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Diagnosis and management of ANCA associated vasculitis

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Cite this as: *BMJ* 2012;344:e26
doi: 10.1136/bmj.e26

Vasculitides associated with antineutrophil cytoplasmic antibodies (ANCAs) are systemic autoimmune diseases of unknown cause that affect small to medium sized blood vessels. They include granulomatosis with polyangiitis (formerly Wegener's granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome). This review mainly focuses on granulomatosis with polyangiitis and microscopic polyangiitis. Although they are relatively rare, they must be diagnosed and treated early because untreated disease may rapidly develop into multiple organ failure and death. With modern treatment, these diseases are no longer fatal but chronic. Early diagnosis and treatment may prevent progression to end organ damage and lengthen healthier life. A recent large survey of patients with ANCA associated vasculitis found a lag of three to 12 months between disease onset and diagnosis, suggesting that diagnostic delay is a problem.[1] We review the diagnosis and management of ANCA associated vasculitides for the generalist reader, drawing on the findings of observational studies, randomised controlled trials, and meta-analyses.

SOURCES AND SELECTION CRITERIA

We searched PubMed (original search performed in August 2011, updated in December 2011) for relevant articles on epidemiology, diagnosis, and management of antineutrophil cytoplasmic antibody (ANCA) associated vasculitis. Where possible, we sought data from prospective randomised clinical trials and meta-analyses. We also screened personal archives for relevant papers and consulted experts in otolaryngology (NR), nephrology (DJ), and rheumatology (RL). All relevant keyword variations were used. All searches contained the keywords "ANCA" or "vasculitis", or both. We limited results to articles written in English.

Who gets it?

The overall annual incidence of ANCA associated vasculitis in Europe and Northern America is about 20 per million (with point prevalence of 130/million for granulomatosis with polyangiitis and 47.9/million for microscopic polyangiitis in the United Kingdom in 2008).[2] Disease onset usually occurs at 65-74 years, although it can occur at any age. Prevalence is generally higher in men, but women more often develop disease at a younger age.[1] The overall prevalence of ANCA associated vasculitis is highest in white people.[1 3] The incidence of granulomatosis with polyangiitis is higher in northern Europe, whereas that of microscopic polyangiitis is higher in southern Europe and Japan.[2 4]

SUMMARY POINTS

- Consider antineutrophil cytoplasmic antibody (ANCA) associated vasculitis when inflammatory disease cannot be ascribed to any other disease and inflammation progresses despite antibiotics
- Avoid diagnostic delay to prevent end organ damage, particularly renal disease
- Test for ANCA in patients with chronic destructive upper airway disease, pulmonary nodules, renal and pulmonary inflammatory disease, rapidly progressive glomerulonephritis, skin vasculitis with systemic illness, mononeuritis multiplex, subglottic stenosis of the trachea, and retro-orbital mass
- Patients should be managed by a specialist in vasculitides
- Remission is usually induced with high dose glucocorticoids and cyclophosphamide, followed by remission maintenance treatment
- Adverse responses to treatment are common, as are relapses, so long term follow-up is needed

How do patients present?

Patients typically present with prodromal "flu-like" symptoms of several weeks' or months' duration,[5 6] such as fever, polymyalgia, polyarthralgia, headache, malaise, anorexia, and unintended weight loss. These non-specific symptoms overlap with symptoms of non-vasculitic processes such as post-viral syndrome, infections, or malignancy. Consider vasculitis as a differential diagnosis in patients with general symptoms and signs of inflammatory disease. Some patients may initially present with focal vasculitic disease such as rash, cutaneous vasculitis, bloody-purulent rhinitis, scleritis, or arthritis. In such patients, careful examination of other organ systems may show other disease manifestations.

The figure shows the many ways in which vasculitis can manifest. Patients may report different symptoms over time. Symptoms of the different ANCA associated vasculitides overlap, but some symptoms are more common in certain diseases. For example, ear, nose, and throat problems—such as hearing loss, otalgia, (bloody) rhinorrhoea, otorrhoea, sinusitis, nasal crusting, and recurrent otitis media—occur in about 90% of patients with granulomatosis with polyangiitis and in 35% of those with microscopic polyangiitis.[5 6] Large observational studies have shown that the airways and lung parenchyma are commonly affected, as are the kidneys, although this may not be apparent until renal failure occurs.[5 7 8] Urinalysis may therefore identify renal involvement early on in the disease. About 50% of patients have cutaneous manifestations of disease such as urticarial rash or tender skin nodules. The eyes and nervous system are also commonly affected.[5 7 8] A careful physical examination is needed to determine the full extent of disease.

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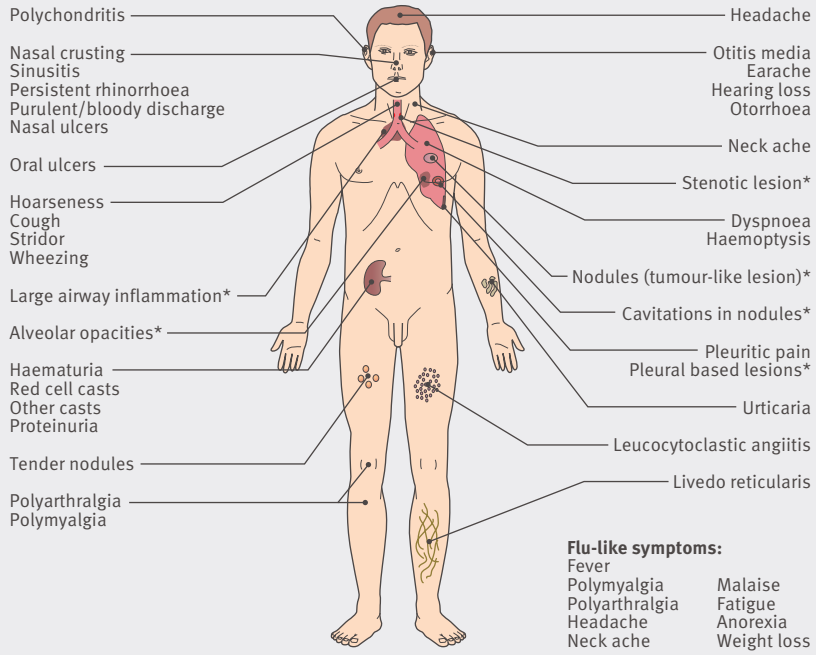

Clinical manifestations of antineutrophil cytoplasmic antibody associated vasculitis. Alveolar haemorrhage is an important cause of mortality. Renal involvement manifests with early detectable haematuria, red cell and other casts, and proteinuria. It is an important cause of morbidity and mortality. The most common skin lesion is leucocytoclastic angiitis, which mostly causes purpura on the lower extremities, sometimes accompanied by focal necrosis and ulcerations. Skin lesions can appear on parts of the body not shown here. Eye disease presents as a painful or painless red eye. Mononeuritis multiplex is seen in 20% of patients. *These lesions can be seen on chest radiography and computed tomography

Properties of ANCA tests and their clinical importance

	PR3-ANCA	MPO-ANCA
Test methods	Finely granular staining of the cytoplasm (c-ANCA) is seen on IIF; PR3 is the antigen in direct, capture, anchor, and luminex ELISAs	Perinuclear staining of the neutrophils (p-ANCA) is seen on IIF; MPO is used as the antigen in direct, capture, and luminex ELISAs
Diagnostic potential	Almost all patients in northern Europe with untreated acute granulomatosis with polyangiitis will be positive	Most patients in northern Europe with untreated acute microscopic polyangiitis and some with granulomatosis with polyangiitis will be positive
Relation to disease activity	Immunomodulatory treatment reduces positivity for PR3-ANCA but positivity increases when treatment is tapered off; reappearance of PR3-ANCA in non-treated patients may reflect disease activity	Immunomodulatory treatment also reduces positivity for MPO-ANCA and it increases when treatment is tapered off, but fluctuations often occur that are not related to disease activity

ANCA=antineutrophil cytoplasmic autoantibody; ELISA=enzyme linked immunosorbent assay; IIF=indirect immunofluorescence; MPO=myeloperoxidase; PR3=proteinase 3.

Box 1 | Targeted testing for antineutrophil cytoplasmic antibodies

Test when patients have one or more of the following sets of symptoms:

- General: Persistent flu-like condition with headache, myalgias, arthralgias, and weight loss
- Ear, nose, and throat: Hearing loss that slowly develops over days to weeks without a preceding cold, but with "chronic flu"; slowly developing nasal stenosis with midfacial pain and increasing bloody-purulent secretion with crust formation that does not respond to antibiotics (granulomatosis with polyangiitis)
- Eyes: Unexplained conjunctivitis combined with general symptoms, uveitis, unilateral proptosis, and paresis of the ocular motor nerves (granulomatosis with polyangiitis)
- Lungs: Slowly developing cough and shortness of breath possibly with bloody-purulent sputum, bilateral infiltrates on radiography that do not respond to antibiotics, non-tuberculous cavitating lesions (granulomatosis with polyangiitis), alveolar haemorrhage (microscopic polyangiitis)
- Skin: Bursts of small cutaneous vasculitis elements, pyoderma gangrenosum, and oedema
- Kidneys: Haematuria, proteinuria, hypertension, decreasing renal function (granulomatosis with polyangiitis and microscopic polyangiitis)

How can it be diagnosed?

Investigations that can be undertaken in primary care

Blood tests requested in primary care may show leucocytosis, thrombocytosis, raised erythrocyte sedimentation rate and C reactive protein values, normochromic-normocytic anaemia, and a raised serum creatinine.[5] Patients with symptoms and signs of vasculitis and abnormalities on these blood tests require urinalysis, including urinary sedimentation, to look for haematuria and proteinuria. An increased serum creatinine indicates that renal damage has already occurred. Chest radiography in patients with pulmonary symptoms such as dyspnoea, cough, or haemoptysis may show infiltrates, nodules, or cavitations in the lung parenchyma.

An ANCA assay can be requested in primary care. The test is indicated in a patient with unexplained illness that has lasted more than a few weeks (box 1) and is associated with a raised erythrocyte sedimentation rate or C reactive protein, particularly if more than one organ system is affected. Four large international randomised controlled trials found that the test is positive in 90-95% of patients with active generalised granulomatosis with polyangiitis or microscopic polyangiitis before treatment.[9-12] Two types of assay are generally used: indirect immunofluorescence (IIF) and the enzyme linked immunosorbent assay (ELISA). The table outlines the properties of these tests. An international multicentre observational study found that IIF is more sensitive but that ELISA is more specific.[13] The current international standard approach is to use IIF as a screening test and ELISA to confirm positive results.[14] ANCA assays should be performed only in experienced laboratories. Testing is not standardised, so sensitivity and specificity vary between laboratories and reference values are unavailable. Although the ANCA test is positive in most patients with untreated disease, a negative result does not exclude the diagnosis of ANCA associated vasculitis because 5-10% of patients do not develop ANCA. Neither does a negative ANCA test exclude the presence of other non-ANCA associated small and medium vessel vasculitic syndromes. Such patients may require more systematic investigation to ascertain the extent of their disease.

Refer any patient with a positive ANCA test result to a specialist in vasculitis, usually a rheumatologist or a nephrologist, or possibly a chest physician or ear, nose, and throat surgeon, depending on clinical presentation. Referral to specialists without experience with vasculitis may delay diagnosis. Many conditions can be associated with a positive ANCA test result, including inflammatory bowel disease, chronic infections (such as tuberculosis), and autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis, and ANCA can be induced by several drugs. This highlights the need

ADDITIONAL EDUCATIONAL RESOURCES

Resources for clinicians

Europe European Vaculitis Society (www.vasculitis.org/) and US Vasculitis Clinical Research Consortium (http://rarediseasesnetwork.epi.usf.edu/vcrc/)—Research collaboratives that focus on vasculitis

Johns Hopkins Vasculitis Center (www.hopkinsvasculitis.org/)—Provides detailed information on vasculitis

Fries JF, Hunder GG, Bloch DA, Michel BA, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. *Arthritis Rheum* 1990;33:1135-6

Resources for patients

Vasculitis Foundation (www.vasculitisfoundation.org)—US website providing relevant information for doctors and patients

Vasculitis Foundation Canada (www.vasculitis.ca)—Canadian website providing information and support for patients

The Dutch Vasculitis Patient Foundation (www.vasculitis.nl)—Dutch website providing useful information for medical professionals and patients

Vasculitis UK (www.vasculitis-uk.org.uk/news.html)—Provides information on vasculitis and on local support groups

A PATIENT'S PERSPECTIVE

Nine years ago I visited my general practitioner with pain in my right knee. He tested twice for rheumatoid arthritis but the results were negative. I was then referred to the rheumatologist at the university clinic. A few months later most of my joints were affected and it seemed that I would be condemned to a wheelchair. The rheumatologist diagnosed rheumatoid arthritis and treated me accordingly. One month later my condition had worsened—I was vomiting two or three times a day, my eyes were reddish, and I had nasal crusting. My rheumatologist had seen a patient with these symptoms once before and she tested me for various factors including antineutrophil cytoplasmic antibody. The next day I was seen by her and a nephrologist. The new diagnosis was Wegener's granulomatosis. This news was a blessing in disguise. I would probably walk again, but I had lost 50% of my renal function. My treatment consisted of heavy immunosuppression including corticosteroids. Over the nine years that followed I had two cataract operations, a prosthetic knee implant, many erythropoietin injections, and a kidney transplant (a gift from my wife); I also experienced Guillain-Barré syndrome, cerebral haemorrhage, and constant bronchitis. Now I am fine. At the age of 69, I now have enough energy to enjoy life.

Henk van Wilpe, Utrecht

for judicious testing. The clinical setting in which the test is performed is crucial for interpreting the results. We recommend ANCA testing routinely in the following circumstances: acute or chronic destructive upper airway disease; evidence of renal inflammatory disease as indicated by an active urine sediment or laboratory parameters indicative of rapidly progressive glomerulonephritis; evidence of pulmonary inflammatory disease as indicated by a variety of clinical symptoms or radiographic abnormalities; skin vasculitis associated with systemic illness; and mononeuritis multiplex. ANCA testing is also indicated in subglottic stenosis of the trachea manifesting as slowly progressive dyspnoea and retro-orbital mass manifesting as protrusion of the eye bulb and diplopia, although these conditions may be difficult to recognise without specialist tests.

Box 2 | Side effects of commonly used immunosuppressive agents

Cyclophosphamide*: Leucopenia or neutropenia, infections (usually respiratory and urinary tract), infertility, cancer (especially bladder cancer and leukaemia), haemorrhagic cystitis, alopecia, and amenorrhoea

Glucocorticoids: Osteoporosis, candida infection (oral and vaginal), other infections, weight gain, hyperglycaemia or diabetes, hypertension, cushingoid appearance, skin atrophy, and cataract

Azathioprine: Nausea, leucopenia or neutropenia, infection, hypersensitivity, cancer, alopecia, cholestasis, and thrombocytopenia

Methotrexate: Nausea, oral ulcers, liver dysfunction, infection, hypertension, leucopenia

Mycophenolate mofetil: infection, leucopenia, gastrointestinal tract manifestations, anaemia, thrombocytopenia

Rituximab: Infections (encephalitis is particularly dangerous), cancer, anaemia, neutropenia, thrombocytopenia, hypogammaglobulinaemia

*Cyclophosphamide can be given in two ways: daily oral cyclophosphamide and pulse cyclophosphamide. In the CYCLOPS trial the group that received pulse cyclophosphamide had significantly less leucopenia than the daily oral group. During pulse administration, the patient can be given prehydration and 2-mercaptoethanesulfonate sodium to protect the bladder against the toxicity of cyclophosphamide.[10]

How is ANCA associated vasculitis currently treated?

Standard treatment consists of inducing remission with high dose glucocorticoids and high dose oral or intravenous pulse cyclophosphamide for three to six months, and maintaining remission with azathioprine or methotrexate while glucocorticoids are slowly reduced and withdrawn.[15]

Treatment requires specialist supervision; it aims to control disease activity to prevent further damage to organs and to prevent the recurrence of vasculitis. Managing treatment toxicity is an important part of patient care, and the general practitioner may be confronted with this problem (box 2).

In the longer term, regular visits to the specialist are needed (every three months at least) to check on disease activity and treatment side effects, and to manage the consequences of irreversible tissue damage, such as renal failure.

With modern treatment ANCA associated vasculitis has changed from being an imminently life threatening condition to a chronic condition prone to relapse throughout life. A large observational study of 107 patients found that about 50% of treated patients experience one or more relapses by five years.[16]

What is the long term outlook for patients with ANCA associated vasculitis?

With modern treatment the disease has changed from being universally fatal to being a chronic relapsing and remitting disease. Several organs are often affected; renal involvement is common, and glomerulonephritis results in end stage renal failure and a need for renal replacement in 20-40% of patients according to observational studies (within a median follow-up of 3.1 to ≥5 years).[17-20]

The risk of death for patients treated with current treatments is still 2.6 times higher than that of age matched background controls.[21] The increased risk of death is greatest in the first year after diagnosis, when infections and active vasculitis account for most early deaths. Patients are at lifelong increased risk of infections and often need treatment with antibiotics. In a population based case-control study, many patients reported fatigue, which affected employment and overall quality of life, as a major problem.[22] The socioeconomic impact of the disease, however, has proved difficult to assess.[23]

What should generalists be aware of with regard to treatment?

Patients may turn to their general practitioner for support and information. The first few weeks of treatment can be difficult because patients usually still have symptoms associated with vasculitis. Frequent hospital visits and blood tests are needed to monitor disease activity and response to treatment.

Before each treatment with high dose cyclophosphamide, platelet and white cell counts, particularly the neutrophil count, must be above the lower limit of normal and liver function must be stable. Creatinine concentrations are needed to make dose adjustments. For daily oral cyclophosphamide, azathioprine, or mycophenolate mofetil, and for weekly methotrexate, routine monitoring of blood counts, liver function, and renal function is important to avoid drug toxicity. It is usually more convenient for patients to attend the primary care practice for these routine blood tests, but this requires good communication between primary care and secondary care. Guidelines on how treatment should be changed in response to unexpected results should be agreed before treatment.

Patients are susceptible to infections particularly during induction treatment (most usually respiratory or urinary tract infections), and early intervention with antibiotics is necessary for confirmed infections. In the case of pulse cyclophosphamide, which is routinely followed by antiemetics and oral antifungal treatment, the most vulnerable time for patients is seven to 10 days after each pulse. The drug suppresses the bone marrow, causing neutropenia and increased risk of infection. Patients are advised not to visit or be visited by anyone with an upper or lower respiratory tract infection during this time. Patients on pulse cyclophosphamide may become profoundly tired in the two to three days after administration but will gradually improve. However, be aware of potential drug interactions. For example, patients with granulomatosis with polyangiitis may be treated with high doses of methotrexate and could develop severe neutropenia if treated for a urinary tract infection with standard dose co-trimoxazole; prophylactic use of low dose co-trimoxazole (960 mg three times a week) is therefore suggested as standard concomitant treatment with methotrexate.

Remember to consider consequences of damage caused by the disease, such as chronic kidney disease, and the effects of treatment, such as osteoporosis and impaired glycaemic control caused by chronic exposure to glucocorticoids. Patients are also at increased risk of cancer and premature and accelerated atherosclerosis, which predisposes them to early cardiovascular disease, including strokes.[24-28] It is important to control and treat all well known cardiovascular risk factors. Three observational studies found an increased incidence of venous thromboembolic events, which did not seem to be attributable to classic prothrombic risk factors.[29-31] Proton pomp inhibitors are prescribed to prevent mucosal damage of the stomach as a result of high doses of glucocorticoids. Patients taking immunosuppressive drugs usually require prophylaxis with co-trimoxazole because of an increased risk of acquiring *Pneumocystis jiroveci* pneumonia (box 3).

Because relapse can occur after many years in remission, patients often remain on indefinite follow-up. Disease flares are common and patients must be encouraged to seek urgent medical attention if they experience a flare—that is, recurrence, deterioration, or new onset of symptoms and signs attributable to active vasculitis (box 4). If patients have a flare or experience serious complications of treatment they may require hospital admission. If

Box 3 | Important points for generalists

Regularly follow up the patient and be aware of some specific problems and prophylactic strategies*

Specific problems and prophylactic strategies

- Osteoporosis: Use of bisphosphonates
- Cardiovascular disease: Use of statins and smoking cessation
- Hyperglycaemia or diabetes: Regular glycaemic control
- Hypertension: Regular blood pressure control
- Gastric mucosal damage: Use of a proton pump inhibitor
- Oral ulcers: Use of folic acid or folinic acid
- *Pneumocystis jiroveci* pneumonia: Prophylactic co-trimoxazole
- Fatigue: Informal support or formal counselling

*The specialist will supervise this, but generalists need to be aware. If one of these problems occurs, the patient must be seen immediately by the doctor in charge at the vasculitis clinic. Rapid referral to specialist care is also needed if patients become ill with no obvious cause, especially if they report unusual symptoms

QUESTIONS FOR FUTURE RESEARCH

What is the optimum duration of maintenance treatment? This question may be answered by the findings of the REMAIN trial (AVERT project BIOMED-2: BMH-CT93-1078, trial registration number REMAIN 08.022006; www.vasculitis.org) conducted by EUVAS, which is investigating benefits of prolonged maintenance treatment

With increasing insights into the pathogenesis of the disease and the detection of new biomarkers might new targeted treatments replace existing standard treatments?

How might we develop patient tailored treatments for patients on the basis of clinical signs and symptoms in combination with genetic information? CCX168, an antagonist of complement factor C5a, is currently a candidate for clinical development

What are the benefits of plasma exchange? A EUVAS/Vasculitis Clinical Research Consortium (VCRC) trial (PEXIVAS), which is designed to confirm and further explore the benefit of adjuvant plasma exchange, is currently under way

A question that is important to patients is "How can fatigue associated with vasculitis and its treatment be managed?"

What causes the development of antineutrophil cytoplasmic antibodies (ANCAs) and how do we prevent ANCA associated vasculitis? More basic research studies are needed to answer these questions

Box 4 | Characteristics of a flare

Flare: Recurrence, deterioration, or new onset of symptoms and signs attributable to active vasculitis

Major flare: Recurrence, deterioration, or new onset of at least one item on the Birmingham vasculitis activity score,[32] indicating a threat to vital organ function as a result of active vasculitis. Examples include:

- 30% increase of creatinine or 25% decrease of glomerular filtration rate within three months
- Evidence of severe pulmonary haemorrhage or granulomata
- Threatened vision (including orbital granuloma and retinal vasculitis)
- Sensorineural deafness
- New multifocal neurological lesions or mononeuritis multiplex
- Gastrointestinal haemorrhage or perforation

Minor flare: Recurrence, deterioration, or new onset of at least three other items on the Birmingham vasculitis activity score related to non-vital organs attributable to active vasculitis. Examples include:

- Epistaxis, nasal crusting, lesions on nasal endoscopy
- Conductive deafness
- Deafness
- Rash
- Myalgia, arthralgia, arthritis
- (Epi)scleritis

Pulmonary symptoms not characteristic of a major relapse

early symptoms are missed or ignored a serious episode of vasculitis with renal or respiratory failure may ensue. Patients are usually educated to look out for early symptoms of relapse so that this kind of avoidable disaster can be prevented.

Contributors: IB had the idea for the article. AB and AG did the literature search. AB, AG, IB, DJ, RL, NR, and JAB wrote and revised sections with which they were most familiar. AB, AG, and IB were involved throughout the process and did the final editing. AB is guarantor.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: DJ has received a grant and consulting fee/honorarium from Roche; RL does consultancy work for Chemocentryx and Nordic, reports for solicitors on individual cases (expert testimony), is in discussion with Nordic for administrative support to oversee data collection for a Nordic funded study in vasculitis (grants/grants pending), gets paid for lectures including service on speakers' bureau for UCB, receives royalties from EPS research for software that he originally designed to manage use of biological therapy within NICE guidelines, and receives travel, accommodation, and registration fees to attend the annual American College of Rheumatology and European League Against Rheumatism meetings; NR is paid for lectures including service on speakers' bureaux for Phadia and EuroDiagnostica; IB does consultancy work for Roche on lupus nephritis; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent obtained.

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