2020 international consensus on ANCA testing beyond systemic vasculitis

Sergey Moiseev[1], MD, PhD, Jan Willem Cohen Tervaert[2], MD, PhD, Yoshihiro Arimura[3], MD, PhD, Dimitrios P. Bogdanos[4], MD, PhD, Elena Csernok[5], MD, PhD, Jan Damoiseaux[6], MD, PhD, Iris Dotan[7], MD, PhD, Marc Ferrante[8], MD, PhD, Luis Felipe Flores-Suárez[9], MD, PhD, Marvin J Fritzler[10], MD, PhD, Pietro Invernizzi[11], MD, PhD, David Jayne[12], MD, PhD, J. Charles Jennette[13], MD, PhD, Mark Little[14], MD, PhD, Stephen P. McAdoo[15], MD, PhD, Pavel Novikov[1], MD, PhD, Charles D. Pusey[15], MD, PhD, Antonella Radice[16], MD, PhD, Alan D. Salama[17], MD, PhD, Judith A. Savige[18], MD, PhD, Mårten Segelmark[19], MD, PhD, Yehuda Shoenfeld[20], MD, PhD, Renato Sinico[21], MD, PhD, Maria-José Sousa[22], MD, PhD, Ulrich Specks[23], MD, PhD, Benjamin Terrier[24], MD, PhD, Athanasios G. Tzioufas[25], MD, PhD, Severine Vermeire[8], MD, PhD, Ming-Hui Zhao[26], MD, PhD, Xavier Bossuyt[27], MD, PhD

[1]Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia,

[2]Department of Medicine, Division of Rheumatology, University of Alberta, Edmonton, Canada and Maastricht University, Maastricht, The Netherlands,

[3]Department of Nephrology and Rheumatology, Kyorin University School of Medicine, Tokyo, Japan,

[4]Department of Rheumatology and Clinical Immunology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Biopolis, Larissa, Greece,

[5]Department of Internal Medicine, Rheumatology and Immunology, Vasculitis-Center Tübingen-Kirchheim, Medius Klinik Kirchheim, University of Tübingen, Kirchheim-Teck, Germany,

[6]Maastricht University Medical Centre, Maastricht, Netherlands,

[7]Sackler Faculty of Medicine, Tel Aviv University, Division of Gastroenterology, Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel,

[8]University Hospitals Leuven, Department of Gastroenterology and Hepatology, KU Leuven, Leuven, Belgium,

[9]Instituto Nacional de Enfermedades Respiratorias, Mexico, Mexico City, Mexico,

[10]Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada,

[11]Division Gastroenterology and Center for Autoimmune Liver Diseases, University of Milano - Bicocca School of Medicine, Monza, Italy,

[12]Department of Medicine, University of Cambridge, Cambridge, UK,

[13]Division of Nephropathology, School of Medicine, University of North Carolina, Chapel Hill, NC, USA,

[14]Trinity Health Kidney Centre, Trinity Translational Medicine Institute, Dublin, Ireland,

[15]Centre for Inflammatory Disease, Department of Medicine, Imperial College London, London, UK,

[16]Microbiology and Virology Institute, ASST Santi Paolo e Carlo, San Carlo Borromeo Hospital, Milan, Italy,

[17]Department of Renal Medicine, University College London, Royal Free Hospital, London, UK,

[18]Department of Medicine, Melbourne Health, University of Melbourne, Melbourne, Australia,

[19]Department of Clinical Sciences, Lund University, Department of Nephrology and Rheumatology, Skane University Hospital, Lund, Sweden,

[20]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, Sechenov First Moscow State Medical University, Moscow, Russia,

[21]Department of Medicine and Surgery, Università degli Studi di Milano-Bicocca, Monza, Italy,

[22]Immunopathology and Autoimmunity Department, Centro de Medicina Laboratorial Germano de Sousa, Lisbon, Portugal,

[23]Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA,

[24]Department of Internal Medicine, National Referral Center for Rare Systemic and Autoimmune Diseases, Hôpital Cochin, Paris, France,

[25]Department of Pathophysiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece,

[26]Renal Division, Peking University First Hospital; Key Laboratory of Renal Disease, Ministry of Health of China; Key Laboratory of CKD Prevention and Treatment, Ministry of Education of China; Peking-Tsinghua Centre for Life Sciences; Beijing, China,

[27]Laboratory Medicine, University Hospitals Leuven, Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium,

This document follows up on a 2017 revised international consensus on anti-neutrophil cytoplasm antibodies (ANCA) testing in granulomatosis with polyangiitis and microscopic polyangiitis and focuses on the clinical and diagnostic value of ANCA detection in patients with connective tissue diseases, idiopathic interstitial pneumonia, autoimmune liver diseases, inflammatory bowel diseases, anti-glomerular basement membrane (GBM) disease, infections, malignancy, and during drug treatment. Current evidence suggests that in certain settings beyond systemic vasculitis, ANCA may have clinical, pathogenic and/or diagnostic relevance. Antigen-specific ANCA targeting proteinase-3 and myeloperoxidase should be tested by solid phase immunoassays in any patient with clinical features suggesting ANCA-associated vasculitis and in all patients with anti-GBM disease, idiopathic interstitial pneumonia, and infective endocarditis associated with nephritis, whereas in patients with other aforementioned disorders routine ANCA testing is not recommended. Among patients with autoimmune liver diseases or inflammatory bowel diseases, ANCA testing may be justified in patients with suspected autoimmune hepatitis type 1 who do not have conventional autoantibodies or in case of diagnostic uncertainty to discriminate ulcerative colitis from Crohn's disease. In these cases, ANCA should be tested by indirect immunofluorescence as the target antigens are not yet well characterized. Many questions concerning the optimal use of ANCA testing in patients without ANCA-associated vasculitis remain to be answered.

Testing for anti-neutrophil cytoplasm antibodies (ANCA) directed towards proteinase 3 (PR3) and myeloperoxidase (MPO) is commonly performed to support the diagnosis of ANCA-associated vasculitides (AAV) that encompasses granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). In 2017, a revised international consensus on testing of ANCA in GPA and MPA was proposed [1]. This consensus document focused on ANCA testing in AAV and briefly described other conditions that were reported to be associated with ANCA positivity, mostly in the context of the differential diagnosis of other inflammatory diseases [2]. The current document is a follow-up on the previous consensus statements [1,3,4] and highlights the clinical and

diagnostic value of ANCA testing in patients with various autoimmune, infectious and neoplastic diseases. However, the number of high quality studies addressing this issue is limited, and many unresolved issues concerning the optimal use of ANCA testing in non-AAV remain to be elucidated.

Methods

This Consensus Statement was prepared by a group of experts based on the results of a comprehensive search in PubMed for disorders that can be associated with ANCA-positivity, by using a variety of search terms, and all relevant available literature was critical reviewed. Additional publications were identified in the references of the available articles. The resulting manuscript was distributed by email to 30 experts from four continents (Australia, Belgium, Canada, China, France, Germany, Greece, Ireland, Israel, Italy, Japan, Mexico, Portugal, Russia, Sweden, the Netherlands, UK, USA). Experts included rheumatologists, nephrologists, pulmonologists, gastroenterologists/hepatologists, pathologists, clinical immunologists and/or specialists in laboratory medicine and were selected based on their expertise and knowledge in clinical and laboratory aspects of ANCA testing. All contributors approved the final document and voted for each statement using a 5-point Lickert scale (strongly disagree, disagree, uncertain, agree, and strongly agree). The definition for consensus included percentage agreement at least 75% and the median score greater or equal to 4.

Methods for ANCA detection and nomenclature

ANCA can be screened by indirect immunofluorescence (IIF) using ethanol fixed neutrophils. The antibodies that bind to the neutrophils are visualized with a fluorescence microscope after staining with fluorescein-labeled anti-human antibodies. A titer and a pattern are reported. Two major patterns are reported: a cytoplasmic pattern (C-ANCA) and a perinuclear pattern (P-ANCA) (with or without nuclear extension). Antibodies to proteinase-3 typically give a C-ANCA pattern with central or interlobular accentuation, whereas antibodies to myeloperoxidase typically give a P-ANCA pattern with nuclear extension [5]. P-ANCA can also be found in patients with antibodies to other antigens such as elastase, cathepsin G, lactoferrin,

lysozyme [5]. P-ANCA is indistinguishable from anti-nuclear antibodies (ANA). Antibodies to bactericidal permeability increasing protein give an atypical C-ANCA without interlobular accentuation [5].

Solid phase immunoassays, e.g. enzyme-linked immunosorbent assay (ELISA), fluoro-enzyme immunoassay, chemiluminescence immunoassay, laser bead immunoassay, dot/line blot, are used for detection of specific antibodies to proteinase-3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA) [6]. The antigens (PR3 or MPO) can be directly attached to the solid phase or indirectly, either through a monoclonal capture antibody or through a smaller anchor molecule (e.g. biotin). Autoantibodies that bind to the antigen (PR3 or MPO) are complexed with a detection antibody.

Rheumatoid arthritis

Draibe and Salama reported 6 patients who developed AAV at a median of 10.5 years after the diagnosis of RA, and 29 additional cases with RA/AAV overlap described in the literature [7]. MPA and MPO-ANCA positivity were most common. Seventy four percent of the reported patients presented with kidney involvement. A few patients with RA and renal-limited AAV have also been reported [8]. Treatment with tumor necrosis factor (TNF) α inhibitors was reported to contribute to the development of AAV in some RA patients [9,10].

P-ANCA, previously called granulocyte-specific antinuclear antibody (GS-ANA), was originally described in patients with Felty's syndrome [11] and later detected in 50% to 70% of patients with RA complicated by vasculitis and in 20% to 40% of patients with RA uncomplicated by vasculitis or Felty's syndrome [12,13]. GS-ANA had been mistakenly thought to be caused by anti-nuclear antibodies until the discovery that MPO-ANCA bind to nuclei causing perinuclear staining (P-ANCA pattern) [14]. In subsequent studies, the reported prevalence of P-ANCA by IIF in RA varied from 16% to 50% [15-19]. However, MPO-ANCA positivity by antigen-specific immunoassays was confirmed in only 0-4% of patients (up to 18% in one study) [18,20]. Some authors suggested that P-ANCA positivity in RA may correlate with disease activity and severity [15-17,19]. However, this correlation was not confirmed in other studies [18,21]. Other ANCA-related autoantigens were detected in RA, including cathepsins, elastase and lactoferrin, but were not found to have clinical utility [22].

In summary, the largest studies reported P-ANCA positivity by IIF in 15-20% of RA patients. However, the presence of MPO-ANCA was a relatively rare finding in RA. The evidence demonstrating clinical implication of ANCA positivity for assessing the disease activity or predicting the progression of joint destruction in RA patients is conflicting. MPO-ANCA testing by antigen-specific immunoassays may be justified in RA patients who develop kidney disease, particularly in the presence of necrotizing pauci-immune glomerulonephritis on renal biopsy, and when other signs of AAV are present such as necrotizing scleritis or mononeuritis multiplex.

Systemic lupus erythematosus

Jarrot et al described 8 patients with systemic lupus erythematosus (SLE)/AAV overlap syndrome through a survey of 3300 cases of vasculitis and identified 31 previously reported cases [23]. Patients with SLE/AAV overlap syndrome were mostly female, and usually presented with MPO-ANCA positive rapidly progressive glomerulonephritis, joint and skin disease, and frequent pulmonary involvement. Renal biopsies, classified as either lupus nephritis or pauci-immune glomerulonephritis, showed overlapping lesions in some cases. All patients were positive for ANA, whereas anti-dsDNA were detected in 50% of cases.

P-ANCA positivity was first documented in patients with SLE in the early 1990's [24]. Schnabel et al. detected ANCA by IIF in 40 of the 157 sera (25%) from patients with SLE [25]. Only a P-ANCA pattern of fluorescence was seen. By ELISA testing, 16 sera reacted to lactoferrin, 8 to elastase, and 4 to lysozyme. Notably, there was no correlation of ANCA results with lupus vasculitis. In a more recent large study, ANCA were detected by IIF in 16.4% of 566 European patients with SLE, whereas MPO-ANCA and PR3-ANCA by ELISA were found in 9.3% and 1.7% of patients, respectively [26]. Of note, ANA, usually at high titres, can produce IIF staining patterns on ethanol-fixed neutrophils that may be indistinguishable from P-ANCA. In smaller studies, the reported prevalence of P-ANCA varied from 14.0 to 31.4%, of MPO-ANCA from 0 to 23.8%, and of PR3-ANCA from 0 to 12.7% [27]. In one study, MPO-ANCA was more frequently encountered in patients with crescentic lupus nephritis than in patients with noncrescentic lupus nephritis (21.2% vs. 0.8%) [28]. As in RA patients, other specificities were found besides those targeting PR3

and MPO. In one study, ANCA for lactoferrin were detected in 14.3% of SLE patients [26].

Recently, Turner-Stokes et al. found that antigen-specific ANCA-positive patients with lupus nephritis tended to have a more segmental and necrotizing pattern of glomerular inflammation on renal biopsy, serologically more active disease, and a worse baseline renal function compared to ANCA-negative patients [29]. However, there was no significant difference in the time to death or renal replacement therapy between the two groups. The authors suggested that ANCA may mediate distinct mechanisms of glomerular inflammation in patients with lupus nephritis, superimposed on the effects of immune complex deposition. In another study, antigen-specific ANCA-positivity in 49 patients with biopsy-proven lupus nephritis was associated with massive haematuria, advanced renal failure, and higher activity index and chronicity index scores, including cellular crescents, interstitial inflammation, tubular atrophy and interstitial fibrosis [30]. In a retrospective case-control study, MPO-ANCA were found prior to clinical lupus nephritis and predicted its development [31].

In summary, SLE may overlap with AAV in a small proportion of patients. By antigen-specific assays, ANCA-positivity (particularly MPO-ANCA) is not uncommon in SLE patients, but this could be due to technical issues. It has been proposed that sera containing high levels of anti-dsDNA antibodies may cause false positive results in MPO-ANCA assays due to charge interactions between DNA in sera and MPO [32,33]. The clinical implication of the presence of ANCA in SLE is not established, although it may be associated with a more severe glomerulonephritis.

Systemic sclerosis

Autoantibody profiles in systemic sclerosis (SSc) are important for diagnosis and a stratified approach to patient management [34,35]. In several relatively small studies, the prevalence of ANCA-positivity (mainly MPO-ANCA) in SSc varied from 0 to 9.1% [36-39]. Only a few ANCA-positive SSc patients had documented AAV. In a clinical database of 2,200 patients with SSc, 8 (0.4%) patients had AAV, usually manifesting as glomerulonephritis and pulmonary fibrosis [40]. In another retrospective study of 3,570 SSc patients, Kant et al identified 7 (0.2%) patients who

developed MPO-ANCA associated crescentic glomerulonephritis within 6 years of the diagnosis of SSc [41].

Quéméneur et al. reviewed 51 SSc cases associated with AAV [42]. D-penicillamine was implicated as a possible cause of AAV in 8 patients. The majority of the 51 AAV patients tested positive for MPO-ANCA and were diagnosed with MPA or renal limited vasculitis with rapidly progressive glomerulonephritis. The latter can be confused with scleroderma renal crisis (SRC) [34]. Normotensive renal failure, although reported in about 10% of cases of SRC, and markers of inflammation, such as fever and elevated acute phase reactants, may indicate underlying AAV [43,44]. A nephritic urinary sediment can help to differentiate renal vasculitis from scleroderma renal crisis, however, a kidney biopsy is required to confirm a diagnosis of pauci-immune crescentic glomerulonephritis.

In the Australian Scleroderma Cohort Study, ANCA was detected by IIF in 116 (8.9%) of 1303 patients, whereas MPO-ANCA or PR3-ANCA tested by ELISA was positive in 31 (2.4%) patients [45]. Only 3 (0.23%) patients had MPO-ANCA associated vasculitis. PR3-ANCA positivity was associated with a significantly higher prevalence of interstitial lung disease (ILD) and pulmonary embolism, whereas MPO-ANCA positivity tended to be only associated with ILD. After adjusting for age and sex, antigen-specific ANCA was also associated with increased mortality. Of note, 6 (19.4%) of 31 PR3-ANCA-positive or MPO-ANCA-positive patients were treated with D-penicillamine, which could contribute to the development of ANCA.

In summary, ANCA positivity is uncommon in patients with SSc, and overt AAV occurs even more rarely. Antigen-specific ANCA in SSc may be associated with a higher incidence of unfavorable outcomes and hence warrant a thorough investigation and follow-up.

Sjögren's syndrome

Guellec et al. reviewed 22 patients with AAV (mostly MPO-ANCA) that occurred concomitantly or subsequently but not prior to primary Sjögren's syndrome [46]. All patients experienced at least one extra-glandular manifestation attributable to primary Sjögren's syndrome. Half of the patients had AAV renal involvement and approximately one third had MPO-ANCA renal-limited AAV.

In 3 other studies, the total prevalence of ANCA as detected by IIF was 9% (31/343) [47-49]. The majority of patients had P-ANCA. The prevalence of MPO-ANCA was even lower (3%), whereas PR3-ANCA was not present. A significant association between ANCA positivity and Raynaud's phenomenon, cutaneous vasculitis, and peripheral neuropathies was demonstrated among patients with primary Sjögren's syndrome [47].

In summary, MPO-ANCA are rarely found in patients with primary Sjögren's syndrome. ANCA positivity seems to be associated with a higher prevalence of extraglandular manifestations and can reveal AAV that infrequently occurs in patients with Sjögren's syndrome.

Autoimmune liver diseases

Autoimmune liver diseases (AILD) include autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and primary biliary cholangitis (PBC). Only eleven cases of GPA, MPA or EGPA have been reported in patients with various AILD [50,51]. In contrast, ANCA are frequently found by IIF in patients with AILD, particularly with AIH and/or PSC. Patients with AILD usually develop atypical P-ANCA, which unlike classical MPO-ANCA and PR3-ANCA may target antigens located at the periphery of the nucleus, and have been referred to as peripheral anti-nuclear neutrophil antibodies (pANNA) [52]. Atypical P-ANCA reacts with beta-tubulin isotype 5 (TBB5), which shares a high degree of structural homology with the bacterial protein FtsZ. The latter is present in almost all bacteria of the intestinal microflora [53]. Vesicular integral membrane protein 36 that plays a role as an intracellular lectin in the early secretory pathway was identified as another potential target antigen of these autoantibodies in AILD [54]. In addition, several neutrophil granule proteins have been proposed as possible targets for atypical P-ANCA, including lactoferrin, cathepsin G, bacterial/permeability increasing protein, catalase, alpha-enolase. However, reactivity to these antigens was found only in a minority of sera from patients with AILD [55]. Atypical P-ANCA positivity is not specific for AILD and can be detected in a significant proportion of patients with both viral and alcohol liver diseases [56].

Adults with AIH are currently subdivided based on their autoantibody profiles into AIH type 1 (frequency of ~95%) and AIH type 2 (frequency of ~5%) [57]. Atypical P-ANCA were frequently reported by IIF in patients with AIH-1 with a prevalence of 65% to 81% [58-61], whereas these autoantibodies were usually negative in patients with AIH type-2 [58]. The prognostic value of atypical P-ANCA positivity in AIH remains controversial, although two studies suggested that it might be associated with relapses of hepatitis or more severe necrotizing inflammatory activity [56,60]. Detection of atypical P-ANCA can be of diagnostic value in suspected cases, particularly in the absence of conventional autoantibodies [57,61].

The reported frequency of atypical P-ANCA in PBC ranged from 26% to 67% [60,62,63]. There is no evidence that atypical P-ANCA positivity has any clinical or diagnostic value in patients with PBC.

PSC can overlap with AIH in 5-10% of cases and is closely associated with inflammatory bowel disease, most often ulcerative colitis (UC) [64]. In several small studies (reviewed in [65]), the prevalence of atypical P-ANCA ranged from 26% to 94% (median of 63%). In one study, atypical P-ANCA emerged as a diagnostically relevant seromarker for PSC [61]. Several investigators suggested that P-ANCA positivity in PSC may be associated with biliary calculi or cholangiocarcinoma [66], more extensive involvement of the biliary tree [67] or liver transplantation [66]. In a recent study, ANCA were found by IIF in 193 (80%) of 241 Norwegian PSC patients, with P-ANCA in 169 (70%) of the patients [68]. These ANCA positive patients were younger at diagnosis and had a lower risk of biliary cancer, while there was no association with IBD status. The differences in biliary cancer frequency had a stronger association with age at diagnosis than with ANCA status. Therefore, firm evidence indicating a prognostic value of atypical P-ANCA positivity in PSC is lacking.

ANCA was detected by IIF in the bile of PSC patients significantly more often (38%) than in non-PSC patients (6%; p = 0.001), and was associated with a ten-fold higher risk of PSC [69]. Biliary ANCA correlated with the severity of bile duct strictures and the ensuing number of interventions. P-ANCA can also be found in small-duct PSC [70].

In several studies, the median frequency of MPO-ANCA and PR3-ANCA in patients with PSC was only 2% (0-33) and 4% (0-44), respectively [65]. Recently, Stinton et al. evaluated the prevalence and clinical significance of PR3-ANCA using ELISA and a new chemiluminescence immunoassay (CLIA) in 244 PSC patients and 254 controls, which included patients with AIH, PBC, hepatitis C and B viral infections, and healthy volunteers [71]. The sensitivity of PR3-ANCA detected by CLIA and ELISA for PSC was low (38.5% and 23.5%, respectively), but much higher than previously anticipated [65]. However, both CLIA and, in particular, ELISA had medium to high specificity, when compared to all control groups, AIH, and PBC (78.5-86.8% and 92.3-100%, respectively). Moreover, PR3-ANCA measured by both CLIA and ELISA was more specific for PSC than the atypical P-ANCA detected by IIF.

In summary, atypical P-ANCA targeting certain nuclear antigens or various neutrophil granule proteins are frequently found by IIF in sera of patients with AILD and may aid diagnosis in patients with AIH-1, particularly in the absence of conventional auto-antibodies. Atypical P-ANCA are not specific for AILD and can be present in patients with viral or alcohol liver diseases. One study showed that PR3-ANCA might be a specific biomarker for PSC, distinguishing it from AIH and PBC. This is true for some PR3-ANCA assays, but not for all. There is no firm evidence confirming clinical and prognostic value of ANCA in patients with AILD.

Inflammatory bowel disease

The two main forms of inflammatory bowel disease (IBD) are Crohn's disease (CD) and ulcerative colitis (UC), which have both overlapping and distinct clinical and pathological features. Sy et al. reviewed 338 patients with both IBD and vasculitis. Only 27 of them had clinical evidence of AAV [72]. Notably, granulomatous inflammation of the bowel mucosa that occasionally develops in GPA and EGPA can mimic the histological picture of IBD [73].

In 1961, Calabresi et al. found P-ANCA in 75% of 24 sera from UC patients [74]. Later it was confirmed that IBD patients frequently test positive for atypical P-ANCA, anti-glycan antibodies, e.g. anti-Saccharomyces cerevisiae antibodies (ASCA), and other antibodies mostly directed against microbial or yeast peptides [75-

77]. ASCA, detected by ELISA, are directed against the cell wall mannan of the yeast Saccharomyces that shares homology with intestinal bacteria [78]. In case of diagnostic uncertainty, serological profiles may be useful for differentiating CD from UC, which has treatment implications especially when surgery is needed. According to a systematic review, ASCA and atypical P-ANCA were found, respectively, in 29-69% and 6-38% of patients with CD, 0-29% and 41-73% of patients with UC, 0-23% and 8% of patients with other gastrointestinal diseases, 0-16% and 0-8% healthy controls. ASCA had the best sensitivity and specificity for CD, and P-ANCA for UC [76]. ASCA positivity was associated with small bowel disease, whereas atypical P-ANCA positivity was associated with a greater likelihood of colonic disease [76].

In some patients with colonic disease, particularly in children, the diagnosis of IBD cannot be further differentiated into CD or UC. The proportion of IBD that remained unclassified (IBD-U) ranged from 1 to 20% in adults and from 4 to 22% in pediatric patients [79], and was on average 6% and 13%, respectively, in a meta-analysis [80]. In a prospective study that included 97 patients with IBD-U, ASCA+/atypical P-ANCA- predicted an ultimate diagnosis of CD in 80% of patients, and ASCA-/atypical P-ANCA+ predicted a diagnosis of UC in 63.6% of patients [81]. The most intriguing observation in this study was that almost half of the patients with IBD-U were negative for ASCA and P-ANCA. A similar trend was found in other studies [82,83]. However, in another prospective study, both atypical P-ANCA and ASCA were of limited utility in predicting a subsequent disease phenotype in patients with IBD-U [84].

High P-ANCA titers were observed in active UC. However, in several studies, there was no association between atypical P-ANCA positivity and activity of UC [85,86], whereas others reported more aggressive UC in seropositive patients [87,88]. In a multicenter retrospective study involving 406 children with UC, atypical P-ANCA+/ASCA- patients more frequently had severe disease at diagnosis and more often required rescue therapy [83]. In a European cohort of 432 UC patients, atypical P-ANCA positivity was associated with an increased risk of relapsing disease and the total number of relapses [89]. In a recent study in 601 UC patients, serum levels of atypical P-ANCA and ASCA were not associated with severe UC, proximal disease extension or colectomy [90]. In UC patients, atypical P-ANCA seronegativity was reported as a predictor of a better early response to infliximab [91,92]. In contrast, in

279 CD patients, there was no relationship between ASCA or atypical P-ANCA and response to infliximab [93].

DNA-bound lactoferrin has been shown to be a major target for P-ANCA in UC patients [94,95].

Recently, PR3-ANCA has emerged as a potential biomarker for IBD. Serum PR3-ANCA, as detected by CLIA, were more prevalent in UC patients than in CD patients (29.2% vs. 2.7%; $P < 0.0001$) [96]. However, no statistically relevant differences were found between PR3-ANCA-positive and PR3-ANCA-negative UC patients with respect to disease location and severity, treatment, and complication rate. In 283 UC patients and 208 CD patients, both PR3-ANCA as tested by CLIA and ELISA accurately discriminated UC from CD [97]. However, CLIA was more sensitive than ELISA. The presence of PR3-ANCA in UC was associated with more extensive colitis and shorter disease duration. In 61 pediatric patients, PR3-ANCA had the most balanced ratio of sensitivity and specificity for UC (58% and 93%, respectively) [98]. In adults, the addition of ASCA-negativity to PR3-ANCA by CLIA only marginally improved the ability to distinguish UC from CD [99]. In another study using CLIA, PR3-ANCA and MPO-ANCA were detected in 39.2% and 12.8% of 102 patients with UC, respectively, whereas the prevalence of PR3-ANCA in patients with CD, intestinal and healthy controls was very low (1.5-6.0%), and no patients or controls were positive for MPO-ANCA [100]. The presence of PR3-ANCA had a sensitivity of 39.2% and specificity of 96.1% for UC in this study. On balance, distinguishing UC from CD based on PR3-ANCA, as is the case for diagnosing PSC, is assay-dependent because CLIA but to a lesser extent fluoroenzyme or multiplexed bead assays provide this distinction [101]. Further, the levels of PR3-ANCA in UC by CLIA are lower than the levels in AAV [101].

Like IBD, celiac disease is characterized by chronic diarrhea and the presence of distinct autoantibodies directed to tissue transglutaminase, deimidated gliadin and other antigens. Damoiseaux et al showed high prevalence of atypical P-ANCA and ASCA in 37 patients with celiac disease (22% and 43%, respectively) [102]. Therefore, the presence of atypical P-ANCA or ASCA in the serum of patients with chronic diarrhea does not exclude the diagnosis of celiac disease.

In summary, atypical P-ANCA can be detected by IIF in up to 40-70% patients with UC, whereas ASCA is found in CD patients. Determination of these antibodies may

aid in discriminating UC from CD in cases of diagnostic uncertainty. Accumulating evidence suggests that PR3-ANCA, as detected by CLIA but not other commonly used PR3-ANCA detection methods, may be a sensitive and specific biomarker for UC compared with CD. The existing data indicating an association between atypical P-ANCA positivity or PR3-ANCA positivity and more extensive or relapsing disease are inconclusive.

Anti-glomerular basement membrane disease

Anti-glomerular basement membrane (anti-GBM), or Goodpasture's disease, is a rare systemic vasculitis characterized by the development of autoantibodies to type IV collagen antigens expressed in the glomerular and alveolar basement membranes [103]. Approximately 50% of patients develop RPGN with concurrent alveolar hemorrhage. Several studies showed that up to 5-9% of ANCA positive AAV patients had detectable circulating anti-GBM antibodies [104-106]. On the other hand, 13 to 47% of patients with anti-GBM disease had ANCA [reviewed in 103], mostly MPO-ANCA (61-90% of double positive cases) [107-112].

Low level ANCA develop years to decades before the diagnosis of anti-GBM disease, followed later by the onset of low level anti-GBM antibodies persisting for years before an acute increase in the weeks to months prior to the onset of clinical disease [113]. These findings indicate that ANCA or their target antigens may play a causative role in the pathophysiology of anti-GBM disease, maybe by perturbing the quaternary structure of the α345NC1 hexamer in GBM, which in turn elicits an autoimmune response [114]. A recent study suggested that sera from over half of patients with anti-GBM disease could recognize deglycosylated MPO, indicating a potential common pathogenetic pathway between anti-GBM disease and MPO-ANCA vasculitis [115].

Bosch et al. suggested that in anti-GBM disease, MPO-ANCA may be a serologic marker of good prognosis identifying a subset of patients who may recover renal function [116]. In a Swedish study, 29 patients who tested positive for anti-GBM antibodies and ANCA were older and tended to have better renal survival than patients with isolated anti-GBM antibodies [107]. On the contrary, in other studies, renal outcomes in double positive patients were worse or comparable to those in

patients with isolated anti-GBM antibodies [105,108,117]. This finding is compatible with animal studies showing that MPO-ANCA increase the severity of anti-GBM-mediated glomerulonephritis in a rat model of anti-GBM nephritis [118].

McAdoo et al. compared clinical features and long-term outcomes in 568 patients with AAV, 41 patients with anti-GBM disease, and 37 double-positive patients with antigen-specific ANCA and anti-GBM disease from four European centers [109]. Double-positive patients shared characteristics of AAV, such as older age, additional extrarenal manifestations and longer symptom duration before diagnosis, and features of anti-GBM disease, such as severe renal disease and high frequency of lung hemorrhage at presentation. Double positive patients showed an intermediate risk of progression to end-stage renal disease (ESRD) compared with patients with AAV or anti-GBM disease without ANCA. More than one-third of the surviving patients who were double positive and required dialysis at presentation regained independent renal function by 3 months vs. only 10% among surviving single-positive patients with anti-GBM disease. There were no disease relapses in patients with ANCA-negative anti-GBM disease. On the contrary, approximately one-half of surviving double positive patients developed relapses at a frequency comparable to that in AAV patients. The authors suggested that anti-GBM disease was the dominant disease phenotype in patients who were positive for both anti-GBM antibodies and ANCA. However, these patients were more responsive to initial immunosuppressive treatment, and, in contrast to anti-GBM disease, had a substantial risk of recurrent disease. The latter was associated with ANCA rather than anti-GBM.

In another recent study, the proportion of double positivity among patients with anti-GBM disease was lower than in the study of McAdoo et al (33% vs. 47%), and none of these double positive patients experienced a disease relapse during a mean follow-up of 2.9 years [119].

Importantly, Rutgers et al. [108] and Sadeghi-Alavijeh et al. [120] reported patients with circulating anti-GBM antibodies and MPO-ANCA positive with focal necrotising crescentic glomerulonephritis but no linear GBM antibody deposition on immunohistochemistry. Therefore, biopsy is critical in deciding on the impact of the circulating antibody, as non-binding anti-GBM antibodies may be associated with significant renal recovery.

Recently, Canney and Little suggested that individuals should be classified as having 'ANCA vasculitis with anti-GBM antibodies' or 'anti-GBM disease with ANCA' based on the demonstration of linear IgG deposition on the GBM [121].

In summary, ANCA, mostly MPO-ANCA, can be detected in approximately one third of patients with anti-GBM disease. Double-positive patients have a clinical phenotype similar to that of anti-GBM disease without ANCA, that is, severe kidney disease frequently requiring renal replacement therapy at presentation, and concurrent alveolar hemorrhage occurring in approximately 40% of patients. Patients who have both ANCA and anti-GBM antibodies may share certain clinical features with AAV, such as older age, the presence of extrarenal manifestations, a greater propensity to renal recovery, as well as the risk of relapses requiring careful long-term monitoring.

Interstitial lung disease

The idiopathic interstitial pneumonias (IIPs), which overlap with ILD, can be classified based on histopathologic, radiographic and clinical parameters (table 1) [122]. Many IIP patients have clinical and/or serological features suggesting an underlying autoimmune disease, but not meeting the established classification criteria for a particular connective tissue disease (CTD). The European Respiratory Society/American Thoracic Society task force has recently proposed the term 'interstitial pneumonia with autoimmune features' (IPAF) and offered classification criteria for this entity from three domains [123]. ANCA were not included in the serologic domain, because, in the opinion of this expert group, they are associated with vasculitides, rather than CTD. This approach is flawed given the ill-defined criteria for CTD, and the fine line between CTD and systemic vasculitides [124].

Table 1. American Thoracic Society/European Respiratory Society classification of idiopathic interstitial pneumonias [122]

Major idiopathic interstitial pneumonias
Idiopathic pulmonary fibrosis
Idiopathic nonspecific interstitial pneumonia
Respiratory bronchiolitis–interstitial lung disease
Desquamative interstitial pneumonia
Cryptogenic organizing pneumonia

Acute interstitial pneumonia

Rare idiopathic interstitial pneumonias

  Idiopathic lymphoid interstitial pneumonia

  Idiopathic pleuroparenchymal fibroelastosis

Unclassifiable idiopathic interstitial pneumonias

ILD is not uncommon in patients with AAV [125-127]. It occurs more frequently in MPA or MPO-ANCA vasculitis than in GPA or PR3-ANCA vasculitis. In addition, ILD often precedes clinical manifestations of MPO-ANCA associated vasculitis [127]. In recent cohort studies, the prevalence of ILD varied from 7.2% to 15.9% in MPA and from 0% to 3.0% in GPA [128-131]. In two studies, ILD was found exclusively in MPO-ANCA positive patients (12%-21%) [130,131]. For most cases, the ILD either has radiographic and histopathologic features of usual interstitial pneumonia (UIP) or nonspecific interstitial pneumonia (NSIP) [125,128]. ILD in AAV is more common in Asian countries (up to 50% in MPA) than in Western countries [132,133].

The prevalence of ANCA in cohorts of patients who initially presented with ILD ranged between 4–36% for MPO-ANCA and 2–4% for PR3-ANCA [reviewed in 125]. During follow-up, 5–10% of ANCA negative patients went on to develop autoantibodies against MPO or PR3, whereas 25% of MPO-ANCA positive patients developed clinical features of MPA [125].

Kagiyama et al. studied the medical records of 504 Asian patients with idiopathic pulmonary fibrosis (IPF) [134], of whom 4.0% had MPO-ANCA and 3.2% had PR3-ANCA when first evaluated. During follow-up, seroconversion to MPO-ANCA and PR3-ANCA occurred in 5.7% and 5.3% of patients, respectively. Nine (25.7%) of 35 patients who were either MPO-ANCA positive at IPF diagnosis or who subsequently seroconverted developed MPA, but none of the PR3-ANCA positive patients progressed to overt vasculitis. None of these nine patients had been previously treated with steroids. In a recent US study, Liu et al retrospectively evaluated the prevalence of ANCA in two independent cohorts of IPF patients. Antigen specific ANCA were detected in 4.0% of 353 and 5.1% of 292 patients, respectively. Two of 6 (33%) and three of 12 (25%) MPO-ANCA positive patients developed AAV during follow-up

[135]. In the combined cohort of 745 patients, median transplant-free survival was not significantly different in patients who were ANCA-positive or ANCA-negative at diagnosis of IPF.

In the study of Hozumi et al., 8.5% of 305 patients who were initially diagnosed with IIP were MPO-ANCA-positive [136]. The cumulative 5-year MPA incidence was 24.3% in the MPO-ANCA-positive patients and 0% in the MPO-ANCA-negative patients (P < 0.0001). The independent risk factors for developing MPA included UIP pattern on HRCT and no immunosuppressive or anti-fibrotic treatment for IIP.

The same authors studied the clinical significance of PR3-ANCA positivity in 16 (4.4%) of 360 patients with IIP [137]. The HRCT patterns of PR3-ANCA-positive IIP patients were more variable than those of the IPF patients, but the high IIP-onset age, male predominance, and prognosis were similar between the groups.

In summary, ANCA positivity can be detected initially or during follow-up in a relatively small proportion of patients with IIP, particularly with a UIP and/or NSIP pattern on HCRT. One quarter of MPO-ANCA positive patients with IIP will develop clinical manifestations of MPO-ANCA associated vasculitis within the following months or years. We suggest that MPO-ANCA and PR3-ANCA should be tested in all patients with IIP and may be included in the serological criteria for IPAF. Currently, ANCA-positivity in ILD/IIP patients may guide treatment decisions, such as the use of immunosuppressive or antifibrotic agents [127].

Infections

Various viral, bacterial, fungal, or protozoal infections can mimic AAV or can complicate the immunosuppressive treatment. Conversely, infections have been implicated as a trigger for ANCA production, AAV developing or relapses [138-140]. ANCA positivity has been reported in patients with many chronic infections of various etiology (Table 2) [139]. Moreover, experiments in rats showed that immunisation with Staphylococcus aureus or Escherichia coli could induce AAV in a few animals [141].

Table 2. Infections associated with ANCA positivity [139].

Viruses	HIV, hepatitis B virus, hepatitis C virus, Parvovirus B-19 Epstein-Barr virus,

	Arbovirus, Ross river virus
Bacteria	*Streptococcus, Staphylococcus, Enterococcus, Bartonella, Gemella, Propionibacterium, Neisseria, Actinobacillus, Pseudomonas, Escherichia, Bacteroides, Campylobacter, Helicobacter, Yersinia, Salmonella, Proteus, Corynebacterium, Stenotrophomonas, Klebsiella, Mycoplasma, Chlamydia, Ricketsia, Treponema, Leptospira, Mycobacterium*
Fungi	*Aspergillus, Histoplasma, Sporothrix, Pneumocystis, Paracoccidioides, Saccharomyces*
Protozoa	*Entamoeba histolytica, Plasmodium, Leishmania*
Multicellular organisms	*Echinococcus, Strongyloides, Toxocara*

Staphylococcus aureus has been found to be associated with PR3-AAV and several lines of investigation suggest that these bacteria contribute to disease pathophysiology [142]. Chronic nasal carriage of *Staphylococcus aureus* is associated with a higher risk of relapse of GPA [143], whereas trimethoprim–sulfamethoxazole prevents relapses [144-146].

In cohort studies, the prevalence of ANCA positivity by antigen-specific immunoassays in patients with chronic hepatitis B and C was low (MPO-ANCA 2% and 7%, PR3-ANCA 8% and 0%, respectively) [147,148], while the findings of studies in patients with tuberculosis were conflicting (from 40% in one study to 0-1.5% in three other studies) [149-152].

Several studies showed that ANCA, mostly PR3-ANCA, can be found in a substantial proportion of patients with infective endocarditis (8-33% by ELISA) [153-156]. The link between PR3-ANCA and infection is especially high with Bartonella endocarditis. In a literature review of 54 cases of *Bartonella* infective endocarditis associated glomerulonephritis reported in 14 publications, 78% were ANCA positive by IIF and/or ELISA, including 67% positive for PR3-ANCA [157]. Langlois et al. suggested that ANCA may be associated with a subacute form of infective endocarditis leading to multiple valve involvement and more frequent renal impairment [155]. Importantly, infective endocarditis should always be excluded in patients presenting with AAV [158,159]. The evidence on the clinical implication of ANCA-positivity in infective endocarditis is inconclusive. ANCA testing may be useful in patients with infective endocarditis associated with renal impairment [160].

ANCA were also reported in symptomatic and asymptomatic HIV-infected patients on highly active antiretroviral therapy. However, their target antigens are not well defined [161,162].

Temporal association of influenza vaccination with onset or relapse of AAV has been reported in isolated cases [163-167]. The nature of this association remains unknown. Jeffs et al. showed that only influenza vaccines that contained viral ribonucleic acid (RNA), the natural ligand for Toll-like receptor-7, were able to stimulate PR3-ANCA production blood from a patient who developed AAV shortly following influenza vaccination [168]. Other lines of evidence have implicated vaccine adjuvants in the induction of autoimmune syndromes, including two females who developed ANCA-associated vasculitis after receiving hyaluronic acid and influenza vaccine [169].

In summary, infections can be associated with ANCA-positivity and can mimic AAV. Infection may induce an ANCA autoimmune response that causes AAV. Exclusion of underlying infection in patients with suspected AAV is crucial, since immunosuppressive therapy can lead to devastating consequences.

Malignancy

Patients with AAV used to have an increased malignancy risk compared with the general population, particularly of the non-melanoma skin cancer (NMSC), leukemia and bladder cancer [170]. As less and less cyclophosphamide is being used for AAV, patients with AAV receiving immunosuppressive therapy currently only show an increased risk of developing NMSC [171]. Some studies suggested an increased incidence of cancer preceding the development of AAV and a causal relationship or shared pathogenic pathways between the two diseases [172,173], whereas an association between malignancies and systemic vasculitis was not confirmed in a recent study in 203 patients with AAV [174]. A possible pathophysiological link between malignancy, particularly, haematologic malignancies and AAV cannot be excluded [175-177]. Fortunately, the occurrence of AAV in these diseases is extremely rare. PR3, the main autoantigen for GPA, is a feedback regulator in myeloid differentiation and may be of relevance for the crosstalk between autoimmunity and hematopoietic proliferation [178,179]. Overexpression of PR3 was shown in acute and chronic myeloid leukemia cell lines [180,181]. PR3 can induce

growth of hematopoietic progenitors cells, which could represent one of the early stages in the development of leukemia [179].

Various malignancies can be associated with ANCA formation without other evidence for systemic vasculitis [182]. Houben et al. detected malignancy in 4 (4.6%) of 87 antigen-specific ANCA-positive patients without AAV and suggested that a higher ANCA titre and multiple affected organs may help to discriminate AAV from other diseases [183]. In a study from Turkey, ANCA positivity was detected by IIF in 13.3% of 60 patients with Hodgkin lymphoma and in none of 119 patients with non-Hodgkin lymphoma [184]. This association is clinically relevant in the context of differential diagnosis since malignancy, particularly lymphoma, with a high serum ANCA level, can resemble AAV [185-187].

Drug-induced AAV

Various drugs can trigger development of AAV, including anti-thyroid medications (prophythiouracil, methimazole), antibiotics (cephotaxime, minocycline, rifampicin), tumour necrosis factor-α inhibitors (adalimumab, etanercept, infliximab), psychoactive agents (clozapine, thioridazine), hydralazine, allopurinol, D-penicillamine, sulfasalazine, and levamisole as found in levamisole-adulterated cocaine [188-194]. The association between biologic therapy and AAV is of particular importance, given the increased use of TNF inhibitors [195]. Also, it has been recently reported that immune checkpoint inhibitors, which are increasingly used to treat various forms of cancer, may induce AAV [196]. Most patients with drug-induced AAV have MPO-ANCA, frequently in combination with antibodies to other neutrophil cytoplasmic proteins (such as PR3 and human neutrophil elastase [HNE]) and anti-nuclear antibodies [193]. Dual positivity for MPO and PR3 antibodies is suggestive of drug-induced disease. Data suggest that the overall prognosis of drug-induced AAV might be better than that of primary AAV, although strong evidence for this suggestion is lacking [189,191].

In several studies, the median prevalence of ANCA-positivity was 30% with propylthiouracil, and 6% with methyl-mercapto-imidazole derivatives [197]. Young age and the duration of antithyroid drug therapy were the main factors contributing to the emergence of ANCA. In total, ANCA positivity was found in 223 of 1056 patients

(21%), irrespective of the type of antithyroid drug administered. Only 33 (3% of the total population or 15% of the ANCA-positive cases) presented with clinical manifestations of AAV. Similar findings were previously also observed in long-term follow-up studies as performed in the Netherlands and China [188,198]. Whether routine screening for ANCA during antithyroid drug therapy should be performed is, however, still controversial.

Cocaine inhalation can induce a destructive chronic inflammatory syndrome of the upper respiratory tract with similarities to GPA. ANCA with reactivities to elastase, cathepsin G have been reported in this setting but PR3-ANCA can also be found, further complicating the differential diagnosis [199]. Systemic vasculitis and/or cutaneous vasculitis associated with both PR3 and MPO-ANCA has been reported following the use of levamisole adulterated cocaine that is either inhaled as cocaine powder or smoked as crack cocaine.

Other diseases

Cholesterol emboli syndrome occurring in patients with severe atherosclerosis is associated with acrocyanosis, livedo reticularis, progressive renal failure, and other signs and symptoms (e.g. fever, weight loss, myalgia, leucocytosis, eosinophilia, raised ESR and CRP) mimicking vasculitis. ANCA-positivity, mostly MPO-ANCA, has been reported in a few patients with this syndrome. Some have responded to treatment with glucocorticoids with or without cyclophosphamide [200,201]. Nevertheless, the role of ANCA in cholesterol emboli syndrome is unclear [202]. In one study, the prevalence of P-ANCA was found to be 5.6% in 286 patients with premature atherosclerosis, whereas the prevalence of MPO-ANCA was 1% [203]. However, ANCA did not appear to play a role in early atherosclerosis given the absence of any differences in the incidence of cardiovascular risk factors or in serum markers of inflammation between ANCA-positive and ANCA-negative patients.

Antineutrophil cytoplasmic antibodies with bactericidal/permeability-increasing protein (BPI-ANCA) specificity have been reported to occur in 17.9% to 83.0% cystic fibrosis patients with a pooled prevalence of 49.5% [204]. ANCA against BPI, an endogenous protein with a potent killing activity against Gram-negative bacteria, such as *Pseudomonas aeruginosa*, develop in response to bacterial infection and

colonization and may decrease host defense responses in the lung parenchyma and slow bacterial clearance. Several studies suggested that BPI-ANCA may be a biomarker for deteriorating lung function and a poor prognosis in patients with cystic fibrosis [205,206]. However, prospective clinical studies are needed to determine the clinical relevance of BPI-ANCA, which were also demonstrated in various CTD and IBD [207].

ANCA with or without PR3 or MPO specificity have been reported in patients with relapsing polychondritis that can mimic GPA [208]. Finally, ANCA may occur in IgG4-related disease [209,210].

Conclusion

Available evidence suggests that in certain settings, e.g. in patients with other autoimmune diseases, such as anti-GBM disease, ANCA may have clinical and pathogenic relevance, whereas in other disorders ANCA testing may be helpful to support the diagnosis or for differential diagnosis (table 3). ANCA testing is mandatory for any patient with clinical features suggesting AAV. In addition, all patients with anti-GBM disease, IIP or infective endocarditis associated with nephritis should be tested for ANCA. In all these patients, PR3-ANCA and MPO-ANCA should be tested according to the 2017 international consensus [1]. In patients with other disorders (e.g. IBD; AILD), ANCA testing may be justified in certain circumstances as listed in table 4. In these cases, ANCA should be tested by IIF as the target antigens are not yet well characterized.

These recommendations are based on current evidence, however they cannot replace clinical judgement, and individual clinicians may have their own reasons for requesting ANCA in a disease of interest.

Table 3. Overview of non-AAV diseases in which ANCA can be found.

For each disease, the ANCA positivity rate is indicated as well as the occurrence of AAV.

Disease	ANCA-positivity (%)	AAV (%)	Comments
Rheumatoid arthritis	P-ANCA by IIF: 16-50% MPO-ANCA by ELISA: 0-4% (up to 18%)	Very rare	The clinical value of P-ANCA that can be detected by IIF in a significant proportion of RA patients is not definitely established. MPO-ANCA positivity was rarely found by antigen-specific immunoassay. Testing for MPO-ANCA may be justified in RA patients with severe kidney disease, particularly necrotizing crescentic glomerulonephritis on renal biopsy.
Systemic lupus erythematosis	P-ANCA by IIF: 14-31.4% MPO-ANCA (ELISA): 0-23.8% PR3-ANCA (ELISA): 0-12.7%	Very rare	SLE can be associated with ANCA positivity in up to 15-20% of patients (particularly MPO-ANCA). One study suggested that the presence of ANCA may be associated with the severity of lupus nephritis and disease activity. However, the clinical implication of ANCA positivity in SLE is not clearly established.
Systemic sclerosis	0-9.1%	0.2-0.4%	MPO-ANCA predominated in all except one study. In one large study (n=1303), ANCA were associated with a higher prevalence of ILD, PE, and death. Rapidly progressive glomerulonephritis in ANCA-positive patients with SSc should be differentiated from SRC.
Primary Sjögren's syndrome	P-ANCA by IIF 5.4-17.0% MPO-ANCA (ELISA) 2.0-6.7%	Very rare	The prevalence of MPO-ANCA in patients with primary Sjögren's syndrome was 3%. ANCA positivity was associated with a higher prevalence of extraglandular manifestations of Sjögren's syndrome. Testing for ANCA may be justified in the presence of renal disease or other features suggesting AAV.

Autoimmune liver diseases	Atypical P-ANCA (IIF): 65-81% in AIH type-1, 26-67% in PBC, 26-94% in PSC	Very rare	Atypical P-ANCA targeting nuclear antigens or neutrophil granule proteins are frequently found by IIF in patients with AILD and may assist diagnosis of AIH type-1 in the absence of conventional auto-antibodies. Their clinical or prognostic value is not established. In one study, PR3-ANCA by CLIA was a specific biomarker for PSC though with a low sensitivity.
Inflammatory bowel diseases	Atypical P-ANCA (IIF): 41-73% in UC and 6-38% in CD PR3-ANCA (CLIA): 29.2-57.6% in UC 1.9-2.7% in CD MPO-ANCA (CLIA): 9.1-12.8 in UC 0-3.6% in CD	Very rare	Atypical P-ANCA and ASCA may aid in discriminating UC from CD in case of diagnostic uncertainty. PR3-ANCA, as detected by CLIA, may be a sensitive and specific biomarker for UC. Routine testing of the serological profile for diagnosis or for predicting the course or response to treatment cannot be recommended.
Anti-GBM disease	MPO-ANCA (more frequent) and PR3-ANCA: 13-47%	-	ANCA-positivity may identify patients who have better response to initial immunosuppressive therapy and a greater propensity to renal recovery, but can relapse during follow-up and require careful long-term monitoring.
Idiopathic interstitial pneumonia	MPO-ANCA 4–36%, PR3-ANCA 2–4%	-	Interstitial lung disease may precede diagnosis of AAV, e.g. MPA develops in up to 25% of MPO-ANCA positive patients initially diagnosed with IIP. ANCA-positivity in IIF cannot guide treatment decision
Infections	IIF: 18-24% ELISA: 8-14% (33% in one study)	-	In IE, ANCA-positivity may be linked with multiple valve involvement and more frequent renal impairment. However, the presence of ANCA seems more important in the context of differential diagnosis with AAV
Malignancy	-	Very rare	The evidence indicating a causal relationship

			between malignancy and AAV is inconclusive. However, it cannot be excluded in some patients.
Drugs	-	Rare	
Other diseases	-	-	Antigen-specific ANCA were reported in patients with midline destructive disease induced by cocaine inhalation, cholesterol emboli syndrome, cystic fibrosis, relapsing polychondritis, and IgG4-related disease. In patients with cystic fibrosis, BPI-ANCA may have prognostic significance.

Note: RA – rheumatoid arthritis, SLE – systemic lupus erythematosus, AIH-1 – autoimmune hepatitis type 1, PBC – primary biliary cholangitis, PSC – primary sclerosing cholangitis , CD – Crohn's diseases, UC – ulcerative colitis, ASCA – anti-*Saccharomyces cerevisiae* antibodies, CLIA – chemiluminescent assay, IIF – indirect immunofluorescence, BPI – bactericidal/permeability-increasing protein.

Table 4. Recommendations statements for ANCA testing in non-AAV

Disease	Statements	Strongly disagree	Disagree	Undecided	Agree	Strongly agree
Any disease	ANCA testing* is mandatory for any patient with clinical features suggesting AAV					x
Rheumatoid arthritis	Routine testing is not recommended. Recommended* in patients with kidney disease with a nephritic sediment	.				x
Systemic lupus erythematosus	Routine testing is not recommended. Recommended* in patients with a kidney biopsy with prominent necrotizing and crescentic lesions					x
Systemic sclerosis	Routine testing is not recommended. Recommended* in patients with kidney disease with a nephritic sediment					x
Primary Sjögren's syndrome	Routine testing is not recommended. Recommended* in patients with kidney disease with a nephritic sediment					x
Autoimmune liver diseases (AIH-1, PBC, PSC)	Routine testing is not recommended. Testing for atypical P-ANCA by IIF may be useful in patients with suspected AIH-1 in the absence of conventional auto-antibodies					x
Inflammatory bowel diseases (CD, UC)	Routine testing is not recommended. Atypical P-ANCA (IIF) and ASCA may be tested in case of diagnostic uncertainty to discriminate UC from CD					x
Anti-GBM disease	Routine testing is recommended*	-				x

Idiopathic interstitial pneumonia	Routine testing is recommended*	-				x
Infections	Routine testing is not recommended. ANCA testing* may be useful in patients with renal impairment, especially associated with infective endocarditis		x			
Malignancy	Routine testing is not recommended	-				x

Note: *MPO-ANCA and PR3-ANCA according to the 2017 consensus. AIH-1 – autoimmune hepatitis type 1, PBC – primary biliary cholangitis, PSC – primary sclerosing cholangitis , CD – Crohn's diseases, UC – ulcerative colitis, ASCA – anti-*Saccharomyces cerevisiae* antibodies.

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