Heart

Invited Review

Aortitis: recent advances, current concepts & future possibilities

Dan Pugh MRCP[1]
Peter C. Grayson MD MSc[2]
Neil Basu PhD FRCP[3]
Neeraj Dhaun PhD FRCP[1]

[1] University/BHF Centre for Cardiovascular Science, The Queen's Medical Research Institute, University of Edinburgh, UK.
[2] National Institute of Arthritis & Musculoskeletal & Skin Diseases, NIH, Maryland, USA.
[3] Institute of Infection, Immunity & Inflammation, University of Glasgow, UK.

Correspondence to: Dr Neeraj Dhaun *(Bean)*
University/BHF Centre for Cardiovascular Science
The Queen's Medical Research Institute
47 Little France Crescent
Edinburgh. EH16 4TJ
Scotland, UK
Telephone: (+44)-0131-242-6786
E-mail: bean.dhaun@ed.ac.uk

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ABSTRACT

Broadly defined, aortitis refers to inflammation of the aorta and incorporates both infectious and non-infectious aetiologies. As advanced imaging modalities are increasingly incorporated into clinical practice the phenotypic spectrum associated with aortitis has widened. The primary large vessel vasculitides, giant cell arteritis and Takayasu arteritis, are the most common causes of non-infectious aortitis. Aortitis without systemic disease or involvement of other vascular territories is classified as clinically isolated aortitis. Periaortitis, where inflammation spreads beyond the aortic wall, is an important disease subset with a distinct group of aetiologies. Infectious aortitis can involve bacterial, viral, or fungal pathogens and, while uncommon, can be devastating. Importantly, optimal management strategies and patient outcomes differ between aortitis subgroups highlighting the need for a thorough diagnostic work-up. Monitoring disease activity over time is also challenging as normal inflammatory markers do not exclude significant vascular inflammation, particularly after starting treatment. Additional areas of unmet clinical need include clear disease classifications and improved short- and long-term management strategies. Some of these calls are now being answered, particularly with regards to large vessel vasculitis where our understanding has advanced significantly in recent years. Work extrapolated from temporal artery histology has paved the way for targeted biologic agents and, although glucocorticoids remain central to the management of non-infectious aortitis, these may allow reduced glucocorticoid-reliance. Future work should seek to clarify disease definitions, improve diagnostic pathways and ultimately allow a more stratified approach to patient management.

INTRODUCTION

'Aortitis' refers to inflammation of the aorta. The primary large vessel vasculitides, giant cell arteritis (GCA) and Takayasu arteritis (TAK), are the most common non-infectious causes. A number of systemic inflammatory diseases have also been implicated including IgG_4-related disease. Although rare, infectious aortitis must always be considered. Regardless of cause, aortitis is associated with significant morbidity.[1, 2] As tissue diagnosis is rarely possible, differentiating aortitis from other pathologies, including atherosclerosis, remains challenging. Here, vascular imaging may be helpful. Once aortitis is confirmed, correctly identifying the disease subtype is a further challenge. This review will address these challenges, outline current best practice and look towards future possibilities for patients with aortitis.

AETIOLOGY & CLINICAL PRESENTATION

Accurate disease classification is vital in aortitis. It influences investigation and management, and longer-term disease monitoring and prognosis. Sub-acute bacterial aortitis, for example, requires intensive short-term antimicrobial treatment but would not typically recur in the long-term. In contrast, aortitis in a patient with TAK usually requires immunosuppression and a lifetime of disease monitoring. The aetiologies of aortitis are discussed below and in **Table 1.**

Infectious aortitis

Infectious aortitis is important as symptoms may be non-specific and outcomes catastrophic. As its presentation may mimic non-infectious aortitis, a high index of suspicion is critical to avoid exposing these patients to immunosuppression. Infection can occur *via* haematogenous spread or directly from neighbouring structures. Pre-existing pathology such as atherosclerosis or aneurysm can increase risk, and men are more commonly affected than women.[3] *Salmonella* sp. is the most commonly isolated pathogen, with *Staphylococcus* and *Streptococcus* sp. also frequently implicated.[3] Tuberculous, fungal, and syphilitic infections are now rare in most healthcare settings. The term *mycotic aneurysm* was initially used in reference to the mushroom-like appearance of bacterial aortic aneurysms, as opposed to an

aneurysm of fungal origin as the name implies. This term is now more generally applied to any infection-related aneurysm, which constitute 2-3% of all aortic aneurysms.[4] Co-existing bacteraemia is found in >50% of cases, with evidence of isolated infection elsewhere (most commonly endocarditis) in 50%.[5]

Non-infectious aortitis

Pathological assessment at time of thoracic aortic surgery demonstrates aortitis in 3-6% of surgical specimens.[1, 6] Interestingly, the majority of patients in these series had no evidence of systemic disease at time of surgery.

Large vessel vasculitis (LVV)

LVV comprises GCA and TAK. Often distinguishable by age at onset, these conditions share many clinical and histological similarities.[7] Increasing availability of high-definition vascular imaging has led to a global rise in the prevalence of LVV.[8] A lack of universally-accepted disease definitions means that some use the term LVV for any non-infectious cause of aortitis. We suggest reserving this term for those with either GCA or TAK.

GCA

Previously considered a condition of the cranial arteries (classically the temporal arteries), evidence from imaging studies, autopsy series, and mounting clinical vigilance now suggest a spectrum of medium and large vessel inflammation, with involvement of the aorta and its primary branches in ~50% of patients.[9, 10] The terms cranial-GCA (C-GCA), large-vessel-GCA (LV-GCA) and C-GCA with LV involvement have been adopted by the European League Against Rheumatism (EULAR) to reflect this (**Figure 1**).[11]

GCA almost exclusively affects those over the age of 50 with incidence rising with age.[12] It is commonest in those of Northern European heritage with an incidence of ~20/100,000 population in Northern Europe and USA.[13, 14] Women are more commonly affected than men

(3:1),[12, 14] although GCA associated with aortitis affects a younger group than classic C-GCA with a higher female predominance.[15]

The clinical features of GCA depend on the vascular territories involved. Aortic involvement is often heralded by constitutional symptoms (fever, weight loss, lethargy) and may exist with or without classical cranial features. Often a late feature of the disease, the risk of aortic aneurysm formation in GCA is ~2-fold higher than in matched controls, with the risk of thoracic aortic aneurysm ~6-fold higher.[16] Aneurysm growth rate is also increased, with a higher growth rate associated with increased risk of dissection.[10]

TAK

TAK affects a younger population than GCA (median age of onset ~35 years) and is therefore associated with years of cumulative morbidity.[17] Again, women are more commonly affected (6:1).[17, 18] Historically considered to be more prevalent in Asia, similar incidence rates of ~2/million have been demonstrated in Japan and the US.[19, 20] The most comprehensive UK study to date has reported incidence and prevalence rates of 0.8/million and 7.5/million, respectively. Interestingly, 62% of the 142 patients included were aged >40 years at time of diagnosis.[21] Although this may reflect diagnostic delay, it casts further doubt on the notion of TAK exclusively affecting those <40 years.

Most cases of TAK involve inflammation of one or more aortic segments, often in combination with branches such as carotid, subclavian or renal arteries (**Figure 1**). In a large French series of 318 patients with TAK, 78% had involvement of at least one aortic region at time of imaging.[17] The remaining 22% demonstrated inflammation of aortic branches only.

Previously termed ‘pulseless disease’, patients with TAK may present with unilateral loss of pulses or symptoms of limb ischaemia. Hypertension is common, either as a consequence of renal artery involvement or due to stenotic or occlusive portions of the aorta (**Figure 2**).[22] Cardiac decompensation may occur with aortic root involvement or increasing afterload.[17]

Clinically isolated aortitis (CIA)

Aortitis may exist without clinical or histopathological evidence of systemic disease, or involvement of other vascular territories. Historically termed isolated aortitis, idiopathic aortitis, or non-syndromic aortitis, 'clinically isolated aortitis' (CIA) has been the preferred term since 2015.[5] The 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides considers CIA a *single-organ vasculitis*, and distinct from LVV – although this distinction is not universally upheld.[23] Compared with GCA and TAK, few studies have sought to characterise CIA.

Many of the available demographic data about CIA come from pathological studies, usually following aortic aneurysm resection.[1, 24] These suggest the ascending aorta is most commonly affected, although this may reflect surgical practice rather than the underlying disease process. More recently, radiologically-defined CIA has become increasingly prevalent with clinical series suggesting that the aortic arch and descending thoracic aorta are more commonly affected.[25] This distinction aside, the demographics of patients with pathologically- or radiologically-defined CIA are similar, with a female predominance and a peak age of onset in the 7th decade.[1, 25, 26] Given the similarities with GCA, many have questioned whether CIA might be the first presentation of a systemic vasculitis – either not clinically evident at presentation or overlooked. Additionally, some suggest that IgG_4-related disease may account for a significant proportion of isolated thoracic aortitis.[27] Indeed, ~20% of patients with CIA will go on to develop an associated inflammatory condition, most commonly GCA, and thus be re-classified.[1] Accordingly, many consider CIA a provisional diagnosis, and clinicians should entertain a high index of suspicion that additional clinical features may develop.

As most cases of CIA are either asymptomatic or present non-specifically, prevalence estimates are limited and it is likely that a significant proportion are undiagnosed.[1] The most robust studies of those found to have aortitis at time of aortic aneurysm repair suggest that

CIA accounts for ~70%, though this likely overestimates the contribution of CIA to aortitis as a whole.[1, 6]

Aortitis associated with other inflammatory conditions

Aortitis may be a manifestation of several other inflammatory conditions detailed in **Table 2**.

Periaortitis

When inflammation extends beyond the aortic wall into the periaortic space it is termed 'periaortitis'. The distinction between aortitis and periaortitis is important as underlying disease processes, diagnostic considerations, treatments and complications differ markedly. Some overlap exists, most notably for IgG_4-related disease which causes both. Periaortitis may be idiopathic or secondary (**Table 1**). The clinical picture is variable and patients may present with constitutional symptoms in association with abdominal or lower back pain. Clinical manifestations due to compression of adjacent structures including lymphatics, retroperitoneal vasculature and ureters should not be overlooked (**Figure 3**).

DISEASE TRIGGERS & HISTOLOGICAL PATTERNS OF INFLAMMATION

Recent work has deepened our understanding of the pathogenesis of LVV, the most common form of aortitis. Innovative mouse models now replicate aortic inflammation and genome-wide association studies are deciphering the genetic basis for both GCA and TAK.[28 29, 30] Despite these advances, specific disease triggers remain largely unknown. Both autoantibody (anti-endothelial cell antibodies) and infectious (*Mycobacterium* sp,, *Chlamydia pneumoniae* and varicella zoster virus) triggers have been postulated.[31, 32] However, many of these studies examined temporal artery tissue and findings may not extrapolate to the aorta. In case-control studies, environmental triggers, including smoking and asbestos exposure, have been linked with retroperitoneal fibrosis.[33]

Different histological patterns of aortic inflammation have been described (**Figure 4 & Table 2**)**.** Granulomatous inflammation is most common and is seen in GCA, TAK and the majority

of CIA. Two distinct inflammatory leucocyte-cytokine signatures have been defined within this pattern.[1 28] The early inflammatory response, isolated to the vessel wall, is mediated by the interleukin(IL)-6/Th17/IL-17 pathway. The IL-12/Th1/interferon(IFN)-γ signature promotes sustained inflammation and vascular smooth muscle cell proliferation. Current biologic agents can target several key components of both pathways including IL-6 (tocilizumab), IL-12 (ustekinumab) and T-cell activation (abatacept). Janus kinase (JAK) inhibitors have also demonstrated efficacy in preclinical and preliminary clinical trials.[34]

DIAGNOSIS & DISEASE MONITORING

Short of histological examination (which is rarely available), there exist no robust diagnostic criteria for aortitis. Thus, distinguishing aortitis from other disease mimics (like atherosclerosis) relies on a combination of clinical judgement and interpretation of imaging and laboratory studies (**Figure 5**). Long-term disease monitoring, including discriminating active inflammation from established vascular sequelae, presents a further challenge.

Laboratory markers

Studies in biopsy-proven GCA suggest that the inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are almost universally raised at diagnosis.[35] However, a study of 196 patients with histologically-confirmed aortitis at time of aneurysm repair found that in those with CIA (n=129), mean CRP and ESR were within the normal range.[1] CRP and ESR are also less likely to be raised in TAK and are less reliable markers of disease activity once immunosuppression has started.[36] Novel markers such as matrix metalloproteinases-3 and -9, and pentraxin-3 may be more specific to large vessel inflammation and discriminate active aortitis from other pathology, although further studies are required.[37, 38]

Imaging

Aortic wall thickening, often used as a surrogate marker of inflammation, can be identified using computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound (US). However, this is not specific for vasculitis and can reflect vascular damage *or* vascular inflammation.[39] CT- and MR-angiography will assess luminal abnormalities, including dilatations and stenoses. MR-angiography also provides information about mural enhancement, a marker of aortic inflammation with sensitivity approaching 90% in TAK.[40] Vessel wall oedema, almost always present in active aortitis but which may persist following inflammation resolution,[39] is more readily identified with MRI than CT and does not require contrast. Both mural enhancement and oedema may provide useful distinctions between aortitis and atherosclerosis. The functional map of inflammation provided by positron emission tomography (PET), usually with ^{18}F-Fluorodeoxyglucose (FDG), provides a valuable assessment of aortic and associated large vessel inflammation. Used in conjunction with CT (PET/CT) or MRI (PET/MR), vascular FDG uptake can identify inflammation not otherwise visible (**Figure 6**).[41] Meta-analysis has demonstrated pooled sensitivities and specificities of 90% and 98% for GCA, and 87% and 73% for TAK.[42] However, PET is not perfect as other aortic pathology (including atherosclerosis) may demonstrate patchy low-grade FDG uptake. Additionally, higher costs, longer procedure times and greater radiation exposure are unavoidable. Radiation exposure can be reduced with PET/MR, which has demonstrated promising diagnostic potential.[43] Future aortitis imaging will incorporate novel PET radiotracers, some of which may predict complications.[44, 45]

All imaging modalities discussed have a role in periaortitis. US may be sufficient to establish abdominal aortic wall thickening or aneurysm with an associated periaortic infiltrate and is also useful in assessing ureteric obstruction. CT and MR provide a more definitive assessment, often demonstrating homogenous fibrotic tissue encompassing the distal aorta and iliac vessels with or without compressive complications (**Figure 3**).[46]

Distinguishing between aortitis subtypes

Clinical features, patient demographics and an 'aortitis screen' may help discriminate aortitis aetiology (**Figure 5 & Table 3**). Imaging helps with diagnostic uncertainty. CT- or MR-angiography should be the initial investigation of choice with imaging extended from the carotid bifurcation to the iliac arteries as the distribution of other abnormal vascular segments will provide diagnostic clues (**Figure 1**).[11] These may also help distinguish infectious and non-infectious causes as infection is likelier to demonstrate peri-aortic and soft tissue fluid or gas accumulation with mycotic aneurysms. Within the aorta, location and disease extent can distinguish disease subtypes (**Table 2 & Figure 2**). Additional PET imaging is useful if symptoms and signs do not align with CT or MRI findings. Although rarely performed in aortitis, CT-guided biopsy may be valuable in some patients with periaortitis, allowing distinction between IgG_4-related disease, Erdheim-Chester disease and lymphoma, with clear implications for management. In the case of apparently 'refractory' inflammatory disease, the possibility of infectious aortitis should be reconsidered.

Disease monitoring

Long-term disease monitoring is critical to identify active disease, detect vascular complications, and guide intervention. This can be challenging as symptoms may be absent, or, if present, may relate to *either* established vascular abnormalities *or* clinically active disease. In LVV, the benefit of disease monitoring to accurately match disease activity with treatment intensity is well established. Radiological and surgical follow-up data for those with CIA suggest grumbling, subclinical aortic inflammation is common with an increased rate of future aortic events compared with matched populations.[25, 47] Accordingly, even without symptoms, most centres advocate radiological aortitis monitoring at least annually.[1]

Despite its importance, disease-monitoring tools are limited. Any imaging modality described can be used, however each has limitations. This is an area of unmet clinical need and novel scanning techniques such as PET/MR may provide a way forward.[43] Emerging MRI contrast agents, such as ultra-small superparamagnetic particles of iron oxide, can be taken up by

aortic wall-resident macrophages and may provide surrogate markers of inflammatory activity.[48]

OUTCOMES & PROGNOSIS

Aortitis is not benign and prognosis depends upon underlying cause. Some patients may have a 'single-hit' non-recurring illness if treated appropriately. In others, an inability to match treatment intensity with disease activity may lead to unchecked subclinical disease progression, relapse or side-effects of over-treatment. In GCA, the presence of aortitis (LV-GCA) is associated with a poorer prognosis than classical C-GCA.[15]

Aortic complications

Aortic dissection, aneurysm or rupture contribute to morbidity and mortality. The existing data – reporting aortic complication rates of ~5-50% – come from surgical series following-up patients who have undergone aortic aneurysm repair.[24, 47] It is difficult to draw firm conclusions from such studies due to significant heterogeneity in disease definition and monitoring.

Some have tried to discriminate complication rates between aortitis phenotypes. Miller *et al* compared outcomes in 45 patients found to have aortitis at ascending aortic resection. They found no difference in aortic complication rates between CIA (n=21) and LVV (n=20) after a follow-up of 83 months.[24] Clifford *et al* reported outcomes from 196 patients with histologically-proven aortitis following thoracic surgery.[1] The majority (66%) were originally classified as CIA. During a follow-up of 56 months, 44% developed new vascular lesions and 40% underwent additional vascular surgery with no difference between CIA and LVV.

Growing evidence discriminates outcomes in those diagnosed radiologically as opposed to histologically. Such studies are more representative of the general aortitis population and in-keeping with our current disease understanding. Ferfar *et al* examined outcomes in 353 patients diagnosed with aortitis either histologically or radiologically.[2] After a follow-up of 52 months, aortic aneurysm occurred in 21%, 25% and 43% of patients with GCA, TAK and CIA,

respectively. Aortic dissection occurred in 5%, 2% and 10%. Interestingly, the poorer outcomes in CIA *versus* LVV occurred despite similar rates of glucocorticoid treatment. The existing data support a need to monitor patients with aortitis for future aortic complications, particularly in those with CIA who may experience higher rates of new aortic lesions despite fewer symptoms.[2]

Other sources of morbidity

Smouldering aortic inflammation can be associated with systemic upset. In a US TAK cohort (median age 27 years at diagnosis), >60% had difficulty with daily activities, and 23% were unable to work due to disability.[22] Population level studies have demonstrated an increased risk of ischaemic heart disease, stroke and peripheral vascular disease in those with LVV *versus* matched healthy controls.[49] As such, primary cardiovascular disease prevention should be part of management. Evidence for antiplatelet use in the absence of cardiovascular disease is limited and decisions should be taken on an individual patient basis.[50]

Mortality

In-hospital mortality rates of 21-44% have been reported for infectious aortitis, usually due to sepsis.[51] Non-infectious aortitis is associated with much lower mortality. In the study by Ferfar *et al*, 7.6% of patients with aortitis had died after 52 months.[2] This equates to a reported 5-year survival for CIA, TAK and GCA of 86%, 100% and 88%, respectively. Mortality has been mostly studied in GCA, with conflicting results. However, data do consistently support an increased mortality in those with aortic disease.[52] Although rare, the mortality associated with ruptured aortic aneurysm due to GCA (80%) is higher than in those without GCA (65-75%).[53]

MANAGEMENT

Non-infectious aortitis may benefit from immunosuppression but management of aortitis associated with other inflammatory conditions is usually determined by the underlying condition, and not by the presence of aortitis (**Table 2**). The management of infectious aortitis

involves targeted and prolonged anti-microbial therapy, often in combination with surgical intervention.

Management of LVV

Glucocorticoids remain the cornerstone of treatment of both GCA and TAK. Almost all patients will receive high dose oral prednisolone (1 mg/kg/day) following diagnosis. A prolonged glucocorticoid taper is typical, targeting ≤5 (GCA) or ≤10 (TAK) mg/day by 1 year or earlier.[54] The presence of aortitis and other large vessel involvement in GCA is associated with higher cumulative glucocorticoid exposure compared with classical C-GCA.[15] Although effective, glucocorticoids have significant side-effects occurring in ~90% of patients.[55] Accordingly, glucocorticoid-sparing agents, both biologic and non-biologic, are an increasingly important part of LVV management. Guidelines suggest a glucocorticoid-sparing agent in combination with prednisolone as first-line management in TAK and in those with refractory or relapsing GCA.[54] Again, those with LV-GCA more frequently require glucocorticoid-sparing therapy than those with C-GCA alone.[15]

Tocilizumab, a humanised monoclonal antibody which inhibits IL-6, is licensed for use in GCA in Europe and the US following the landmark GiACTA (Giant Cell Arteritis Actemra) study.[56] In 251 randomised patients, GiACTA demonstrated lower cumulative glucocorticoid exposure and higher rates of sustained remission at 1 year in those treated with tocilizumab plus glucocorticoids *versus* glucocorticoids and placebo. Questions remain regarding tocilizumab use in LVV, including difficulties with disease monitoring and masking active disease.[57] Additionally, the majority of those recruited to GiACTA had C-GCA without evidence of aortitis.

Although limited evidence supports the use of other glucocorticoid-sparing agents in LVV, in our practice methotrexate and mycophenolate mofetil have proven useful.[58, 59] Biologic agents such as ustekinumab and abatacept target key pathways involved in generating aortic inflammation and have shown promise in early clinical trials.[60, 61]

Management of CIA

This remains controversial. Patients with isolated histological aortic inflammation at time of aneurysm resection are unlikely to be symptomatic. In this group, treatment is directed at preventing future aortic events. Studies do not universally support the use of glucocorticoids, particularly as significant cumulative glucocorticoid exposure would be required to prevent a relatively rare event, but more evidence is required.[1, 25] Those with CIA diagnosed radiologically are perhaps more likely to present with non-specific symptoms which could be attributed to aortic inflammation. Such patients may benefit from immunosuppression but, again, opinion is divided. As such, treatment decisions should be taken on an individual patient basis, taking into consideration symptom burden, disease extent and perceived likelihood of progression. Few data inform the latter, although being male may be associated with an increased risk of future events.[2] Glucocorticoids are probably the treatment of choice in this setting, however, other agents such as azathioprine, cyclophosphamide, methotrexate and tocilizumab have been used.[1, 25]

Management of periaortitis

Most causes of periaortitis, including retroperitoneal fibrosis and IgG_4-related disease, are glucocorticoid sensitive. In glucocorticoid-refractory cases, cyclophosphamide and, more recently, rituximab, potentially in combination with methotrexate or mycophenolate mofetil, have shown promise.[62, 63]

Surgical and endovascular intervention

Aortic dissection and aneurysm formation/rupture are feared complications of aortitis. Surgical and endovascular interventions are potential options here, regardless of underlying aetiology. Ideally, any surgical intervention should be performed during disease remission. When this is not possible, ‘pre-treatment’ with immunosuppression may be useful. Aneurysm repair in patients with aortitis is typically performed as an open procedure, however, endovascular

approaches are possible and offer the potential for reduced manipulation of inflamed aortic tissue.[64]

CONCLUSION

Aortitis is increasingly recognised in the clinic. Accurate diagnosis and disease monitoring are critical for optimal management. Identifying those patients in whom potentially life-threatening complications might develop is an area of unmet clinical need. Novel vascular imaging techniques provide potential tools to differentiate aortitis from aortopathy, identify disease subtypes and to monitor inflammation over time. Although treatment options are improving for LVV, the most common form of aortitis, the optimal management for CIA remains unclear. This will be important to address as almost half of those diagnosed with CIA will develop new lesions and progress. Improving disease definitions and providing clarity regarding the phenotypic spectrum of aortitis may help to eliminate heterogeneity in clinical practice. Global collaborations within the vasculitis community are key to achieving this.

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Table 1. Causes of aortitis

Infectious Aortitis

- Bacterial
    - Most commonly *Salmonella*, *Staphylococcus*, *Streptococcus*, *Treponema pallidum*
- Fungal
- Mycobacterial

Non-infectious Aortitis

- Large vessel vasculitis
    - Giant cell arteritis
    - Takayasu arteritis
- Clinically isolated aortitis
- Aortitis associated with alternative inflammatory conditions
    - Ankylosing spondylitis
    - Behçet's disease
    - Cogan's syndrome
    - Granulomatosis with polyangiitis
    - IgG_4-related disease
    - Relapsing polychondritis
    - Rheumatoid arthritis
    - Sarcoidosis
    - Systemic lupus erythematosus

Periaortitis

- Histiocytosis (Erdheim-Chester disease)
- Idiopathic
    - Inflammatory abdominal aortic aneurysm
    - Retroperitoneal fibrosis
- IgG_4-related disease
- Neoplastic
- Radiotherapy

IgG_4, immunoglobulin G4.

Table 2. Histological, topographic and clinical features associated with aortitis subtypes

Condition	***Prevalence of aortitis***	***Histology & typical aortic involvement***	***Clinical features***
Ankylosing spondylitis	Aortic involvement in 20-80%, although prevalence of aortitis specifically unknown[65]	Lymphoplasmacytic; Aortic valve & root	Symptoms of spinal inflammation +/- extra-articular involvement including uveitis, psoriasis, colitis
Behçet's disease	<10%[66]	Mixed inflammatory; Saccular pseudoaneurysms, thoracic & abdominal aorta	Recurrent oral and genital ulceration +/- GI, neurological, joint, skin, eye disease
CIA	100%	Granulomatous/giant cell *or* lymphoplasmacytic; Thoracic aorta	May be asymptomatic or present with non-specific symptoms, or symptoms related to aortic complications
Cogan's syndrome	~10%[5]	Mixed inflammatory; Aortic valve	Interstitial keratitis and vestibulo-auditory dysfunction
GCA	~30-80%[9, 10]	Granulomatous/giant cell; See Figure 1	Constitutional symptoms +/- limb claudication, cranial symptoms including visual disturbance, PMR
GPA	Uncommon	Granulomatous/giant cell with extensive necrosis & neutrophil involvement; Thoracic & abdominal aorta	Constitutional symptoms +/- evidence of specific organ involvement (*eg.* kidney, lung, ENT, nerve, skin)
IgG_4-RD	6-36%[67, 68]	Lymphoplasmacytic *and/or* periaortitis, IgG_4+ plasma cells present; Thoracic & abdominal aorta	Development of sub-acute mass typically involving salivary glands, autoimmune pancreatitis, retroperitoneal fibrosis

Infectious aortitis	100%	Suppurative (bacterial) or granulomatous/giant cell (mycobacterial/fungal); Mycotic aneurysms, areas of previous aortic damage/disease	Fever, abdominal pain, back pain, features of infection elsewhere
RA	1-5%[5, 69]	Granulomatous/giant cell; Aortic valve +/- thoracic/abdominal aorta	Classical articular + extra-articular features of RA; aortitis more common if other features of rheumatoid vasculitis present
Relapsing polychondritis	Aortic disease in ~10% although active aortitis uncommon[70]	Mixed inflammatory; Aortic valve & root	Largely cartilaginous inflammation involving ears, nose, eyes, joints and respiratory tract
Sarcoidosis	Uncommon	Granulomatous/giant cell with non-caseating granulomas, *or* lymphoplasmacytic; Thoracic & abdominal aorta	Respiratory symptoms (or incidental radiological abnormalities) +/- constitutional symptoms, skin involvement, lymphadenopathy, uveitis
SLE	Uncommon	Lymphoplasmacytic; Thoracic & abdominal aorta	Wide-ranging. Constitutional symptoms +/- arthralgia, Raynaud's phenomenon, skin rash, pulmonary disease, renal disease, haematological disease, cardiac disease
TAK	~80%[17]	Granulomatous/giant cell; See Figure 1	Constitutional symptoms +/- pulse discrepancies, hypertension, limb claudication, cardiac insufficiency

CIA, clinical isolated aortitis; ENT, ear, nose and throat; GCA, giant cell arteritis; GI, gastrointestinal; GPA, granulomatosis with polyangiitis; IgG_4-RD, immunoglobulin G4-related disease; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TAK, Takayasu arteritis.

Table 3. 'Aortitis screen' laboratory investigations

Investigation	Interpretation
FBC	Useful baseline investigation; Leucocytosis, thrombocytosis and/or anaemia may reflect inflammation or infection
Kidney function	Useful baseline investigation; Kidney function may be abnormal in GPA, SLE, sarcoidosis, and with any involvement of renal arteries (*eg.* in TAK)
Liver function	Useful baseline investigation
CRP	Likely to be elevated at diagnosis regardless of cause of aortitis; May be suppressed once treatment initiated despite ongoing disease activity
ESR	Likely to be elevated regardless of cause of aortitis; May be suppressed once treatment initiated despite ongoing disease activity
Serum calcium	May be elevated in sarcoidosis
Serum immunoglobulins	May be elevated in sarcoidosis; Total IgG & IgE may be elevated in IgG_4-RD; IgG_4 elevated in ~2/3 of patients with IgG_4-RD;[71] Those with aortitis as a manifestation of IgG_4-RD may have lower levels of IgG_4 than those without aortic involvement[72]
Serum complement	C3 & C4 may be reduced in SLE & IgG_4-RD
Serum ACE	Limited value & non-specific, but may be elevated in sarcoidosis
ANA	May be positive in SLE, RA & other inflammatory conditions
ANCA	Positive in 90% with GPA[73]
RF	Reported sensitivity of 69% & specificity of 85% in RA;[74] In those with rheumatoid aortitis, RF positivity may be higher (>85%)[75]
Anti-CCP antibodies	Reported sensitivity of 67% & specificity of 95% in RA[74]
HLA-B27	Positive in ~90% with AS but non-specific[76]; Not a routine screening test but useful if AS strongly suspected
Blood culture	Necessary investigation to help exclude infectious aortitis
Syphilis serology	Useful if syphilis suspected or history of disease
Tuberculosis testing	Necessary if suspicion of active or latent tuberculosis

ACE, angiotensin converting enzyme; ANA, antinuclear antibodies; anti-CCP, anti-cyclic citrullinated peptides; ANCA, anti-neutrophil cytoplasmic antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; AS, ankylosing spondylitis; C3/4, complement component 3/4; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBC, full blood count; GPA, granulomatosis with polyangiitis; HLA-B27, human leucocyte antigen-B27; IgG, immunoglobulin G; IgE, immunoglobulin E; IgG_4-RD, immunoglobulin G4-related disease; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; TAK, Takayasu arteritis.

Figure 1. Classification of giant cell arteritis and Takayasu arteritis. Patterns of disease involvement such as those demonstrated here may help to differentiate LVV from mimics such as atherosclerosis which cause a more diffuse pattern of injury.

C-GCA, cranial giant cell arteritis; LV-GCA, large vessel giant cell arteritis; TAK, Takayasu arteritis.

Figure 2. MR-angiography showing 3D reconstructed images of vascular involvement in two patients with Takayasu arteritis. The red arrow denotes an area of mid-aortic stenosis.

Figure 3. Red arrows denote an area of fibrotic tissue encompassing the abdominal aorta with compression of the iliac arteries and of the right ureter leading to hydronephrosis of the right kidney in a patient with periaortitis. Biopsy revealed a dense B cell infiltrate with granulomatous inflammation. The patient responded well to rituximab.

Figure 4. The four main histological forms of aortitis. Granulomatous inflammation, the most commonly observed pattern, is seen in GCA, TAK and the majority of CIA. A lymphoplasmacytic pattern of inflammation may be seen with several inflammatory conditions such as ankylosing spondylitis and systemic lupus erythematosus. This is also typical of periaortitis in IgG_4-related disease. Behçet's disease may present a mixed inflammatory picture, as may Cogan's syndrome and relapsing polychondritis. A suppurative pattern is typical of bacterial infection, most commonly due to *Salmonella*, *Staphylococcus* or *Streptococcus* sp.

VSMCs, vascular smooth muscle cells.

Figure 5. Flow diagram – a potential approach to the diagnosis of aortitis subtypes.

CTA, computed tomography angiography; MRA, magnetic resonance angiography; PET, positron emission tomography; BP, blood pressure; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; ANCA, anti-neutrophil cytoplasmic antibodies; PMR, polymyalgia rheumatica; C-GCA, cranial giant cell arteritis; TB, tuberculosis; FBC, full blood count; U&E,

urea & electrolytes; LFTs, liver function tests; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptides; ACE, angiotensin converting enzyme; IgG_4, immunoglobulin G4; US, ultrasound; CIA, clinically isolated aortitis; LVV, large vessel vasculitis; TAK, Takayasu arteritis; GCA, giant cell arteritis.

Figure 6. (A) PET/CT image showing inflammation isolated to the ascending aorta. (B) CT angiography image showing thickening and contrast enhancement of the wall of the ascending aorta. Although disease mimics such as atherosclerosis can cause increased FDG uptake in the aortic wall, circumferential high-grade FDG uptake combined with wall thickening, as demonstrated here, is more likely to be a consequence of aortitis.