the initial dose of prednisolone is 1 mg/kg/day, with a maximum dose of 60 mg/day, maintained for a month and tapered gradually, avoiding alternate day tapering, as it is associated with higher risk of relapses [53].

In Giant Cell Arteritis, according to the British Society of Rheumatology and British Health Professionals in Rheumatology guidelines, the sole clinical suspicion, even in the absence of histological confirmation on temporal artery biopsies, must prompt glucocorticoid therapy initiation [69] (Fig. 2.4). The starting protocol depends on the clinical picture at the time of diagnosis (stage of disease):

- Uncomplicated GCA (with no jaw claudication or visual disturbance): 40–60 mg prednisolone daily;
- Complicated GCA with evolving visual loss or *amaurosis fugax*: 500 mg to 1 g of i.v. methylprednisolone for 3 days before oral glucocorticoids;
- Complicated GCA with established visual loss: 60 mg prednisolone daily to protect the contralateral eye.

Patients often report a rapid response to therapy initiation, with early (hours or few days) recovery especially from systemic symptoms (malaise, fever, headache and polymyalgia), then from laboratory markers of early phase inflammation. Symptoms related to ischemic consequences of arterial stenosis may take more days or weeks to relieve (jaw claudication, temporary visual impairments, arm claudication). Temporal artery biopsy can remain positive for up to 6 weeks after treatment commencement. On the other hand, histological negativity should not exclude diagnosis of GCA in the presence of other three criteria (Table 2.3), whereas lack of rapid response to therapy in terms of systemic inflammation signs should induce to reconsideration of the diagnosis

Table 2.3 Diagnostic criteria for giant cell arteritis (according to the American College of Rheumatology)

Age of 50 years or more at disease onset
New localized headache
Temporal artery abnormalities to palpation (tenderness or decreased pulsation)
Erythrocyte sedimentation rate >50 mm/h
Mononuclear cell infiltration or granulomatous inflammation with or without giant cells in arterial biopsy

If at least three criteria are present, the diagnosis is made, with sensitivity and specificity of 94 and 91 % respectively

(Fig. 2.4). Only after disappearance of clinical symptoms, generally after at least 3–4 weeks, gradual dose tapering can be started [69]:

- dose is reduced by 10 mg every 2 weeks to 20 mg;
- thereafter, the dose is reduced by 2.5 mg every 2–4 weeks to 10 mg;
- finally it is reduced by 1 mg every 1–2 months provided there is no relapse.

Prevention of osteoporosis (calcium, vitamin D and bisphosphonate) and gastrointestinal protection (proton pump inhibitors) should be considered, since glucocorticoid therapy is generally prolonged for several years (5–6 on average) [70]. In order to reduce steroid-related untoward effects, adjunct of other immunosuppressors has been tested. Only one published trial used azathioprine to this purpose, with the result of reducing the total dose of steroids administered over 52 weeks, however with a high rate of withdrawal because of azathioprine side-effects [71]. Methotrexate adjunctive therapy was tested in GCA patients three studies with conflicting results [72–74]: however, a meta-analysis including those three studies revealed that methotrexate allowed a significant reduction in the cumulative dose of corticosteroids at 48 weeks of therapy, but not in the frequency of adverse events, and significantly

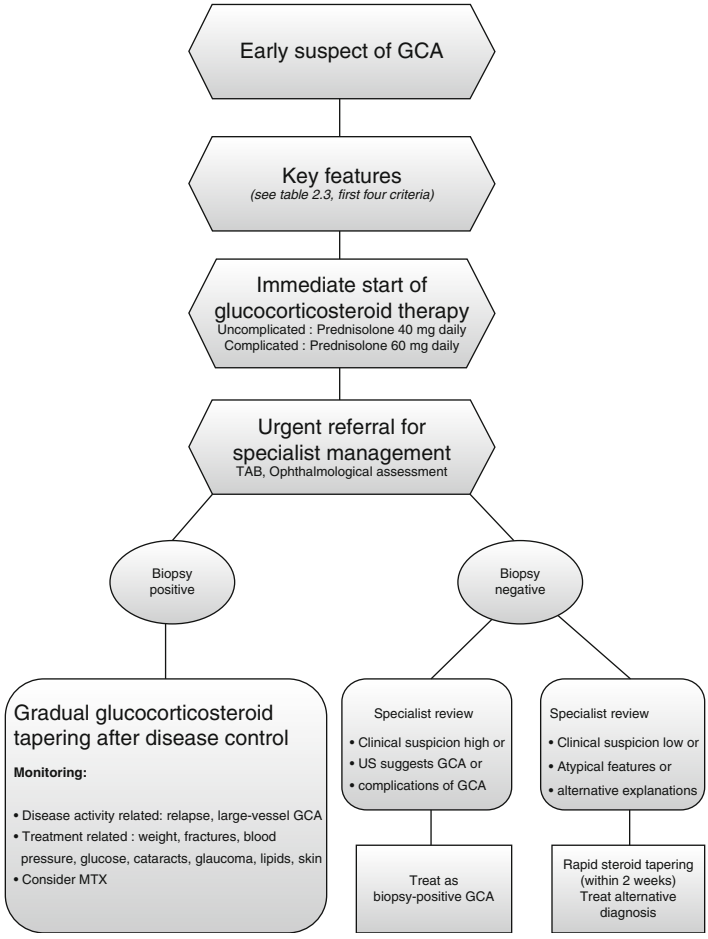

FIGURE 2.4 Schematic flowchart of diagnosis and treatment initiation for giant cell arteritis. Note that the existence of forms with negative temporal artery biopsy prompts to commence treatment even before a specialist review has confirmed the diagnosis (Modified and readapted from Ref. [69] by permission of Oxford University Press on behalf of the British Society of Rheumatology)

reduced the risk of a first and second relapse [75]. In those trials, of note, methotrexate was administered at doses between 7.5 and 15 mg/week, throughout the follow-up period (mean 55 weeks), whereas it has been suggested that higher doses (20–25 mg/week) should be evaluated in GCA patients [75].

GCA patients presenting with aortic involvement are treated with corticosteroids at the same doses as patients with cranial GCA, although it is currently not known whether they would benefit from higher doses. The frequent occurrence of aortic aneurysm, and, more rarely but earlier in the natural history, of aortic dissection in GCA patients suggests that corticosteroid doses sufficient to revert the signs and symptoms of temporal arteritis may be inadequate to suppress or prevent vasculitis of the large arteries. Data on aortic complications in patients under steroid treatment are sparse and based on small series, however the emergence of novel adjuvant therapies (including TNF-α-antagonists and IL-6 receptor antibodies; *see next section*) holds promise to address the possible need for more effective suppression of the immunitary and inflammatory response in large-vessel forms of GCA. Indeed, the improvement in the knowledge of GCA pathophysiology has brought about new concepts affecting treatment protocols. The most important of those novel concepts is that the local vascular inflammatory component of the pathogenesis follows mechanisms of development at least in part independent from those underlying the systemic immune response. Vasculitis has been found to persist even after systemic syndrome remission with glucocorticoid therapy [76], and IL-6 levels increase after discontinuation of steroids, suggesting that the usual doses given to patients induce a rapid remission of the systemic inflammatory response, even though the local arteritis persists for a greater duration [77].

Aspirin has been suggested in addition to steroid therapy, with the aim to reduce ischemic complications, however with contrasting evidences from non-randomized studies [78, 79]. Experimentally, aspirin has been shown to suppress IFN-γ transcription and enhance the suppression exerted by dexamethasone in GCA lesions [80], therefore it has been

suggested to also have a possible immuno-modulating effect; whether it can be useful within steroid-sparing strategies needs to be confirmed in clinical controlled trials. A low dose (75–150 mg/day) is today recommended by the EULAR [53] in all GCA patients unless contraindications exist.

Since there is no completed placebo-controlled randomized clinical trial, the level of evidence for the management of *Takayasu's Arteritis* is low, generally reflecting the results of open studies, case series and expert opinion [53, 81–83]. The first-line medical treatment of TKA includes corticosteroids and conventional immunosuppressive agents, such as methotrexate, mycophenolate mofetil (MMF), azathioprine, cyclophosphamide. In patients who remain resistant and/or intolerant to these therapies, biologic agents (*see next section*) appear a promising adjunct. Antiplatelet treatment may lower the frequency of ischemic events in patients with TA [81–83].

The EULAR recommendation of starting therapy with 1 mg/kg/day of prednisolone or equivalent applies also to TKA treatment. As for GCA, such treatment must commence as soon as the diagnosis is done. The initial dose is maintained for at least 1 month, then if symptoms of active disease show resolve and acute-phase reactants normalize, doses are gradually tapered. A suggested tapering protocol includes [82]:

- reduction by 5 mg/week to reach 20 mg/day;
- reduction by 2.5 mg/week to reach 10 mg/day;
- reduction by 1 mg/week until discontinuation.

During steroid tapering it is quite common to observe relapses of the inflammatory activity: these are usually managed by up-titration of steroids and/or adjunction of immunosuppression. There is no evidence showing which of the different immunosuppressive agents is superior in the treatment of TKA, as no randomized study has compared their efficacy. Since methotrexate is inexpensive, easily available and relatively safe, it represents the first choice of many physicians (0.3 mg/kg/week, up to 15 mg/week) [84]. Methotrexate should be accompanied with folic acid 1 mg/day and trimethoprim/sulfamethoxazole double strength three times per week for

prophylaxis against *Pneumocystis* pneumonia. Azathioprine is usually commenced at a dose of 2 mg/kg/day, MMF at 1.5 g twice per day and cyclophosphamide at 2 mg/kg/day [53, 82]. When the adjunct of immunosuppression fails to maintain disease remission, then TKA is classically considered to be refractory to conventional therapy. More recently, a Turkish study [85] defined refractory disease as angiographic or clinical progression despite treatment or the presence of any of the following characteristics: (1) prednisolone dose >7.5 mg/day after 6 months of treatment, despite administration of conventional immunosuppressive agents; (2) new surgery due to persistent disease activity; (3) frequent attacks (more than three per year) and (4) death associated with disease activity.

Of note, the rate of need for surgical revascularization in patients with stenotic evolution of arterial vasculitis can be high (about 70 %) notwithstanding good response to therapy in terms of inflammatory activity, which is achieved in as high as 60–80 % patients, regardless of the duration of remission; however, about 50 % of patients who present a first remission, can experience at least one relapse episode [81–83]. Novel vascular lesions are also observed in patients who received timely diagnosis and underwent prompt treatment, and the common belief of experts is that currently established medical treatments for TKA are severely flawed. In this perspective, the relatively low rate of disease relapse that have been reported in patients receiving adjuvant biologic agents, such as anti-TNF-α therapy, is noteworthy (*see next section*) [86]. However, confirmation of these observations in rigorous randomized controlled studies is warranted.

As for aortitis associated with GCA and TKA, also aortitis associated with other vasculitides and systemic rheumatic syndromes is treated by the same pharmacologic protocols as the primary disease. Even for those conditions that more frequently present with aortic involvement (e.g. ankylosing spondylitis, Cogan's syndrome, Behçet's disease), no specific treatment modifications are contemplated when the aorta is involved. Pharmacotherapy is based on glucocorticoids and immunosuppressive agents, whereas biologic agents are

being tested in either experimental or already clinical settings, but they do not have a well-established role yet. The use of initial high dose intra-venous corticosteroids (methylprednisolone, 15 mg/kg of ideal body weight/day for the first 3 days) has been found in a single small randomized controlled trial [87] to allow for more rapid tapering of oral steroids and higher frequency of patients experiencing sustained remission of their disease after discontinuation of treatment, in the setting of GCA. This protocol is today incorporated in the official recommendations [53, 69] for complicated GCA, but independent of aortic involvement: whether it could be advantageous in this specific severe form and in the other non-infectious forms of aortitis is still to be investigated.

Novel Therapies for Non-infectious Aortitis

Glucocorticoids are the keystone of medical treatment for aortitis, but this disease is still affected by a high incidence of morbidity, and even mortality, because of the disease and its treatment. During the initial treatment with high dose glucocorticoids a dramatic improvement of symptoms is usually observed, but still a high incidence of side effects is ascribed to steroid agents, such as bone fractures, avascular necrosis of the hip, diabetes mellitus, infections, hypertension, gastro-intestinal hemorrhage, posterior sub-capsular cataract and hypertension [70]. Not of secondary importance, long term steroid therapy may affect connective tissue remodeling inside the aortic media, thus being a concomitant cause of aneurysm development and dissection occurrence in the setting of rheumatic aortitis [88]. For this reasons, the need for novel therapeutic strategies has been advocated, in order to safely allow steroids tapering and minimize the risk of disease relapse.

The last frontier is represented by biologic agents, that are immunoglobulins targeted against inflammatory mediators such as TNF-α, IL-6, IL-1, IFN-γ, or their receptors (Fig. 2.5): for some of them, the data available on their chronic use in vasculitides potentially involving the aorta are absolutely

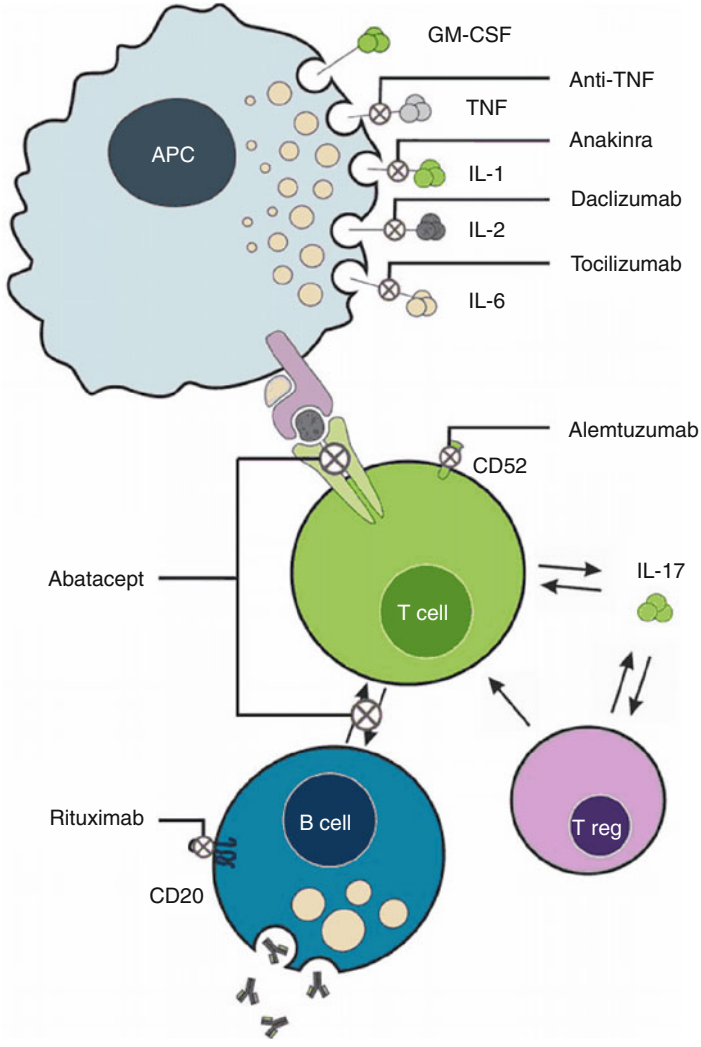

FIGURE 2.5 Cartoon depiction of the immune response steps targeted by different classes of biologic agents. Of those here represented, anti-TNF-α agents and the immunomodulator rituximab have been both employed as adjuvant therapies in large-vessel vasculitides (From Amezcua-Guerra [89])

preliminary and, although promising, the results still need confirmation in large series.

Anti-TNF-α molecules have been experimented in GCA and TKA, after the evidence of a pathogenic role for TNF-α in granulomatous inflammation. TNF-α is a product of different white blood cells involved in the chronic inflammation such as macrophages, T-cells, and natural killer (NK) cells. With an autocrine mechanism, TNF-α stimulates macrophages to produce IL-12 and IL-18 that contribute to amplify the inflammatory response acting on $CD4^+$ T-lymphocyte differentiation and NK cells activation. IFN-γ production that leads to macrophages recruitment and activation on the inflammation site, is itself stimulated by IL-18 [86]. High circulating levels of TNF-α have been reported in GCA and TKA, and TNF-α is expressed by macrophages and dendritic cells in granulomatous vascular infiltrates, suggesting that this cytokine might be responsible for both systemic and local manifestations of the disease [90, 91] and providing the rational for anti-TNF-α therapy in both GCA and TKA.

There are three commercially available anti-TNF-α agents: *etanercept*, *infliximab* and *adalimumab*. Etanercept is a fusion protein of two subunits of the TNF receptor with the Fc portion of human IgG1. Infliximab is a murine-human chimeric monoclonal IgG1 antibody that binds to human TNF, causing its inactivation. Adalimumab is a recombinant, fully human IgG1 monoclonal anti-TNF-α antibody that specifically binds to the cytokine, blocking its interaction with the cell surface TNF receptors and thereby modulating TNF-induced or -modulated biological responses. The majority of the studies about the use of anti-TNF-α in large-vessel vasculitides assessed the effects of etanercept or infliximab; currently, there are limited data on the use of adalimumab to treat any form of vasculitis [92, 93]. A randomized, placebo-controlled, double-blind, multicenter trial was published, aiming at determining whether in patient with newly diagnosed GCA infliximab (5 mg/kg at weeks 0 and 6, and every 8 weeks thereafter), added to a standardized glucocorticoid protocol therapy, would provide benefits in terms of relapses, steroid

doses and toxicity. The study was prematurely stopped because an interim analysis showed no significant effect of infliximab on any of the outcome variables of the study, while there was a non-significant trend for more infections in the infliximab than in the placebo group [92]. TNF-α inhibitors have proved more effective in patients with longstanding, relapsing GCA. Seventeen patients affected by biopsy-proven GCA, controlled by conventional therapy but presenting steroid-related comorbidities, were randomized to receive etanercept (25 mg twice a week subcutaneously) or placebo, and therefore glucocorticoids were tapered following a fixed schedule. Efficacy analysis showed that 50 % of the patients in the etanercept group compared to 22 % in the placebo group reached the primary end point of glucocorticoid withdrawal at 12 months. Etanercept group also had a significant lower dose of accumulated prednisone and a minor percentage of patients in this group suffered from relapses. These differences, however, did not reach statistical significance, possibly owing to the small sample size. These results suggest that etanercept may be beneficial and well tolerated in the subgroup of GCA patients with GC-refractory disease [93].

A promising preliminary evidence of TNF modulators efficacy in Takayasu's arteritis has been observed in two open-label small studies [86, 94]. Sixty-seven percent of 15 patients with steroid-resistant TKA treated with anti-TNF-α therapies achieved sustained remission of disease that lasted 1–3.3 years [86]. The long-term efficacy and safety of anti-TNF-α therapy was thereafter assessed in 25 patients with refractory TKA treated with either etanercept (25–50 mg twice a week) or infliximab (at initial dose of 3–5 mg/kg every 8 weeks): remission was achieved and prednisone was discontinued in 60 % of patients and successfully tapered below 10 mg/day in an additional 28 % of patients, while 9 out of 18 patients treated with other immunosuppressive agents could taper or discontinue the additional agent [94]. Verifying the efficacy of anti-TNF therapy in a larger randomized trial will be crucially important.

Another molecule involved in the transition from acute to chronic inflammation is IL-6. This cytokine triggers the synthesis of acute phase proteins, promotes the activation, proliferation and differentiation of different lines of T-cell lymphocytes and also leads the terminal differentiation of B cells, prolongs the survival of plasma-cells and stimulates monocytes, endothelial and stromal cells to take part in the inflammatory process [95]. Both in GCA and in TKA, IL-6 levels, both circulating and in the vessel, correlate with the activity phase of the disease. Based on this evidence, the humanized monoclonal IL-6 receptor antagonist *tocilizumab* has been proposed as a new treatment for large-vessel vasculitis, to limit auto-reactive lymphocyte differentiation in the affected vessels.

There are in the literature only case reports and very small series of tocilizumab treatment in patients affected by GCA (mostly refractory forms, but also few newly diagnosed disease cases), for a total of about 20 patients. Most common tocilizumab dosage used in those studies was 8 mg/kg every 4 weeks. The agent proved to be effective in lowering steroid dosage and in obtaining a 2-to-6-month relapse-free interval after tocilizumab discontinuation. Tocilizumab has been tolerated without major adverse events, and common side effects were cytopenia and increased levels of liver enzymes. However, persisting histological inflammation has been reported, suggesting that although tocilizumab may lead to symptomatic improvement, it is not curative [96].

In patients affected by TKA, IL-6 might be involved both in the early stage of the disease, stimulating T-cell differentiation and recruiting monocytes, and at the later stage in the processes of angiogenesis and fibrosis. There are 17 fully published cases of tocilizumab therapy in TA mostly refractory to high doses of GC and other concomitant immunosuppressive therapies. The introduction of tocilizumab achieved disease control in all patients, and helped to reduce GC dosage after 3–6 months of combined therapy. Only three cases of relapses occurred while still on tocilizumab, another one relapsed after 3 months of discontinuation of the therapy [97].

Regarding monitoring of disease activity during therapy with tocilizumab, it should be noted that anti IL-6R molecules act directly on the liver, to block the production of acute phase proteins. Therefore, monitoring should rely on clinical and radiological findings more than on the currently available laboratory markers.

B-lymphocytes represent an attractive target for providing more specific immunosuppression in the setting of vasculitis. In animal models, B-cells have been shown to be necessary not only for the development of diseases traditionally thought to be antibody driven, but also for diseases in which B-cells were believed to play a minor role. B-cells are not only the precursors of plasmacells, but they also exert "antibody-independent" functions influencing the immune response [98], including the expression of co-stimulatory molecules and release of mediators that drive $CD4^+$ response, T-reg differentiation and maintenance of T-cell memory. Presence of B-cells has been demonstrated in affected vessels of GCA patients, thus they might be pathogenetic [7]. Also in TKA, a role for B lymphocytes has been postulated, based on the evidence of inflammatory infiltrates from aortic specimens containing B-cells and of anti-endothelium antibodies levels in the serum reflecting disease activity; moreover, an increased number of circulating plasmablasts and memory B cells have been reported in the active phase of the disease [96].

Rituximab is a chimeric IgG1 antibody that binds to CD20 expressed on the surface of B-lymphocytes and depletes circulating naive and memory B cells for 6–12 months via FcgR-mediated antibody dependent cell cytotoxicity and complement dependent cytotoxicity.

One single patient report is available demonstrating dramatic response to rituximab (1,000 mg) preceded by methylprednisolone intravenously (100 mg) in a patient previously showing relapsing GCA on high dosage of prednisone plus intravenous cyclophosphamide (500 mg). A drop in the B lymphocyte count was observed, associated with symptom improvement and disease remission confirmed both by laboratory markers and 18FDG-PET imaging, maintained for the entire follow-up time of 6 months [99].

The use of rituximab in TKA is reported in three case series with good results in five of six patients, all refractory to previous therapy with multiple immunosuppressive agents. Although promising, the very limited number of patients and the short follow-up (the longest one being 14 months) calls for further investigations to better understand the real impact of rituximab in this setting [96].

In the recently expanding pharmacological armamentarium against large-vessel vasculitis, also *leflunomide* has been introduced, an immunomodulating agent already widely used in rheumatoid arthritis, that interferes with dendritic cell maturation, reducing the production of pro-inflammatory cytokines and T-cells stimulation. Leflunomide can reduce IL-6 levels, known to be elevated in large vessel vasculitis, but unlike tocilizumab, it is orally administered and less expensive.

In a case series, leflunomide at doses of 10–20 mg was used as adjunctive therapy on 23 patients with difficult-to-treat GCA and *polymyalgia reumatica*. It was well tolerated, with favorable impact on both clinical and laboratory picture and helped steroid tapering in the majority of cases [100]. In a recent prospective study leflunomide was used at 20 mg/day in 15 patients with TA whose disease was refractory to GC and other immunosuppressant agents. Twelve patients had a favorable clinical response, i.e. a reduction of disease activity scores, CPR levels and dose of prednisone after a mean treatment duration of 9 months. However, two patients had imaging evidence of relapses, and at the end of follow-up the mean daily prednisone dose in the entire series was still superior to 10 mg [101].

Concerning the other, rarer forms of vasculitis that can be accompanied by aortitis, also in Cogan's syndrome (*see One definition for multiple diseases: classification, epidemiology, etiopathogenesis of this chapter*) novel biological therapies have been used: etanercept proved not effective in preserving hearing loss, however, it improved word identification and recognition; infliximab appeared to be effective in inducing and maintaining remission in patients with therapy-resistant CS, and it is believed to provide even greater benefit when initiated at an early stage of the disease [14]. The successful use of infliximab, adalimumab and also rituximab in single case reports of

patients with relapsing-polychondritis-associated aortitis (*see first section*) has been reported, however not always capable to prevent aortic aneurysm development [102]. A metaanalysis including 20 studies with data from 3,096 patients affected by ankylosing spondylitis confirmed the beneficial effect of adjunctive therapy with TNF-α blockers in terms of both disease activity and functional capacity [103]. A promising opportunity for the use of anti-TNF-α therapy in Behçet-disease-associated vasculitides (*see first section*) arises from a number of studies that mainly evaluated this therapy in the setting of ocular inflammation. However, until results from adequately powered, randomized trials become available, anti-TNF-α agents should continue to be used with caution in BD, and their use should be limited to those patients with severe manifestations that have not responded to traditional treatments [102, 104].

Further studies are needed for a comprehensive knowledge of the immunopathogenetic mechanism of the individual vasculitides possibly involving the aorta, in order to identify new biomarkers to monitor disease activity and find new potential targets for pharmacotherapy. Studies are also warranted to establish with a higher level of evidence the role of biological agents in the adjuvant treatment of the large-vessel forms of vasculitides.

Pharmacotherapy in Infectious Aortitis

Antibiotic therapy is a fundamental part of the treatment of infectious aortitis, along with surgery. As soon as diagnosis is suspected, intravenous antibiotics should be initiated with broad antimicrobial coverage, even before microbiologic results are available. Later, antibiotic therapy may be shift accordingly to the microorganisms identified form blood cultures and their antibiotic susceptibility. If there is no high risk of impending aortic rupture, it is reasonable to start antibiotics for 2–4 weeks before surgery to improve local infection and therefore reducing the risk of post-operative infective complications [105].

There is no consensus concerning length of antibiotic therapy because it depends on surgical treatment, bacteria, aortic localization, and patient's risk factors. Commonly antibiotics are prolonged for 6–12 weeks after surgical debridement, or even longer in case of immunosuppressed patients, or persistent positive blood cultures and high biochemical parameters of inflammation. Some authors recommend life-long antibiotics in cases of difficult microorganisms or in situ prosthetic bypass [105]. Despite aggressive therapy, mortality associated with infectious aortitis remains high, mostly due to a high rate of aortic rupture.

Non-typhoid Salmonella spp., reported to be the most frequent causative microorganisms for infectious aortitis, are susceptible to fluoroquinolones and third generation cephalosporins. High-dose bactericidal therapy should be maintained for at least 6 weeks after the operation. Subsequently, long-term suppressive therapy with a bactericidal antibiotic should be used [106].

For systemic streptococcal infection a synergistic bactericidal association of benzylpenicillin (or vancomycin in cases of penicillin resistance) with gentamicin is usually administered [107]. Vaccination with polysaccharidic multivalent vaccine is recommended, notably for immunodeficient patients, to prevent mycotic aneurysm caused by *S. pneumoniae* [41].

For severe staphylococcal infections, flucoxacilline is the antibiotherapy of choice, in association, especially as start therapy, with gentamicin or oral fusidic acid or rifampicin. Erythromycin, vancomycin or parental cephalosporine can be considered in case of penicillin allergy [108].

Late syphilis is treated with penicillin G bezathine, 2.4 million units i.m. weekly for a total of three administrations. Doxycycline or ceftriaxone can be used as an alternative protocol in case of documented penicillin allergy [109].

Mycobacterial aortitis is rare and antibiotic treatment should follow the therapeutic scheme provided for general mycobacterial infections, with an association of isoniazid (300 mg/day three times weekly), rifampicin (450–600 mg/day three times weekly), pyrazinamide (1.5–2 g/day three times

weekly) and also ethambutol (15 mg/kg weekly) in cases of suspected drug-resistant organisms, for a total of 2 months of treatment. The continuation therapy should be maintained for 4 months with isoniazid and rifampicin [110].

The Role of Invasive Treatment in Aortitis

Immunosuppressive drugs and antibiotics are the mainstay of the treatment of non-infectious and infectious aortitis respectively and no invasive treatment is required for non-complicated aortitis under medical treatment. However, when complications occur, invasive treatment is the only possible approach: such complications include chronic aneurysmal dilatation (more often of the aorta itself) and progressive stenosis (more often of its branches). Acute complications are represented by the life-threatening occurrence of acute aortic rupture or dissection, with or without aneurysm, and by stroke.

In non-infectious aortitis, the indications to invasive treatment do not differ from those for other etiologies causing similar complications, such as degenerative aneurysms or atherosclerotic stenosis. Both surgical and endovascular approaches have been applied in the management of aortic complications of aortitis, both for the prevention of aortic catastrophes and for the relief of chronic ischemic organ damage [111]. However, with both approaches, all guidelines concord in recommending elective surgery during the remission phase of the inflammatory disease: when emergency interventions are performed without previously controlling the inflammatory process, postoperative complications such as anastomotic dehiscence, pseudoaneurysm and restenosis are frequent [32, 53, 69].

In Takayasu's arteritis, it has been estimated that the need for invasive treatment is encountered in at least 50 % of patients under immunosuppressive therapy [112], in some cases even in apparent remission phase. The longer the follow-up after anti-inflammatory/immunosuppressive treatment start, the higher the rate of complications requiring surgery or

endovascular therapy, reaching as high as 70 % over a mean period of 3 years [82]. There are no randomized trials of surgical versus endovascular treatment in TKA-associated aortitis.

Concerning stenotic lesions, percutaneous trans-luminal angioplasty (PTA) was widely used for relief of short-segment lesions, and initial reports revealed excellent results [113]; however, since restenosis can occur in more than three-fourths of the procedures, PTA might be better used only in selected cases [81]. It has been suggested that endovascular aortic repair (EVAR) can be advantageous inasmuch as it isolates a tract of the vessel wall from flow, by covering it with a stent graft, with a possible benefit for the inflammatory process [114]: reported restenosis rate is 17 % over 2 postoperative years [115]. Some authors also administer aspirin and clopidogrel perioperatively, to reduce the incidence of restenosis [81]. Surgical intervention has been demonstrated to improve long-term survival in TKA, with restenosis rates ranging between 8 and 30 % during 6 postoperative years [116], and it is considered the treatment of choice in the presence of long-segment stenosis, extensive periarterial fibrosis or complete occlusion. However, the results of bypass surgery in TKA are worse than in atherosclerotic occlusive disease, also due to the existence of clinically silent but locally active forms of vasculitis [117].

The presence of aneurysmal evolution, compared to stenosis, is a more unfavorable condition in TKA, with respect to surgical results: anastomotic pseudoaneurysm has been reported in up to 12 % patients only 2 years following surgery [118]: this prompts continuous and assiduous clinical and imaging surveillance of patients in the postoperative long-term.

When GCA is complicated by axillary or subclavian artery stenosis or occlusion, treatment involves surgical revascularization, with arterial bypass grafting from the common carotid artery, more often than EVAR, since stenosis in GCA usually involves longer segments. [119]. Open aortic reconstructive surgery is generally the standard of treatment also for aortic aneurysms associated with GCA, although endovascular techniques have been used [120]. Although endovascular treatment

has the theoretical advantage of avoiding extensive manipulation of inflamed aortic tissue, there have been no head-to-head trials of the optimal strategy for managing aortic aneurysm in patients with aortitis.

Idiopathic aortitis, when complicated by inflammatory aneurysm of either thoracic or abdominal aorta, requires surgical operation, which in such cases usually results more technically demanding than in other forms of aortitis, owing to the hostile operative field with usual abundant peri-aneurysmal fibrosis and adherence with surrounding structures [121]. Consequently, perioperative mortality is threefold increased compared to surgery for other aortitides. EVAR has been demonstrated to be safer, although with higher rates of reoperations in the follow-up, mainly due to endoleaks [121].

An infectious aortitis is usually discovered late, compared to the time of onset of the infective process, and generally when diagnosis is made a mycotic aneurysm has already developed. Therefore, although antibiotherapy can "sterilize" an infected aneurysm, the definitive treatment, aimed at preventing potentially lethal rupture, is surgical, and surgery is usually required during the same hospitalization as for initial medical treatment [24]. The indications for mycotic aneurysm management do not differ from those for other aortic aneurysms (i.e. aortic diameter exceeding 5.5 cm) [28]. Two different approaches exist in surgery for infective aortitis, namely extra-anatomical bypass and direct repair with interposed grafts. The bypass approach, with debridement and ligation of the infected (generally abdominal) aorta, offers the advantage of being less prone to dehiscence and recurrence of infection, since the grafts are brought through uninfected tissue, however they imply a risk of graft thrombosis with consequent need for reoperation. Graft interposition, with removal of the affected segment, is the procedure of choice today, implying however a higher risk of early graft infection. This latter complication seems less likely to occur with the use of human allografts than with prosthetic grafts [122]. EVAR has been proposed and applied also in infectious aortitis and aneurysms, and a meta-analysis including

48 patients showed a 12-month mortality of 10 %, lower than with surgery. However reinfection of the treated segment, especially in *Salmonella spp*. infections, can occur and it carries a very high incremental risk of mortality, since surgical removal of the endograft is needed. Randomized trials to define the best invasive treatment approach to infective aortitis are still lacking [105].

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