British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis

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Guideline

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British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis: executive summary

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Introduction

GCA, or temporal arteritis, is a large-vessel vasculitis affecting older people [1]. Without high-dose glucocorticoid treatment, GCA can lead to occlusion of cranial blood vessels, which may result in blindness or stroke [2]. Most occurrences of blindness or stroke happen either before treatment or during the first week of treatment [3]. GCA is therefore a medical emergency requiring immediate treatment. Many patients with GCA have inflammation of the aorta and its proximal branches (extracranial large-vessel involvement), which can lead to aortic aneurysm, dissection or rupture [4]. Recent years have seen new evidence emerge regarding the diagnosis and treatment of GCA, requiring a major update of the 2010 British Society for Rheumatology (BSR) guideline [5].

Objectives: To provide guidance for clinicians in the diagnosis and treatment of GCA, supported by evidence where possible.

Target audience: This guideline is intended for doctors and allied health professionals who work in a primary or secondary care setting and manage patients with suspected and/or established GCA.

Areas not covered: Takayasu arteritis [6], isolated PMR [7, 8] and management of glucocorticoid-related complications such as osteoporosis [9].

For details concerning each section please refer to the full guideline published online.

This guideline was developed using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) to produce evidence-based recommendations [10].

General principles

'General principles' are not necessarily evidence-based but are a description of generally accepted best medical practice. Each general principle carries a consensus score (mean rating on a 0–10 scale). Further practical guidance for clinicians is also provided where relevant.

How should suspected GCA be treated?

1. Patients in whom GCA is strongly suspected should be immediately treated with high-dose glucocorticoids. Consensus score: 9.61.

'Strongly suspected' GCA means that in the assessing clinician's judgement, GCA is a more likely explanation for the patient's symptoms than any other condition. For doses, see Treatment of GCA, below.

How quickly should patients with suspected GCA be referred for evaluation?

2. GCA is a medical emergency. Each local healthcare organization should have information available to front-line clinicians, such as general practitioners and clinicians working in acute care, on how to refer patients with suspected GCA urgently for local specialist evaluation: patients should be evaluated by a specialist ideally on the same working day if possible and in all cases within 3 working days. Consensus score: 9.17.

GCA is a medical emergency and therefore 'fast-track' referral pathways for urgent specialist evaluation of suspected GCA are beneficial. On suspicion of GCA, primary care providers should initiate glucocorticoids alongside an urgent referral to the local GCA pathway.

To whom should patients with suspected GCA be referred?

3. Patients with suspected GCA should be evaluated by a clinician with appropriate specialist expertise, usually a rheumatologist. Patients presenting with a history of new visual loss (transient or permanent) or double vision should be evaluated as soon as possible on the same calendar day by an ophthalmologist. Consensus score: 9.61.

What evaluations should be performed when starting treatment?

4. When starting glucocorticoids for suspected GCA, diagnostically relevant symptoms and signs should be documented. Blood should be taken for full blood count, CRP and ESR before or immediately after commencing high-dose glucocorticoids. If GCA is strongly suspected, the first dose of glucocorticoid can be given without waiting for laboratory results. Consensus score: 9.61.

Diagnostically relevant symptoms and signs of GCA include headache; scalp tenderness/hyperaesthesia jaw or tongue claudication; temporal artery tenderness, nodularity or reduced pulsation; visual manifestations including diplopia or changes to colour vision; limb claudication; PMR (pain and stiffness of the shoulder and hip girdles) and fevers, sweats or weight loss. Less commonly, patients may have carotidynia, audiovestibular symptoms, dry cough or indications of tongue or scalp ischaemia that may precede necrosis. However, as none of these symptoms are entirely specific for GCA, each is of limited use if taken in isolation [11] and a differential diagnosis must also be considered. GCA causes an elevation in the platelet count, CRP and ESR. Plasma viscosity can be used where ESR is unavailable. These markers all decrease with glucocorticoid therapy,

Table 1 A proposed list of clinical assessments that could be carried out at or near diagnosis of GCA

History and examination	Investigations
Height and weight Features of GCA relevant to prognosis: fever, sweats or weight loss; ischaemic manifestations (jaw claudication, tongue claudication) Signs and symptoms indicating involvement of extracranial arteries, e.g. bruits, different blood pressures in the two arms, limb claudication Ophthalmological evaluation for patients with transient or permanent visual loss or diplopia History of comorbidities and medications that might predispose to glucocorticoid-related adverse effects: infection, hypertension, diabetes, osteoporosis, low-trauma fracture, dyslipidaemia, peptic ulcer, psychiatric adverse effects Features that may suggest alternative diagnosis, e.g. neurological deficits, very severe constitutional symptoms or localized ear, nose and throat signs	Measures of activity of GCA: laboratory markers of inflammation (CRP for all patients, plus either ESR or plasma viscosity) and full blood count (platelet count may be elevated in GCA) Consider serum protein electrophoresis and urine Bence–Jones protein/serum free light chains if ESR elevated out of proportion to CRP Baseline laboratory tests of major organ system function (plasma glucose, renal and liver function tests, calcium and alkaline phosphatase) Screening tests for risk of serious infection[a] (may include urine dipstick, chest radiograph, tests for latent tuberculosis according to local or national protocol) Screening tests for osteoporosis risk[a] [may include TSH, vitamin D, bone density test (DXA)]

[a]Screening tests for infection and osteoporosis to be considered in light of relevant local and national guidelines.
TSH: thyroid stimulating hormone; DXA: dual-energy X-ray absorptiometry.

therefore all patients should have blood drawn prior to starting treatment, unless there is evidence of critical ischaemia, such as visual loss or diplopia, and no immediate access to phlebotomy.

What evaluations should be performed soon after starting treatment for GCA?

5. Patients treated for GCA should be evaluated for features of the disease relevant to prognosis, such as clinical and laboratory features of a marked inflammatory response at diagnosis, ischaemic manifestations such as transient visual loss or jaw/tongue claudication and signs or symptoms indicating involvement of the aorta and its proximal branches and for comorbidities relevant to treatment, such as diabetes mellitus, hypertension and bone fracture risk. Consensus score: 9.53.

Table 1 summarizes recommended assessments for patients with GCA. As well as confirmatory tests for GCA (see Key Recommendation 1), alternative explanations for patients' symptoms should be considered, particularly if these confirmatory tests are negative.

It is best practice for the prescriber of glucocorticoid therapy to ensure that patients are evaluated for hypertension and hyperglycaemia (blood glucose for acute changes and/or haemoglobin A1c to identify patients that might be at greater risk) within the first 2 weeks of commencing high-dose glucocorticoids. Patients receiving high-dose glucocorticoids are at an elevated risk of osteoporosis and bone fracture; this risk should be managed appropriately.

In GCA, involvement of the aorta and its proximal branches is often asymptomatic but may cause vascular bruits or reduced blood pressure in one or both arms. Clinicians should be aware of an increased risk of thoracic aortic aneurysm and dilatation; this may occur at any time during the disease course [4]. However, routine aortic imaging for all GCA patients remains of uncertain cost-effectiveness. The optimal method and timing of imaging is still unclear [12]. Therefore clinicians are advised to use their own discretion regarding selection of patients for aortic imaging.

How should ongoing management of GCA be individualized?

6. Full assessment of the disease and comorbidities and consideration of the patient's personal priorities should inform decisions about glucocorticoid tapering and initiation of additional treatments such as glucocorticoid-sparing therapies. Involvement of and clear communication with primary care physicians is critical, especially for management of multimorbidity. Consensus score: 9.67

Table 2 shows an example of glucocorticoid tapering for GCA. This is an example of glucocorticoid tapering based on that described in the 2010 BSR guidelines for GCA [5] and similar to the control arm of a recent clinical trial [13]. High-quality evidence comparing different glucocorticoid taper schedules in GCA is not available. Alternative approaches include, for example, reducing prednisolone by 10 mg/week in patients who are in remission on >20 mg daily and/or reducing the dose slower than stated here in patients who are on ≤ 5 mg daily. In all cases, taper schedules should be individualized based on the patient. For relapse management, see Table 3.

What education should patients be offered?

7. All patients with GCA should be provided with information about GCA and its treatment. Patients should receive advice on diet, physical activity and stopping smoking. Consensus score: 9.47.

Information should be available in a written format and ideally in multiple formats. Dietary considerations include mitigating the potential effects of glucocorticoid therapy on body weight, post-prandial glycaemia and bone fracture risk. Recommendations on physical

Table 2 An example of glucocorticoid tapering for GCA

Daily prednisolone dose	Example rate of reduction in daily prednisolone dose	Notes
40–60 mg oral prednisolone: initial dose for patients with active GCA	Continue at same dose until GCA symptoms and acute phase markers resolve	Purpose: induction of clinical remission
In clinical remission, and >20 mg prednisolone	Reduce daily dose by 10mg every 2 weeks	Aim to reach 20 mg prednisolone once the patient has been in remission for 4–8 weeks . If symptoms suggestive of GCA relapse occur during taper, consult Table 3
In clinical remission, >10 mg prednisolone but <20 mg	Reduce daily dose by 2.5 mg every 2–4 weeks	
In clinical remission, and on ≤10 mg prednisolone	Reduce daily dose by 1mg every 1–2 months	

Table 3 Examples of symptoms that may signify relapse of GCA during glucocorticoid taper that require further evaluation and, if judged to be due to GCA relapse, escalation of glucocorticoid treatment

Symptom	Possible significance in a patient with GCA	Action to consider if symptom is judged to be due to GCA relapse
Return of headache symptoms	Possible GCA relapse without ischaemic manifestations	Return to previous higher prednisolone dose
Jaw or tongue claudication	Possible GCA relapse with ischaemic manifestations	Consider high-dose oral prednisolone (40–60 mg) with or without glucocorticoid-sparing agent
Weight loss, fever, night sweats, anaemia, persistent acute phase response, new/recurrent PMR symptoms, limb claudication, abdominal pain or back pain	Possible GCA-related inflammation of the aorta and/or its proximal branches	Investigate with vascular imaging (MRI, CT or FDG-PET/CT); consider increasing oral prednisolone and/or adding glucocorticoid-sparing agent

activity in inflammatory arthritis and osteoarthritis [14] may be tailored to individual patients with GCA. Patients should be signposted to relevant patient support groups or charities as sources of peer support. Patients should be advised of potential symptoms of glucocorticoid withdrawal, although these are uncommon in practice. Patients should be advised about alteration of the glucocorticoid dose in intercurrent illness, especially including advice for seeking emergency attention if they suffer a vomiting illness necessitating parenteral glucocorticoid.

What plans should be made for possible future GCA relapses?

8. During glucocorticoid tapering and after glucocorticoid cessation, patients should be informed what symptoms may suggest GCA relapse and what action the patient should take in these circumstances, including first point of contact for medical advice and how to contact the team providing specialist care. Consensus score: 9.81.

Table 3 shows examples of symptoms that may signify relapse in patients with GCA and how they might be managed. This table outlines how new symptoms in GCA patients, in the absence of other risk factors or significant comorbidities, may influence management decisions. New visual loss or diplopia should be urgently evaluated by an ophthalmologist. Acute phase markers should be measured and, if found to be elevated, may increase the clinical suspicion of GCA relapse. At present, the only agents with any evidence for glucocorticoid-sparing in GCA are methotrexate and tocilizumab.

Key recommendations

The following evidence-based recommendations are graded as strong or conditional, with the quality of the evidence given as ++++ to + (unless no evidence was found) and a consensus score to indicate mean strength of agreement. Further essential elaboration is added below where necessary. The underlying evidence and additional explanatory notes are presented in more detail in the full guideline document.

Diagnostic tests for GCA

Which additional confirmatory diagnostic tests should be performed in all patients with suspected GCA? [Patient, Population or Problem, Intervention, Comparator, Outcome (PICO) 1, 2]

1. Strong recommendation: Patients with suspected GCA should have a confirmatory diagnostic test. This could be either a temporal artery biopsy at least 1 cm in length or an ultrasound of the temporal and axillary arteries, or both. Quality of evidence (QoE): +++. Consensus score: 9.33.

In selecting and interpreting the results of confirmatory diagnostic tests, pretest probability (established on clinical grounds) should be taken into account [15]

Fig. 1 A possible approach to using rapid-access vascular ultrasound to assist in clinical diagnostic decision making in suspected cranial GCA

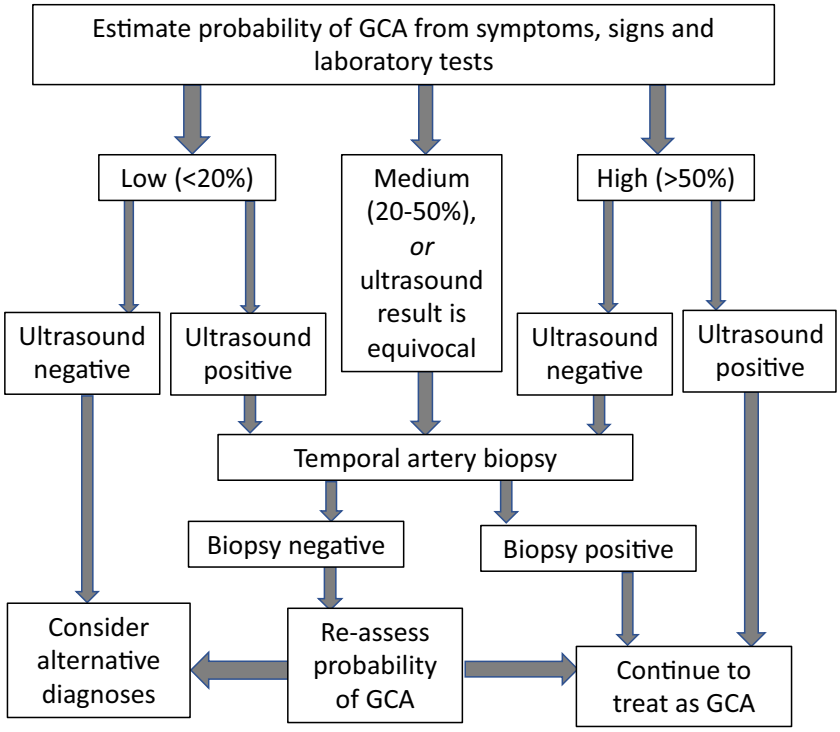

Figure 1 illustrates a possible approach to using rapid-access vascular ultrasound, if available, in suspected GCA. Estimation of the probability of GCA is based on all information available (symptoms, signs, laboratory tests and alternative non-GCA explanations for the clinical picture) and can be updated based on new information (clinical course, results of temporal and axillary ultrasound and/or results of temporal artery biopsy). This assessment is based on clinical judgement and should ideally be performed by an individual with specialist expertise. Note that for a medium (20–50%) estimated probability of GCA, it may be useful to perform an ultrasound prior to biopsy, in case the biopsy is negative. For a high clinical probability of GCA, a positive ultrasound alone may be sufficient, as illustrated here; however, in these cases it is still acceptable to perform a biopsy in addition to ultrasound in order to further increase diagnostic certainty. In the absence of clinical features of cranial GCA, temporal artery biopsy can still be positive, but imaging of the extracranial large vessels may be considered instead of, or in addition to, temporal artery biopsy. Recently various clinical prediction rules have been proposed to assist clinicians in the estimation of probability of GCA; the performance of a clinical prediction rule developed in another setting should ideally be checked using local audit data prior to adoption into local clinical practice. If rapid-access vascular ultrasound is not available, patients treated for suspected GCA should all have a temporal artery biopsy. None of these tests should delay the prescribing of high-dose glucocorticoid therapy for patients with strongly suspected GCA.

(Fig. 1). A positive temporal artery biopsy showing features of inflammation characteristic of GCA, such as giant cells or panarteritis [16], confirms the diagnosis of GCA. Isolated vasa vasorum vasculitis is not diagnostic of GCA. Due to the possibility of skip lesions, the length of the biopsy should be at least 1 cm (post-fixation). Ultrasound is operator dependent and requires adequate training but has the advantage of access to both superficial temporal arteries in their entirety [15]. Where temporal artery histology findings are ambiguous (e.g. low-level inflammation restricted to the adventitia), discussion between the requesting clinician and the pathologist is desirable. In the absence of inflammatory infiltrate, a report of healed arteritis is not sufficient to diagnose GCA.

If neither vascular ultrasound nor biopsy is possible, and local MRI facilities and radiology support are available, then high-resolution 3T MRI of the cranial arteries could be used instead [15].

Which tests can be used to evaluate involvement of the aorta and its proximal branches in GCA? (PICO 2, 3)

2. Conditional recommendation: 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), magnetic resonance angiography (MRA), computed tomography angiography (CTA) or axillary artery ultrasound may be used to evaluate involvement of the aorta and its proximal branches. QoE: +. Consensus score: 9.36.

Since involvement of the aorta and its proximal branches in GCA may be asymptomatic or associated only with constitutional symptoms, in some circumstances directed vascular imaging of the aorta and its proximal branches can be useful to detect inflammation, stenosis or dilatation. FDG-PET can be useful for assessment of vascular inflammation, although it provides less detailed anatomic definition of the involved arteries compared with MRA or CTA. Imaging may also be useful for follow-up assessments. Additional advantages of FDG-PET and CT include potential value in the workup of alternative diagnoses such as malignancy and infection. Ultrasound can assess the axillary arteries, but ultrasound evaluation of the deeper arteries is more difficult.

Treatment of GCA

What is the best dose and route of initial glucocorticoid therapy for GCA in the absence of ischaemic visual manifestations? (PICO 1–3)

3. Conditional recommendation: The standard initial glucocorticoid dose for GCA is 40–60 mg oral prednis(-ol)one per day. QoE: +. Consensus score: 9.44.

The vast majority of patients with GCA respond symptomatically within 1–7 days to a 40–60 mg daily dose of prednis(ol)one, apart from irreversible sequelae such as established visual loss, stroke or tissue necrosis. Failure to respond to this dose should prompt re-evaluation of the diagnosis.

What is the best dose and route of initial glucocorticoid therapy for GCA in the presence of ischaemic visual manifestations? (PICO 4)

4. Conditional recommendation: GCA patients with acute or intermittent visual loss may initially be given 500 mg–1 g intravenous methylprednisolone daily for up to 3 consecutive days before commencing oral prednis(ol)one therapy. If intravenous therapy is not immediately possible, this should not delay initiation of oral prednis(ol)one. QoE: +. Consensus score: 9.00.

Acute visual loss due to ocular ischaemia in GCA requires immediate action. If intravenous glucocorticoid therapy is not possible, 60–100 mg oral prednisolone may be given for up to 3 consecutive days. Clinical trials have not been conducted in patients with acute ocular ischaemia, but observational data indicate that the vast majority of visual loss in GCA occurs before initiation of glucocorticoid therapy [3].

How should glucocorticoid dose be tapered in GCA? (PICO 5)

5. Conditional recommendation: Glucocorticoid dose should be tapered to zero over 12–18 months, providing there is no return of GCA symptoms, signs or laboratory markers of inflammation. A more rapid dose reduction is appropriate for patients at high risk of glucocorticoid toxicity and/or those receiving concomitant glucocorticoid-sparing therapy. QoE: +. Consensus score: 8.81.

All taper schedules assume close and regular clinical follow-up and good communication between patients and care providers should symptoms change (see Tables 2 and 3).

What dosing frequency of oral glucocorticoid should be used in GCA? (PICO 6, 7)

6.Conditional recommendation: Patients should be prescribed a single daily dose of glucocorticoid rather than alternate-day dosing or divided daily dosing. QoE: +. Consensus score: 9.53.

Should modified release prednisone be used in place of standard therapy? (PICO 8)

7.No recommendation can be made for the use of modified release prednisone in the treatment of GCA. QoE: insufficient evidence. Consensus score: 9.72.

When should further, non-biologic immunosuppression be added to glucocorticoid therapy for GCA? (PICO 9, 10)

8. Conditional recommendation: Methotrexate might be considered for GCA, in combination with a glucocorticoid taper, in patients at high risk of glucocorticoid toxicity or who relapse. There is insufficient evidence to recommend any other oral immunosuppressive agent in GCA, including azathioprine, leflunomide or mycophenolate mofetil. QoE: ++. Consensus score: 8.92.

Methotrexate, which may be given orally or by subcutaneous injection, has been used at doses of 7.5–15 mg weekly in clinical studies and up to 25 mg weekly in clinical practice. On the basis of three randomized controlled trials, conducted in patients with recent-onset GCA, the evidence for methotrexate as a glucocorticoid-sparing agent in GCA remains equivocal, acknowledging limitations of the evidence base. In contrast, other immunosuppressants (including azathioprine, leflunomide and mycophenolate) have not been adequately tested in clinical trials. The potential toxicity of dapsone or ciclosporin is likely to outweigh any possible benefit and their use is not recommended.

Which biologic agents can be used for GCA in addition to standard therapy? (PICO 11, 12)

9. Strong recommendation: Tocilizumab can be considered for GCA in combination with a glucocorticoid taper, especially in patients at high risk of glucocorticoid toxicity or who relapse. TNF inhibitors are not recommended in GCA. QoE: +++. Consensus score: 9.61.

Tocilizumab was approved for GCA by the US and European regulatory authorities in 2017 on the basis of two randomized clinical trials [13, 17] of 1 year of tocilizumab *vs* placebo, alongside tapering oral glucocorticoid therapy, demonstrating efficacy for tocilizumab in GCA.

Although efficacy was demonstrated both in new-onset and relapsing GCA, the cost-effectiveness of a glucocorticoid-sparing therapy in GCA is likely to be better in those with relapsing GCA and in those GCA

patients for whom the dose required to control disease activity exceeds the maximum glucocorticoid dose acceptable for that individual, for example, due to comorbidities such as neuropsychiatric glucocorticoid-related adverse effects, previous fragility fractures or difficult-to-control diabetes mellitus.

UK prescribers should be aware that at the time of writing a limited duration of tocilizumab therapy for GCA has been approved by the Scottish Medicines Consortium and by National Health Service England for defined patient groups, taking into account cost-effectiveness data available at the time of the technology appraisal by the National Institute for Health and Care Excellence (TA518).

Clinical trials of TNF inhibitors have failed to demonstrate efficacy in GCA. One small trial of abatacept for GCA has been reported [18], but so far there is insufficient evidence to make a treatment recommendation for this agent.

Should anticoagulant or antiplatelet agents be given for GCA? (PICO 12–15)

10. The routine use of antiplatelet or anticoagulant agents for GCA is not recommended. QoE: insufficient evidence. Consensus score: 9.28.

There is a lack of evidence for the use of antiplatelet or anticoagulant agents specifically for GCA. National and society guidelines for the secondary prevention of coronary and other atherosclerotic vascular diseases should be followed.

Should cholesterol-lowering agents be given for GCA? (PICO 16)

11. The routine use of cholesterol-lowering agents such as statins for GCA is not recommended. QoE: insufficient evidence. Consensus score: 9.53.

There is a lack of evidence for the use of cholesterol-lowering agents specifically for GCA. National and society guidelines for the secondary prevention of coronary and other atherosclerotic vascular diseases should be followed.

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Disclaimer: The views expressed are those of the authors and not necessarily those of the National Institute for Health Research or the UK Department of Health and Social Care.

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