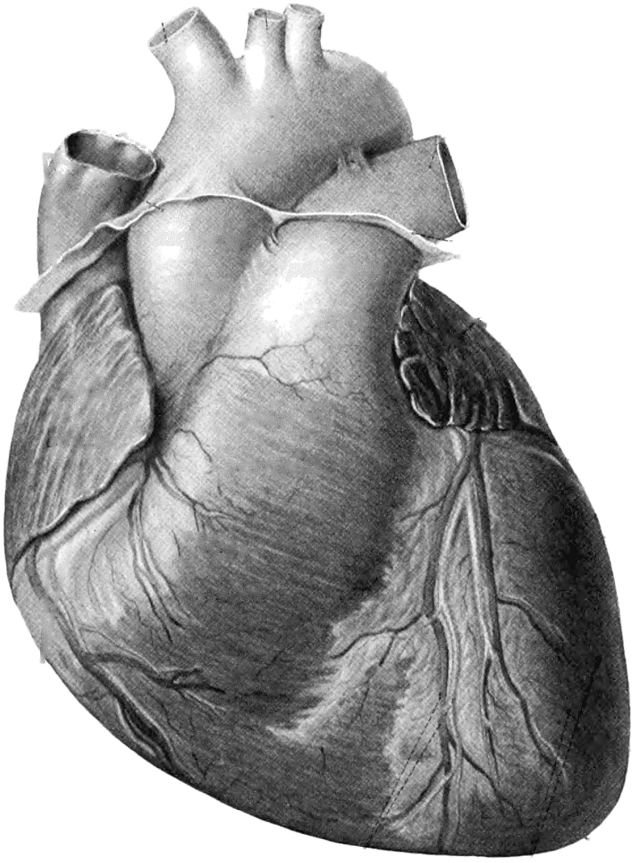

THE LABS

THE HEART IN AUTOIMMUNE, AUTOINFLAMMATORY AND RARE DISEASES

A Concise Guide to Laboratory Medicine

BRAHIM ABDELOUAEB
Author and Scientific Editor

CARDIOIMMUNOLOGY

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The Labs

Cardioimmunology

The Labs

The Heart in Autoimmune, Autoinflammatory and Rare Diseases

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Brahim Abdelouaeb

Author and Scientific Editor



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Editorial and Legal Notices

The Book

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Status of the Text

This book is a concise guide to laboratory medicine. It is neither a professional society guideline nor a binding clinical standard. Tests, thresholds and monitoring intervals are reported from their cited sources. **Current professional society guidance and the applicable national diagnostic and care protocols remain the sole authority for clinical decisions.** Laboratory thresholds depend on the assay and the laboratory; the reference limits supplied by the reporting laboratory apply.

French National Diagnostic and Care Protocols (PNDS) and French Summaries of Product Characteristics (SmPCs) retain their jurisdiction and dates. Translation into English does not convert them into US or universal recommendations. Original publication titles in the reference lists are retained in their publication language.

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In the French edition, each test, threshold, monitoring interval and recommendation grade is linked to a cited source, checked against the passage that supports it; what could not be verified was not written, or is stated with the reservation of its source. National diagnostic and care protocols (PNDS) are cited with their date and status. The English edition keeps these links and the three tiers: essential for a defined indication, useful depending on the clinical context, or a matter for specialist assessment.

The book contains no personal patient data.

Current guidelines remain authoritative for clinical decisions: this book organizes the ordering and interpretation of laboratory tests; it does not replace them. Errors reported after publication will be recorded and corrected in subsequent editions.

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Key Abbreviations

β2GPI β2-glycoprotein I
ACE Angiotensin-converting enzyme
aCL Anticardiolipin
ACR American College of Rheumatology
ADA Adenosine deaminase
ADA2 Adenosine deaminase 2
AGS Aicardi-Goutières syndrome
AHA American Heart Association
AL Immunoglobulin light chain amyloidosis
ALBIA Addressable laser bead immunoassay
ALT Alanine aminotransferase
ANA Antinuclear antibodies
ANCA Antineutrophil cytoplasmic antibodies
AOSD Adult-onset Still disease
aPL Antiphospholipid antibodies
APS Antiphospholipid syndrome
aPTT Activated partial thromboplastin time
ASAS Assessment of SpondyloArthritis international Society
ASDAS Ankylosing Spondylitis Disease Activity Score
ASH American Society of Hematology
ASTCT American Society for Transplantation and Cellular Therapy
ATS American Thoracic Society
ATTR Transthyretin amyloidosis
AV Atrioventricular
BAFF B-cell activating factor
BCG Bacillus Calmette-Guérin
BNP B-type natriuretic peptide
BPI Bactericidal permeability-increasing protein
CANDLE Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
CAPS Cryopyrin-associated periodic syndromes
CAR-T Chimeric antigen receptor T cells
CBC Complete blood count
CCP Cyclic citrullinated peptides
CD Cluster of differentiation, nomenclature for leukocyte surface markers
CD163 CD163 marker, macrophage hemoglobin scavenger receptor
CD4 CD4-positive helper T lymphocyte
CH50 Total hemolytic complement activity
CK Creatine kinase
CMV Cytomegalovirus
cN1A Cytosolic 5′-nucleotidase 1A
CPIC Clinical Pharmacogenetics Implementation Consortium
CRP C-reactive protein
CRS Cytokine release syndrome

CSF Cerebrospinal fluid
CT Computed tomography
CTLA-4 Cytotoxic T-lymphocyte-associated antigen 4
CXCL9 C-X-C motif chemokine ligand 9
CYP3A4 Cytochrome P450 3A4
DADA2 Deficiency of adenosine deaminase 2
DAS28 Disease Activity Score in 28 joints
dFLC Difference between involved and uninvolved free light chains
DLCO Diffusing capacity for carbon monoxide
DNA Deoxyribonucleic acid
DRESS Drug reaction with eosinophilia and systemic symptoms
EBV Epstein-Barr virus
ECG Electrocardiogram
EDTA Ethylenediaminetetraacetic acid
eGFR Estimated glomerular filtration rate
EGPA Eosinophilic granulomatosis with polyangiitis
ELISA Enzyme-linked immunosorbent assay
ENA Extractable nuclear antigens
ESC European Society of Cardiology
ESOT European Society for Organ Transplantation
ESR Erythrocyte sedimentation rate
EULAR European Alliance of Associations for Rheumatology
FISH Fluorescence in situ hybridization
FMF Familial Mediterranean fever
FVC Forced vital capacity
GBM Glomerular basement membrane
GCA Giant cell arteritis
GPA Granulomatosis with polyangiitis
HAQ Health Assessment Questionnaire
HbA1c Glycated hemoglobin
HBsAg Hepatitis B surface antigen
HBV Hepatitis B virus
HCV Hepatitis C virus
HDL High-density lipoproteins
HE Hypereosinophilia
hERG Human ether-à-go-go-related gene
HES Hypereosinophilic syndrome
HHV-6 Human herpesvirus 6
HIV Human immunodeficiency virus
HLA Human leukocyte antigen
HLA-B27 Human leukocyte antigen B27
HLH Hemophagocytic lymphohistiocytosis
HTLV-1 Human T-lymphotropic virus type 1
IC-OS International Cardio-Oncology Society
ICI Immune checkpoint inhibitor
IgA Immunoglobulin A
IgD Immunoglobulin D
IgE Immunoglobulin E

IgG Immunoglobulin G
IgG4 Immunoglobulin G subclass 4
IgG4-RD IgG4-related disease
IgM Immunoglobulin M
IGRA Interferon-gamma release assay
IIF Indirect immunofluorescence
IL-18 Interleukin 18
IMPS Inflammatory myopericardial syndrome
INR International normalized ratio
IWWM International Workshop on Waldenström's Macroglobulinemia
JAK Janus kinase
LDH Lactate dehydrogenase
LKM Liver-kidney microsomes
MAP kinase Mitogen-activated protein kinase
MAS Macrophage activation syndrome
MKD Mevalonate kinase deficiency
MOG Myelin oligodendrocyte glycoprotein
MPA Microscopic polyangiitis
MPO Myeloperoxidase
MRI Magnetic resonance imaging
mTOR Mechanistic target of rapamycin
NICE National Institute for Health and Care Excellence
NK Natural killer cells
NLRC4 NLRC4 inflammasome, NLRC4-associated syndromes
NLRC4-MAS NLRC4-associated macrophage activation syndrome, including infantile autoinflammatory enterocolitis
NLRP3 NLRP3 inflammasome
NSAIDs Nonsteroidal anti-inflammatory drugs
NT-proBNP N-terminal pro-B-type natriuretic peptide
OMERACT Outcome Measures in Rheumatology
P-gp P-glycoprotein
PAH Pulmonary arterial hypertension
PAN Polyarteritis nodosa
PCNSV Primary central nervous system vasculitis
PCR Polymerase chain reaction
PD-1 Programmed cell death protein 1
PlGF Placental growth factor
PNDS French National Diagnostic and Care Protocol
PR3 Proteinase 3
PRA Panel reactive antibodies, anti-HLA antibodies in a transplant candidate
PRAAS Proteasome-associated autoinflammatory syndrome
PReS Paediatric Rheumatology European Society
proBNP Pro-B-type natriuretic peptide
QTc Corrected QT interval
RA Rheumatoid arthritis
RF Rheumatoid factor
RNA Ribonucleic acid

RP Relapsing polychondritis

RT-PCR Reverse transcription polymerase chain reaction

SAA Serum amyloid A protein

SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2

SAVI STING-associated vasculopathy with onset in infancy

sFLC Serum free light chains

sFlt-1 Soluble fms-like tyrosine kinase 1, the soluble form of vascular endothelial growth factor receptor 1

SLE Systemic lupus erythematosus

SmPC Summary of Product Characteristics

SSc Systemic sclerosis

TNF Tumor necrosis factor

TPMT Thiopurine methyltransferase

TRAPS Tumor necrosis factor receptor-associated periodic syndrome

TSH Thyroid-stimulating hormone

TTP Thrombotic thrombocytopenic purpura

TTR Transthyretin

VEXAS Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic; associated with UBA1 mutations

WHO World Health Organization

PART I

Interpreting a Laboratory Workup

1

The three tiers of laboratory assessment: essential, context-dependent and specialist

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1.2 Depending on the clinical context 4
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1.4 A tier is neither an evidence grade nor a testing interval 6

A test is only as useful as the question it resolves. The same assay may be essential in one situation, irrelevant in another and restricted to a reference laboratory in a third. Assigning each test to one of three tiers, always tied to a specific indication, makes it possible to order fewer tests and interpret them better.

1.1 Essential for a defined indication

In the Treatise: § 8.1, § 8.3, § 9.4, § 10.2 and § 13.6

The first tier includes tests without which the question remains unanswered. The word "essential" never describes a test in absolute terms. It describes it for a defined indication: a named clinical situation at a named time, whether diagnosis, initial assessment or reassessment. Outside that indication, the same test may become optional again and routine ordering adds only noise. The first question for any request is therefore: for what indication is this test being ordered?

When systemic lupus erythematosus is clinically suspected, testing for antinuclear antibodies (ANA) by indirect immunofluorescence (IIF) on HEp-2 cells (a human cell line) is the reference method; a negative result, with a titer below 1:80, makes the diagnosis extremely unlikely[1]. In a meta-regression involving 13,080 patients with lupus, ANA sensitivity was 97.8% at a titer of 1:80, with a specificity of 74.7%[2]: the test is far more useful for ruling out the disease than for confirming it. When antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is suspected, ANCA testing is considered essential because its specificity in a vasculitis setting approaches 100%[3]. When systemic sclerosis is suspected, autoantibody testing and nailfold capillaroscopy are the first-line investigations[4].

The first tier is not limited to diagnosis. The initial assessment of systemic sclerosis includes, among other tests, electrolytes, serum creatinine, C-reactive protein (CRP), creatine kinase, N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP), thyroid-stimulating hormone (TSH) and serum ferritin[4]. In ANCA-associated vasculitis, CRP monitoring is recommended at each reassessment[3]. Here, the indication is a point in the care pathway, rather than a symptom.

Cardiology follows the same logic. When heart failure is suspected, a natriuretic peptide assay is recommended, interpreted in light of age, obesity and other factors known to affect its concentration (Class I, Level C). The complete blood count, kidney function, including estimated glomerular filtration rate and urine albumin-to-creatinine ratio, electrolytes, liver tests, thyroid function, glycated hemoglobin, lipids and iron status, including transferrin saturation and ferritin, are used to screen for comorbidities (Class I, Level C)[5]. With new, persistent or increasing suspicion of hemophagocytic lymphohistiocytosis or macrophage activation syndrome (MAS), ferritin should be measured even if a previous measurement was normal[6]. The same analyte also rises in iron overload, cancer and hepatitis[6]: it is essential for the indication, but that does not make it specific.

In primary care, first-tier tests are usually ordered through a local laboratory. When ANCA-associated vasculitis is suspected, these comprise anti-proteinase 3 (PR3) and anti-myeloperoxidase (MPO) ANCA, a complete blood count, CRP, serum creatinine with estimated glomerular filtration rate, urine dipstick testing, a spot urine protein-to-creatinine ratio and assessment for microscopic hematuria. Waiting for these results should not delay treatment, and a definitive diagnosis is established in cooperation with a reference

or competence center[3]. When lupus is suspected, initial care may be provided by the primary care physician, but confirmation by a physician experienced in the disease is preferable; the extent of involvement is assessed from the outset, particularly in the kidneys by testing for proteinuria[1].

1.2 Depending on the clinical context

In the Treatise: § 8.1, § 8.3, § 9.4 and § 13.6

The second tier includes tests justified by a particular situation: a sign, a patient characteristic, a previous result or a treatment. They are not ordered initially for every patient; they are ordered when the context calls for them. A request in this tier should be able to name that context. If it cannot, the test has no place in the assessment or belongs to another tier.

Cardiac biomarkers provide the clearest example. The French systemic sclerosis protocol includes NT-proBNP (or BNP) in the initial and annual assessments, but reserves troponin testing for suspected coronary ischemia or myocarditis[4]. In ANCA-associated vasculitis, troponin and BNP or NT-proBNP, and possibly cardiac magnetic resonance imaging, are useful in eosinophilic granulomatosis with polyangiitis (EGPA) or suspected cardiac involvement[3]. For systemic immune-mediated diseases as a whole, the European working group states that natriuretic peptides should not be measured routinely, but only when cardiac symptoms or signs, such as dyspnea, suggest involvement[7]. The general rule and the disease-specific protocol do not conflict: the latter defines an indication that the former does not cover.

In systemic lupus erythematosus, CRP is usually normal except in infection, serosal involvement or MAS; during follow-up, it is requested according to the context, for example in serositis[1]. Likewise, anti-nucleosome, anti-ribosomal P protein, anti-Ku and anti-C1q antibodies are not tested routinely; their presence may contribute to the diagnosis when anti-double-stranded DNA antibody testing is negative[1]. Here, the context is a negative result that is not enough to close the question.

A previous result may also establish an indication. Specific immunoassays for anti-PR3 and anti-MPO ANCA may fail to detect them; when clinical suspicion is strong, they may be supplemented in a second step by IIF or another confirmatory test[3]. In systemic sclerosis, ANA and specific antibodies are retested at 6 to 12 months if absent at the initial assessment or if the ANA had no defined specificity, because they may become positive later[4].

In primary care, a request in this tier states the context, because the laboratory specialist can interpret a test better when its rationale is known: interpreting myositis antibody fluorescence patterns, for example, requires a laboratory specialist informed of the clinical context of the request[8]. In systemic sclerosis, NT-proBNP (or BNP), TSH and ferritin are measured at least annually during follow-up, along with an annual electrocardiogram and echocardiogram; troponin testing is reserved for suspected coronary ischemia or myocarditis[4]. In other systemic immune-mediated diseases, a natriuretic peptide is measured for dyspnea or another cardiac sign, rather than routinely[7]. In lupus, antiphospholipid antibodies and anti-SSA (Sjögren syndrome antigen A) antibodies may be rechecked when pregnancy is being considered[1]. In the lupus protocol, the term denotes anti-Ro60 antibodies; anti-Ro52 antibodies, directed against TRIM21 (tripartite motif-containing protein 21), are not anti-SSA antibodies[1]. The report should therefore specify the target: anti-Ro60 antibodies support diagnosis, anti-Ro52 antibodies are requested explicitly in the setting of a long QT interval (see 2.5, 4.6 and 18.2), and the risk of neonatal

lupus concerns the fetuses and infants of women with anti-SSA/Ro antibodies of 52 or 60 kDa, or anti-SSB/La (Sjögren syndrome antigen B) antibodies[1].

1.3 Specialist assessment

In the Treatise: § 8.1, § 10.2 and § 12.7

The third tier includes tests whose performance or interpretation requires a specialized laboratory or team: uncommon techniques, results that make sense only in light of the complete record and decisions that an isolated number should not trigger. This tier is not an inferior rank. It is the tier in which a test is not ordered without the person who will know how to interpret it.

Lupus provides two examples. Serum interferon alpha assays and type I interferon transcriptomic scores are performed in highly specialized laboratories in France; for now, they should not be used routinely to diagnose lupus or guide treatment. Persistent elevation, however, particularly during remission and outside infection, supports a Mendelian type I interferonopathy[1]. The Farr assay, the reference test for anti-double-stranded DNA antibodies, is restricted to laboratories authorized to handle radioisotopes, and IIF on *Crithidia luciliae* to specialized laboratories[1].

MAS provides a third example. Specialized biomarkers, including soluble interleukin-2 receptor, CD163 (a macrophage hemoglobin scavenger receptor), interleukin-18 and C-X-C motif chemokine ligand 9 (CXCL9), are increasingly available in reference laboratories; the 2022 European and American recommendations advise measuring them when available and interpreting them with consultants' help[6]. The same recommendations note that results often arrive too late for the initial decisions and are often unavailable outside academic centers[6].

Thrombotic thrombocytopenic purpura (TTP) provides a final example. When TTP is suspected in lupus, activity of the protease ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) is measured, together with anti-ADAMTS13 antibody testing if activity is below 10%[1]. Activity below 10 IU/dL, or 10% of normal activity, is the hallmark of TTP; between 10 and 20 IU/dL, the result is equivocal and continuing or stopping treatment depends on clinical judgment; above 20 IU/dL, other diagnoses should be considered[9]. It is precisely this equivocal zone that makes the test an expert investigation.

In primary care, these tests are not used for office triage and their turnaround time should not delay referral. When TTP is suspected, plasma for ADAMTS13 testing is collected before the first plasma exchange and before any blood product, but, when suspicion is strong, plasma exchange and corticosteroids begin without waiting for the result[9]: suspected TTP therefore requires immediate referral to the hospital team that provides these treatments. When MAS is suspected, routine tests, led by ferritin together with markers of inflammation, coagulopathy and organ injury, are sufficient to raise the alarm. The syndrome is life-threatening (see 3.4), and specialized biomarkers return too late for the initial decision[6].

1.4 A tier is neither an evidence grade nor a testing interval

In the Treatise: § 7.3, § 8.1, § 8.4, § 9.2, § 9.4 and § 9.5

A tier identifies where a test belongs in the assessment. It does not indicate the strength of the recommendation supporting it. Professional societies assign a class and level of evidence to their statements: measuring a natriuretic peptide when heart failure is suspected is a Class I, Level C recommendation[5]; the diagnostic recommendations for TTP are conditional, based on low-certainty evidence[9]. A test can therefore be essential despite a modest level of evidence, and its tier should never be cited instead of its recommendation grade.

Nor does a tier indicate how often a test should be repeated. ANA, essential for diagnosing lupus, are not markers of disease activity and are not routinely repeated[1]; the same applies to most autoantibodies (see 4.5).

When a recommendation sets a testing interval, it defines its limits. During lupus follow-up, repeating anti-double-stranded DNA antibodies more often than every 6 to 12 months is generally of no value[1]. During follow-up of ANCA-associated vasculitis, anti-PR3 and anti-MPO ANCA are often measured every 3 to 6 months; their trajectory alone should not guide treatment but may prompt closer monitoring[3]. In cardiac amyloidosis, no study has established the optimal follow-up schedule; a common approach combines visits every 6 months with NT-proBNP and troponin testing, and annual echocardiography and Holter monitoring[10].

Interpreting a laboratory assessment therefore comes down to three questions. For what indication is this test being ordered? To which tier does it belong for that indication? At what interval does repeating it change a decision? Each question is asked before ordering, rather than when the result arrives. When no recommendation sets a schedule, the interval is not standardized and depends on clinical judgment.

In primary care, between specialist consultations, shared laboratory follow-up uses published intervals. In quiescent lupus, clinical assessment takes place every 3 to 6 months (every 3 months in children in particular), and monthly during active disease, with dipstick screening for proteinuria at least at every consultation; any change in treatment calls for specialist assessment[1]. In giant cell arteritis, CRP and fibrinogen are measured at least monthly[11]. In cryoglobulinemia, follow-up covers cryoglobulin concentration, complement component C4, inflammatory markers, kidney function, proteinuria and, if present initially, the monoclonal component. Severe forms are reviewed monthly at first, then every 3 to 6 months, and every 6 months once remission is achieved; in quiescent forms, an annual consultation is desirable[12].

Table 1.1. The three tiers of laboratory assessment, tier by tier

Tier	Defining feature	Example
Essential for a defined indication	Without it, the question remains unanswered	ANA by IIF on HEp-2 cells when lupus is suspected[1]; ANCA when vasculitis is suspected[3]
Depending on the clinical context	Justified by a sign, a patient characteristic, a result or a treatment	Troponin in systemic sclerosis when coronary ischemia or myocarditis is suspected[4]
Specialist assessment	Performance or interpretation restricted to an expert team	Interferon alpha and interferon scores[1]; specialized MAS biomarkers[6]

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2

Getting specimen collection right: preanalytical pitfalls

Chapter contents

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An incorrect result is often produced before analysis: at the wrong time, in the wrong tube, during transport or during a treatment that the request did not mention. The laboratory cannot correct what it does not know. The preanalytical phase is therefore planned at the bedside with the laboratory specialist, before specimen collection.

2.1 Timing specimen collection: before treatment, when possible

In the Treatise: § 9.2 and § 10.2

Treatment sometimes erases what the assessment was meant to show. In giant cell arteritis, a systemic inflammatory response is almost universal, to the point that its absence makes the diagnosis unlikely unless corticosteroids have already been started[1]. A C-reactive protein (CRP) sample taken after the first corticosteroid doses has therefore lost some of its value. At diagnosis, only CRP is required; other inflammatory parameters are investigated only if it is normal or nearly normal[1]. When the arteritic origin of ischemic optic neuropathy is uncertain, the same protocol favors immediate CRP measurement and emergency corticosteroid treatment while awaiting expert advice[1]: specimen collection precedes the first dose but does not delay it.

Macrophage activation syndrome (MAS) requires the same discipline for other investigations. Corticosteroids may obscure the diagnosis or classification of leukemia or lymphoma; sampling intended to establish these diagnoses, whether bone marrow, a lymph node or another tissue, is therefore attempted before administration when possible[2]. Serology samples are collected before intravenous immunoglobulin infusion when feasible[2]. Ferritin is measured in every patient with suspected disease, even if a previous measurement was normal[2].

Thrombotic thrombocytopenic purpura (TTP) provides the clearest example. Plasma for ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) testing, including activity and inhibitor or anti-ADAMTS13 antibodies, is collected before the first plasma exchange and before any blood product; when suspicion is strong, plasma exchange and corticosteroids begin without waiting for the result[3]. This twofold rule applies beyond TTP: collect first, treat without waiting.

In primary care, any unusual, recent-onset headache after age 50, especially after age 70, should prompt consideration of giant cell arteritis and CRP measurement[1]. Confirmatory investigations are performed as soon as possible: Doppler ultrasonography, magnetic resonance angiography and positron emission tomography lose diagnostic performance 3 to 7 days after corticosteroids begin, whereas temporal artery biopsy lesions persist for at least 15 days, so biopsy does not delay treatment[1]. Ophthalmic involvement makes corticosteroid therapy an absolute therapeutic emergency, and prednisone may then be started in primary care[1]. Transient visual symptoms often leave a normal ophthalmic examination, which should neither reassure nor delay treatment[1]. Hospital fast-track pathways accelerate diagnosis, and physicians who suspect the disease are strongly advised to contact their internal medicine or rheumatology colleagues[1].

2.2 The tube, temperature and turnaround time

In the Treatise: § 9.5

Some tests allow no approximation. Cryoglobulins precipitate in vitro below 37 °C; their concentration is often below 1 g/L and the first detection step is purely visual, requiring a sufficient blood volume[4]. Testing requires close communication between the clinician and technical team. A sample that cools before processing risks a false-negative result, because the cryoglobulin may precipitate in the tube as soon as the temperature falls below 37 °C[4].

The French protocol specifies the conditions[4]. Collection equipment is preincubated at 37 °C, and a transport device at 37 °C is ready before the procedure. The patient has avoided dietary fat for at least 4 to 6 hours. Two or three 5 mL no-additive tubes without separator gel are required; they are kept at approximately 37 °C and sent immediately to the laboratory. If the collecting laboratory sends the test elsewhere, it incubates the tubes for at least 2 hours at 37 °C, centrifuges them, ideally at 37 °C, and separates the serum before shipment. If these conditions cannot be met, it is better not to collect the sample and to refer the patient to a laboratory that can meet them.

Reading the test requires patience of its own. It takes place after 7 days of serum storage at +4 °C, although an initial reading at 24 or 48 hours may reveal early cryoglobulins; a negative result is issued only if no precipitate is present at 7 days[4]. Lipids in a nonfasting patient and hemolysis may interfere. During follow-up, a change of more than 25% above or below the initial concentration is required to establish a rise or fall; concentrations above 50 mg/L are considered pathological by most teams, but a very low cryoglobulin concentration is also interpreted in light of suggestive signs[4].

A negative result must therefore be interpreted with its collection conditions. The absence of detectable cryoglobulin does not exclude cryoglobulinemic glomerulonephritis when the cryoglobulin concentration is low or collection conditions were suboptimal; low complement component C_4 or rheumatoid factor should prompt a search for cryoglobulinemia[4]. By contrast, N-terminal pro-B-type natriuretic peptide (NT-proBNP) has the advantage of greater stability at room temperature, allowing reliable measurement both in hospital and in primary care[5].

In primary care, before ordering cryoglobulin testing, it is preferable to check that the community laboratory can meet the collection requirements. If it sends the test elsewhere, it incubates and centrifuges the sample and separates the serum before shipment, after which transport may take place at room temperature; if it cannot do so, the patient is referred to a laboratory that can[4]. The report gives a negative result only after 7 days at +4 °C, and a positive or uncertain result is supplemented by quantification and identification of the cryoprecipitate; its type guides the etiologic investigation[4]. Repeated testing on three consecutive days is no longer practiced, except in a suggestive clinical setting after an initial negative result[4]. Testing often requires a specialized laboratory, and a definitive diagnosis is established in cooperation with a reference or competence center[4].

2.3 Current treatments

In the Treatise: § 8.1, § 8.5, § 9.2 and § 13.6

Blocking interleukin-6 signaling rapidly normalizes CRP, erythrocyte sedimentation rate, fibrinogen and haptoglobin. In giant cell arteritis, these parameters become uninterpretable for follow-up and infection detection: during tocilizumab treatment, they generally do not rise even with relapse or an intercurrent infection, and a genuine infection may progress without elevated inflammatory markers[1]. A normal CRP during this treatment provides no reassurance about either relapse or infection.

Natriuretic peptides are interpreted alongside the medication list. Their concentrations are lowered by angiotensin receptor–neprilysin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, mineralocorticoid receptor antagonists and sodium-glucose cotransporter 2 inhibitors[5]. Sacubitril-valsartan may, conversely, increase B-type natriuretic peptide (BNP), whose degradation it alters; NT-proBNP is unaffected by this mechanism[5]. During this treatment, the N-terminal form therefore remains interpretable and falls, as it does with the other heart failure treatments listed above[5].

Anticoagulants interfere with lupus anticoagulant testing and may cause false-positive or false-negative results. The French antiphospholipid syndrome protocol ideally calls for testing without any anticoagulant treatment, but accepts testing during treatment when necessary, with precautions specific to each agent[6]. With a vitamin K antagonist, the usual procedure is followed if the international normalized ratio (INR) is below 1.5; between 1.5 and 3, testing is performed directly on a mixture with control plasma using an adjusted positivity threshold, and the report notes the risk of a false-negative result for a weak lupus anticoagulant; above 3, testing is not performed. With low-molecular-weight heparin, the sample is collected just before the next injection, and the laboratory specialist measures residual anti-Xa activity to assess whether testing is feasible; with unfractionated heparin, anti-Xa activity is used to check that the heparin concentration does not exceed the reagent's neutralization capacity. With a direct oral anticoagulant, even very low concentrations risk false-positive results, particularly with the dilute Russell viper venom time: testing is not performed[6]. The laboratory can apply these rules only if it knows the treatment. Interference also works in the other direction: variable thromboplastin sensitivity to lupus anticoagulant may make the INR unstable in a patient taking a vitamin K antagonist[7].

The treatment itself can be measured. In lupus, the blood hydroxychloroquine concentration is measured primarily when nonadherence is suspected, particularly during a flare; the protocol lists it among follow-up tests alongside the complete blood count, serum creatinine, complement components and anti-double-stranded DNA antibodies[8]. A flare during a treatment that is not being taken is not treatment failure.

In primary care, a laboratory request mentions treatments that distort interpretation. For lupus anticoagulant testing, the request specifies the anticoagulant, dose and administration time, which determine whether the test can be performed and how the result is interpreted[6]. In a patient taking sacubitril-valsartan, the peptide to monitor is NT-proBNP, which the combination does not distort: a fall during treatment is expected[5]. During tocilizumab treatment, an infection may have very subtle clinical features and progress without elevated inflammatory markers; this is why the giant cell arteritis protocol reserves prescribing this treatment for experienced physicians[1]. During a lupus

flare, particularly if adherence is uncertain, a blood hydroxychloroquine concentration is requested before concluding that treatment has failed[8].

2.4 The laboratory's method and threshold

In the Treatise: § 7.3, § 8.1, § 8.5 and § 17.1

A threshold belongs to a technique. For anticardiolipin and anti-β2-glycoprotein I antibodies, the French lupus protocol notes that the criteria suggest, for guidance, 40 units for a moderate titer and 80 for a high titer by enzyme-linked immunosorbent assay (ELISA), and that chemiluminescence tests use different thresholds[8]. The 2023 American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) classification criteria set these thresholds for standardized ELISA, not automated platforms. According to a study cited by these criteria, an immunoglobulin G (IgG) anticardiolipin titer of 40 to 79 ELISA units corresponded to 200 to 400 chemiluminescence units; this correspondence has no direct application yet, and the criteria ask that results from different platforms not be mixed in clinical research[9]. These thresholds serve classification. For diagnosis, the French antiphospholipid syndrome protocol considers IgG or immunoglobulin M (IgM) anticardiolipin above 40 units or the 99th percentile, and IgG or IgM anti-β2-glycoprotein I above the 99th percentile, to be significant when measured by standardized ELISA; newer chemiluminescence or multiplex bead tests express their values differently from ELISA[6].

Lupus anticoagulant is detected by prolongation of a phospholipid-dependent clotting time that is not corrected by adding normal plasma but is corrected by excess phospholipids[8]. It is assessed in citrated plasma after double centrifugation, in three stages: screening, mixing and confirmation; the two recommended screening tests are the dilute Russell viper venom time and an activated partial thromboplastin time with a lupus anticoagulant-sensitive reagent[6].

The choice of assay matters as much as its threshold. Both troponin I and T can be used to diagnose immune checkpoint inhibitor-associated myocarditis, but clinical observations suggest that troponin T may be falsely elevated in a patient with myositis without myocarditis[10]. For anti-double-stranded DNA antibodies, quantitative immunologic methods are more sensitive and less specific than the Farr assay; in an uncertain presentation, a weakly positive result by these methods may warrant confirmation by the Farr assay or on *Crithidia luciliae*[8].

Two other methodological rules recur in cardiac assessments. Serum and urine protein electrophoresis should always be accompanied by immunofixation, which increases sensitivity for low concentrations of monoclonal proteins; serum and urine immunofixation combined with serum free light chain measurement has 99% sensitivity for the precursor of immunoglobulin light chain (AL) amyloidosis[11]. Erythrocyte sedimentation rate varies with hypergammaglobulinemia or anemia independently of inflammation; this is why the giant cell arteritis protocol favors fibrinogen as a marker with slow kinetics[1].

In primary care, an antiphospholipid antibody titer is interpreted against the thresholds of the laboratory that measured it, because chemiluminescence does not share ELISA thresholds[8]; the report should therefore specify the technique, and results obtained by different techniques should not be compared number for number. A change in cryoglobulin concentration is accepted only beyond 25% of the initial concentration[4]. When cardiac amyloidosis is sus-

pected, the request combines serum and urine protein electrophoresis with immunofixation and serum free light chain measurement; diagnosis should be obtained promptly because prognosis depends largely on early treatment, particularly in AL amyloidosis[11].

2.5 False-positive and false-negative results

In the Treatise: § 8.4, § 9.4, § 12.2, § 13.6 and § 20.7

Some false-positive results arise from the target. The anti-SSA (Sjögren syndrome antigen A) antibodies relevant to Sjögren syndrome diagnosis are anti-Ro60, not anti-Ro52; most laboratories report "anti-SSA" only for anti-Ro60, but this should be checked. Isolated anti-Ro52 antibodies, also called anti-TRIM21 (tripartite motif-containing protein 21), are nonspecific and occur in healthy individuals or other autoimmune diseases. Isolated anti-SSB (Sjögren syndrome antigen B) antibodies are usually a laboratory false-positive result just above the threshold[12].

Some false-negative results arise from the screening technique. In rare cases, anti-SSA/Ro60 antibodies are present without fluorescence on HEp-2 cells (a human cell line); when clinical suspicion exists, testing may still be requested[12]. Myositis antibody methods are not standardized; confirmation with a second method may be justified for weak positivity, discordance with the immunofluorescence pattern or discordance with a strongly suggestive clinical presentation. These errors remain uncommon, and the laboratory specialist should know the clinical context of the request[13].

Immunoassays for anti-proteinase 3 and anti-myeloperoxidase antineutrophil cytoplasmic antibodies (ANCA) may yield false-negative results; when suspicion is strong, indirect immunofluorescence or another confirmatory test supplements them[14]. Conversely, ANCA, often atypical but sometimes anti-proteinase 3-specific, occur in infections, particularly infective endocarditis, bartonellosis and tuberculosis, and in inflammatory bowel disease; after use of levamisole-adulterated cocaine, they are common, often with dual anti-proteinase 3 and anti-myeloperoxidase specificity[14].

Troponin has its own analytical pitfalls. Hemolysis and biotin may lower it and fibrin microclots may increase it; heterophile antibodies, rarely, or macrotroponin complexes, whose half-life can reach several weeks, may produce elevated values without myocardial injury[15]. Interference is suspected when troponin does not fit the clinical picture or varies illogically between measurements; discordance between troponin I and T, or between two troponin I assays, is highly suggestive[15].

Finally, a value can be interpreted only in relation to its population. The neutrophil count is interpreted in light of patient ancestry, because neutropenia may be physiological in patients of African ancestry[8]: this nonpathological phenotype, associated with the Duffy-null blood group, occurs mainly in people of African or Middle Eastern ancestry[16]. NT-proBNP concentrations are closely linked to age and lose specificity in older adults (see 3.2)[5]. The troponin 99th percentile, which defines myocardial injury, is sex-specific and lower in women[15].

In primary care, a report of "positive anti-SSA" is checked: it should mean anti-Ro60, and the laboratory should be asked if the wording does not specify it[12]. An unexpectedly elevated troponin is remeasured in a new sample before any conclusion is drawn[15]; if doubt persists, an assay using another method can identify interference, and macrotroponin testing requires a specialized laboratory[15]. A positive ANCA does not remove the need to look for infective

endocarditis, an important differential diagnosis that may be accompanied by ANCA, sometimes with anti-proteinase 3 specificity[14].

Table 2.1. The preanalytical phase of laboratory assessment, pitfall by pitfall

Pitfall	What to do
Corticosteroids, immunoglobulins or plasma exchange already started	Collect samples beforehand when possible, without delaying treatment[1, 2, 3]
Cryoglobulin sample allowed to cool	Arrange 37 °C handling from collection to the laboratory, with the patient fasting; otherwise, do not collect[4]
CRP during tocilizumab treatment	Do not interpret a normal CRP as absence of relapse or infection[1]
Lupus anticoagulant during anticoagulant treatment	State the agent, dose and administration time; no testing with a direct oral anticoagulant or an INR above 3[6]
Antiphospholipid antibody thresholds	Interpret the value against the local threshold for the technique used; do not compare two techniques number for number; the 40 and 80 unit thresholds apply to classification using ELISA[6, 8, 9]
Troponin T and myositis	Interpret elevated troponin T cautiously in myositis; troponin I may be used[10]
Troponin discordant with the clinical picture	Remeasure in a new sample; suspect interference[15]

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3

Common cardiac biomarkers: troponin, natriuretic peptides, C-reactive protein and ferritin

Chapter contents

3.1 Troponin 17
3.2 Natriuretic peptides 18
3.3 C-reactive protein 19
3.4 Ferritin 20

Four routine assays recur in almost every assessment of an immune disease affecting the heart. None names a disease. Each measures an impact or a process, and each has blind spots that should be understood before interpreting the number.

3.1 Troponin

In the Treatise: § 6.2, § 7.3, § 13.6, § 17.1 and § 20.7

Troponin indicates that myocardium is being injured; it does not say why. The European working group on myocardial and pericardial diseases states this for systemic immune-mediated diseases as a whole: elevated troponin or N-terminal pro-B-type natriuretic peptide (NT-proBNP) may reflect myocardial involvement regardless of cause; troponin may also rise in extracardiac disease, such as pulmonary embolism; and myocarditis may occur without any troponin release[1]. The marker is therefore fallible in both directions.

The Fifth Universal Definition of Myocardial Infarction, published in 2026, establishes the terminology. Acute myocardial injury is defined by a rise or fall in troponin, with at least one value above the sex-specific 99th percentile upper reference limit; its nonischemic mechanisms include autoimmune, infectious or toxic myocarditis and immune checkpoint inhibitors[2]. Chronic injury is considered when at least two values exceed this threshold in a stable patient; it is up to five times more common with troponin T than with troponin I, and halving the glomerular filtration rate doubles the baseline troponin concentration[2].

An ischemic cause is excluded first. In many systemic immune-mediated diseases, accelerated coronary artery disease and coronary microvascular dysfunction may dominate or contribute to the presentation; an ischemic cause should therefore be excluded first when clinically indicated[1]. Only then does troponin become a disease-specific warning signal: an unexplained rise in troponin I or NT-proBNP in lupus, or an unexplained more than 3-fold elevation in creatine kinase or troponin in systemic sclerosis[1].

In inflammatory myopericardial syndromes, the 2025 European guideline assigns troponin three roles. It rises with myocardial involvement and usually reflects cardiomyocyte necrosis; its baseline measurement is essential for assessing myocarditis severity; it is typically elevated in infarct-like presentations[3]. In chronic myocarditis, however, myocardial injury biomarkers are usually normal[3]. A normal troponin later in the course therefore does not close the question.

During immune checkpoint inhibitor treatment, troponin forms part of the definition of myocarditis itself. Clinical diagnosis combines a new troponin elevation or a significant change from baseline with one major or two minor criteria, after excluding acute coronary syndrome and acute infectious myocarditis[4]. Troponin I and T may both be used, but troponin T may be falsely elevated with associated myositis without myocarditis[4]. Myocarditis that does not resolve or worsens despite high-dose methylprednisolone, clinically or through persistently elevated troponin after other causes have been excluded, defines the steroid-refractory form[4].

Disease-specific protocols define the indication. In systemic sclerosis, troponin is requested when coronary ischemia or myocarditis is suspected[5]; in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, it is requested in eosinophilic granulomatosis with polyangiitis (EGPA) or suspected cardiac involvement[6]. In immunoglobulin light chain (AL) amyloidosis, troponin and NT-proBNP form part of Mayo Clinic staging, revised in 2012 to

add free light chain burden[7]. One point is assigned for each of the following: a difference of at least 18 mg/dL, or 180 mg/L, between involved and uninvolved light chains, troponin T of at least 0.025 ng/mL, or 25 ng/L, measured by a conventional rather than high-sensitivity assay, and NT-proBNP of at least 1,800 pg/mL; this defines four stages, from 0 to 3 points[8]. In cardiac amyloidosis, a common follow-up schedule includes troponin and NT-proBNP every 6 months[7].

In primary care, when symptoms or signs of myocarditis are present in a patient seen in the office, the initial assessment includes troponin, NT-proBNP, C-reactive protein and a complete blood count, alongside electrocardiography and echocardiography (Class I); elevated troponin prompts hospital referral[3]. The value is interpreted against the sex-specific 99th percentile for the assay used, and an elevated value is generally repeated to distinguish acute from chronic injury[2]. Before immune checkpoint inhibitor treatment, an electrocardiogram, a natriuretic peptide and troponin are recommended in all patients (Class I, Level B); this baseline value will serve to assess any subsequent elevation[4].

3.2 Natriuretic peptides

In the Treatise: § 7.3, § 11.2 and § 13.6

A natriuretic peptide assay is recommended to support a diagnosis of heart failure. NT-proBNP is the most widely used in Europe; it has two advantages: greater stability at room temperature and a result that is not distorted by sacubitril-valsartan, whereas the combination alters B-type natriuretic peptide (BNP) degradation; during this treatment, NT-proBNP falls as it does with other heart failure treatments (see 2.3). Some regions use BNP or mid-regional pro-atrial natriuretic peptide[9].

Thresholds depend on age. In outpatients, the 2026 European guideline adopts the thresholds proposed by the Heart Failure Association of the European Society of Cardiology (ESC), above which heart failure is likely: NT-proBNP of at least 125 pg/mL before age 50, 250 pg/mL between ages 50 and 75 and 500 pg/mL above age 75; data are insufficient to define age-specific BNP thresholds[9]. The 2021 European guideline used a single rule-out threshold, NT-proBNP below 125 pg/mL; although simple, this threshold lacks specificity in older adults because peptide concentrations are closely linked to age: more than 75% of a healthy population over age 80 exceeds 125 pg/mL[9].

Many situations shift the number. Concentrations rise, among other settings, with myocarditis, pulmonary hypertension, atrial fibrillation, pulmonary embolism, left ventricular hypertrophy, kidney dysfunction, severe anemia or infection, age and female sex. They fall with obesity, African ancestry, several heart failure treatments and one disease, constrictive pericarditis[9]. Kidney dysfunction raises NT-proBNP, but this is not a reason to discard the assay; and the higher the concentration, the more likely heart failure becomes[9].

In systemic immune-mediated diseases, measurement follows an indication. The European working group calls for testing to be aligned with heart failure guidelines, rather than performed routinely, and limited to cardiac symptoms or signs[1]. The French systemic sclerosis protocol includes NT-proBNP or BNP in initial and annual assessments[5]; the ANCA-associated vasculitis protocol proposes them for EGPA or suspected cardiac involvement[6]. In both protocols, the two peptides are alternatives, rather than assays to combine. Monoclonal gammopathy creates another indication: in patients with this condition, the 2026 British guideline adds NT-proBNP and urine protein-to-creatinine and

albumin-to-creatinine ratios to routine investigations at baseline and at every follow-up (Grade 1A). Troponin testing may be considered if NT-proBNP is abnormal; an unexplained NT-proBNP above 332 pg/mL or a progressively rising concentration should raise strong suspicion of cardiac amyloidosis. Falling albumin and elevated alkaline phosphatase are noted and investigated if persistent (Grade 1A); progression to AL amyloidosis may occur without a substantial rise in clonal light chains (Grade 1A)[10].

The peptide also serves prognosis. When myocarditis is suspected, baseline measurement is recommended; it may be repeated at discharge and during follow-up to assess event risk, and NT-proBNP predicts heart failure whether ejection fraction is normal or impaired[3]. In transthyretin cardiac amyloidosis, the National Amyloidosis Centre system combines NT-proBNP at a threshold of 3,000 pg/mL and estimated glomerular filtration rate at a threshold of 45 mL/min/1.73 m^2 [7]. Finally, because constrictive pericarditis is among the causes of lower concentrations, a low peptide does not exclude it[9].

In primary care, the peptide to measure is NT-proBNP: its stability at room temperature allows reliable testing outside hospital[9]. When heart failure is clinically suspected, it supports the diagnosis, is interpreted against age-specific thresholds and helps avoid unnecessary echocardiograms and specialist consultations[9]. In English primary care data, patients with heart failure and NT-proBNP above 2,000 pg/mL had a twofold higher risk of early heart failure hospitalization; this high-risk group warrants expedited specialist assessment[9]. The result is interpreted alongside the medication list, age, weight and kidney function[9]. In systemic sclerosis, NT-proBNP is measured at least annually, together with annual electrocardiography and echocardiography[5].

3.3 C-reactive protein

In the Treatise: § 5.2, § 9.2 and § 9.4

C-reactive protein (CRP) is a sensitive but nonspecific marker of inflammation, induced primarily by interleukin-6. In autoimmune diseases characterized by a type I interferon signature, it appears unreliable[3]. Lupus is the example: CRP is usually normal except in infection, serosal involvement or macrophage activation syndrome (MAS)[11]. An elevated CRP in a patient with lupus therefore first prompts investigation for one of these three causes. At the other end of the spectrum, monogenic autoinflammatory diseases involve elevated acute-phase proteins, such as CRP, without high-titer autoantibodies[1].

In pericarditis, CRP is elevated in up to 80% of patients, as in acute myocarditis, and contributes to diagnosis; a negative result does not exclude the diagnosis[3]. The noninflammatory pericarditis phenotype, without elevated CRP or with only a small rise in inflammatory markers, affects 10 to 20% of patients[3]. In pericarditis, CRP is an activity marker that may guide the duration of anti-inflammatory treatment[3].

In vasculitis, CRP is monitored but does not determine decisions alone. In ANCA-associated vasculitis, monitoring is recommended at every reassessment; its elevation and concentration are insufficiently correlated with activity to make it a predictive test on its own. Persistent or new elevation during follow-up prompts investigation for potential infectious foci and other signs of activity[6]. In giant cell arteritis, CRP generally normalizes within 1 to 3 weeks after starting treatment; during follow-up, the protocol recommends measuring CRP and a slow-kinetics marker, fibrinogen, at least monthly; during tocilizumab treatment, these markers generally do not rise even during relapse

or infection[12]. CRP is also included in the initial assessment of systemic sclerosis[5].

In primary care, CRP is the most widely shared follow-up test. In giant cell arteritis, a renewed rise, with or without recurrent symptoms, signals possible renewed activity, which the primary care physician has a role in identifying[12]. In ANCA-associated vasculitis, persistently elevated or rising CRP first prompts a search for an infectious focus[6]. Pericarditis without high-risk features may be treated as an outpatient, with early reassessment after one or two weeks; CRP monitoring helps assess remission and adjust treatment duration in complicated or difficult cases, whereas clinical follow-up alone is sufficient in uncomplicated cases[3].

3.4 Ferritin

In the Treatise: § 10.2 and § 13.6

Ferritin has two faces. As a marker of iron stores, it forms part of iron status together with transferrin saturation, recommended when screening for comorbidities in suspected heart failure[9]. As an inflammatory marker, it usually rises in any inflammatory syndrome[13]. The same number is therefore interpreted differently depending on the question, and iron status cannot be interpreted without the patient's inflammatory state.

In MAS and hemophagocytic lymphohistiocytosis, ferritin is a sensitive test. The 2022 European and American recommendations call for measurement in every patient with new, persistent or increasing suspicion, even if a previous measurement was normal; it is elevated in almost all patients with the systemic form and appears in every existing set of criteria[14]. Initial follow-up may include daily CRP and ferritin measurements; a higher baseline ferritin and failure to decrease during treatment are associated with a less favorable course[14].

The threshold is the difficulty. In children, a threshold of 500 ng/mL had 84% sensitivity for hemophagocytic lymphohistiocytosis, but it is poorly specific in other settings; thresholds used range from 500 to 2,000 ng/mL in children and often exceed 10,000 ng/mL in adults, in whom infectious and malignant causes predominate. Iron overload, cancer and hepatitis often raise ferritin without any MAS[14]. No threshold applies to every situation.

In adult-onset Still disease, ferritin supports diagnosis mainly when markedly elevated. A value above 4 times normal is found in only 67% of patients, with 85% specificity; a fall in the glycosylated fraction below 20%, compared with a normal value of 60 to 80%, is additional support but is not always present[13]. The usefulness of these two markers during follow-up has not been demonstrated, although a rise in ferritin or a fall in its glycosylated fraction might reflect a flare[13].

In lupus, suspected MAS prompts testing for hypofibrinogenemia, hyperferritinemia, hypertriglyceridemia, elevated lactate dehydrogenase and a mixed pattern of hepatic injury; hemophagocytosis on bone marrow aspirate supports diagnosis, but its absence does not exclude it[11]. Ferritin is therefore interpreted with fibrinogen, triglycerides and liver enzymes, rather than alone. Ferritin is also included in the initial and annual assessments of systemic sclerosis[5].

In primary care, ferritin is requested with transferrin saturation whenever heart failure is suspected (Class I, Level C)[9]. A very high ferritin in a febrile patient with cytopenias, coagulopathy or liver involvement suggests MAS; this syndrome is life-threatening, can progress rapidly and has required intensive

care in nearly half of affected adults: suspicion calls for immediate hospital advice[14]. The 2022 recommendations are also directed at primary care physicians[14].

Table 3.1. Common cardiac biomarkers, marker by marker

Marker	What it indicates	What it does not indicate	Main pitfall
Troponin	Myocardial injury above the sex-specific 99th percentile, regardless of cause[1,2]	The cause; a normal value does not exclude myocarditis[1]	Troponin T elevation from associated myositis[4]; analytical interference[2]
NT-proBNP or BNP	Probable cardiac impact, increasingly likely as the concentration rises[9]	Ejection fraction; a low value does not exclude constriction[9]	Age, kidney function, obesity and treatments[9]
CRP	Inflammation[3], mainly mediated by interleukin-6	Vasculitis activity on its own[6]	Normal in lupus outside infection, serositis or MAS[11]; generally does not rise during tocilizumab treatment[12]
Ferritin	Inflammation or iron stores[9,13]	MAS on its own[14]	Iron overload, cancer, hepatitis[14]

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4

Autoantibodies: techniques, titers and the meaning of a result

Chapter contents

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An autoantibody is a supporting finding, rarely proof. Its value depends on the technique that detected it, the titer reported and the clinical question that prompted testing. Interpreting a result means working back through these three levels before drawing a conclusion.

4.1 Techniques

In the Treatise: § 8.1, § 8.3, § 9.4 and § 12.2

Antinuclear antibody (ANA) screening relies on indirect immunofluorescence (IIF) on HEp-2 cells (a human cell line), the reference method. If positive, the laboratory specifies the titer and pattern; it may, on its own initiative, test for anti-double-stranded DNA antibodies and antibodies to extractable nuclear antigens (ENA), even if they were not ordered[1]. IIF is a screening test: it indicates the presence of antibodies directed against the nucleus, and the fluorescence pattern points toward their target without always identifying it.

For antineutrophil cytoplasmic antibodies (ANCA), the testing sequence has changed. Testing used to combine IIF with a method specific for myeloperoxidase (MPO) and proteinase 3 (PR3), using enzyme-linked immunosorbent assay (ELISA), flow fluorimetry or dot blot. In 2017, an international consensus proposed using antigen-specific tests from the outset, as they are more sensitive and specific than IIF, without prior IIF screening; in severe presentations, dot blot provides anti-PR3 and anti-MPO results within hours[2]. Other ANCA targets, such as elastase, cathepsin G or lactoferrin, have no clinical relevance and should not be tested[2].

Specificities are identified by their own techniques. In systemic sclerosis, anticentromere antibodies are defined by the fluorescence pattern, anti-topoisomerase I by immunoblot, anti-RNA polymerase III by ELISA or immunoblot, and antibodies in myositis overlap syndromes, anti-PM-Scl (polymyositis-scleroderma) and anti-Ku, by immunoblot or immunodot[3]. Myositis antibodies are tested by immunodot, addressable laser bead immunoassay (ALBIA) or ELISA, after HEp-2 IIF whose nuclear or cytoplasmic pattern requires an experienced laboratory specialist informed of the clinical context[4].

Anti-double-stranded DNA antibodies are tested, in decreasing order of specificity, by the Farr assay, IIF on *Crithidia luciliae* and quantitative immunologic methods; antibodies to denatured DNA and immunoglobulin M (IgM) anti-double-stranded DNA antibodies have no diagnostic value for systemic lupus erythematosus[1]. Antiphospholipid antibodies comprise a coagulation test, lupus anticoagulant, and immunologic tests for immunoglobulin G (IgG) and IgM anticardiolipin and anti-β2-glycoprotein I antibodies[1].

In primary care, the request names the technique and target. It asks for "antinuclear antibodies by indirect immunofluorescence on HEp-2 cells," and a positive ANA report should give the titer and pattern; the laboratory may add anti-double-stranded DNA and anti-ENA testing on its own initiative[1]. It asks for "anti-PR3 and anti-MPO ANCA," because antigen-specific tests serve as first-line screening; elastase, cathepsin G and lactoferrin are not requested[2]. For myositis antibodies, it states the clinical context, on which fluorescence interpretation depends[4].

4.2 Titer and threshold

In the Treatise: § 8.1, § 8.3 and § 8.5

A titer is interpreted against a threshold. In the 2019 systemic lupus erythematosus classification developed by EULAR, then the European League Against Rheumatism and now the European Alliance of Associations for Rheumatology, and the American College of Rheumatology (ACR), the entry criterion is an ANA titer of at least 1:80 on HEp-2 cells or by an equivalent test; below this titer, the diagnosis becomes extremely unlikely[1]. In a systematic review involving 13,080 patients with lupus, HEp-2 ANA sensitivity was 97.8% at 1:80 and 86.0% at 1:320, with specificities of 74.7% and 96.6%. At the low threshold, the test helps rule lupus out; only a high titer points toward it[5]. In systemic sclerosis, more than 90% of patients have ANA above 1:160 or 1:200, with two main patterns, centromere and nucleolar; in 20 to 30% of cases, however, no target antigen is identified[3].

For antiphospholipid antibodies, the threshold depends on the technique. The French lupus protocol notes that the criteria suggest, for guidance, 40 units for a moderate titer and 80 for a high titer by ELISA; chemiluminescence does not use the same thresholds[1]. The 2023 ACR/EULAR classification criteria define a moderate titer as 40 to 79 units and a high titer as at least 80 units by ELISA; IgG and IgM isotypes are not added together; "persistent" positivity requires two positive results at least 12 weeks apart[6]. These are classification criteria for research, rather than diagnostic criteria.

A weakly positive result should be confirmed. In an uncertain presentation, weakly positive anti-double-stranded DNA antibodies by a quantitative method may warrant confirmation by the Farr assay or on *Crithidia luciliae*, to avoid an incorrect lupus diagnosis[1]. For myositis antibodies, a second method may be justified in weak positivity or discordance[4]. Isolated anti-SSB (Sjögren syndrome antigen B) antibodies are usually a false-positive result just above the threshold[7].

In primary care, a titer is interpreted with its laboratory's threshold and technique. Lupus anticoagulant testing in an anticoagulated patient follows the rules set out in section 2.3: the request specifies the agent, dose and administration time[8]. Elevated C-reactive protein (CRP) and fibrinogen may cause a false-positive result and pregnancy a false-negative result: testing is repeated well after the thrombotic event, once inflammation has resolved, or from the third month postpartum[8]. Anticardiolipin and anti-β2-glycoprotein I antibodies are not affected by anticoagulants, but newer techniques produce values that cannot be compared with ELISA values[8].

4.3 What a positive result allows

In the Treatise: § 8.1, § 8.3, § 8.4, § 8.5 and § 9.4

Positive ANA alone allow almost no conclusions. Their presence is poorly specific: they occur in other systemic diseases, some liver diseases, hematologic conditions and viral infections, with certain medications and even in healthy individuals. Autoantibodies alone do not diagnose lupus, which is first suspected from compatible symptoms[1]. In a suggestive presentation, however, a significant ANA titer together with anti-double-stranded DNA antibodies allows the diagnosis to be established[1]. Isolated anti-DFS70 (dense fine speckled 70 kDa protein) antibodies occur in healthy individuals and have no diagnostic value[1].

A positive ANCA allows more in the right context. Detection of anti-PR3 or anti-MPO ANCA may be sufficient, without histologic confirmation and

in a suggestive presentation, to establish a diagnosis of ANCA-associated vasculitis and begin treatment promptly[2]. Yet ANCA, often atypical but sometimes anti-PR3-specific, occur in infections, particularly infective endocarditis, bartonellosis and tuberculosis, and in inflammatory bowel disease; they are common after levamisole-adulterated cocaine use[2]. A positive ANCA therefore does not remove the need to exclude endocarditis when the presentation suggests it.

A specificity provides direction without setting limits. Systemic sclerosis antibodies identify forms at greater risk of particular visceral complications, but these associations are neither automatic nor exclusive: a patient with anti-topoisomerase I may have no lung involvement, and a patient with anticentromere antibodies may have severe interstitial lung disease[3]. Anti-ribosomal P protein antibodies are statistically associated with neuropsychiatric and hepatic lupus involvement, without individual diagnostic value; anti-C1q antibodies are associated with proliferative glomerulonephritis[1]. Anti-U1-RNP (U1 nuclear ribonucleoprotein) antibodies, in contrast, are the defining laboratory criteria for mixed connective tissue disease[1].

Anti-SSA (Sjögren syndrome antigen A) antibodies require the target to be checked. Those relevant to Sjögren syndrome diagnosis are anti-Ro60; isolated anti-Ro52, or anti-TRIM21 (tripartite motif-containing protein 21), are nonspecific. Most laboratories report anti-SSA only for anti-Ro60, but this should be checked with the laboratory. Anti-SSA/Ro60 points toward two diseases, Sjögren syndrome and lupus[7]. Anti-Ro52 antibodies are in fact misnamed: directed against TRIM21, they are not anti-SSA antibodies[1].

Antiphospholipid antibodies are common in lupus even without thrombosis or obstetric complications[1]. Their significance depends on the profile. The 2019 European recommendations define a high-risk profile by lupus anticoagulant, double or triple positivity or persistently high titers[9]. Antiphospholipid syndrome can be established only when a marker remains persistently present 12 weeks after the first test[1].

In primary care, positive anti-PR3 or anti-MPO ANCA in a suggestive presentation call for prompt specialist advice: they may be sufficient to establish the diagnosis and begin treatment, and definitive diagnosis is established in cooperation with a reference or competence center[2]. Infective endocarditis, an important differential diagnosis that may be accompanied by ANCA, is investigated from the initial assessment[2]. Anti-RNA polymerase III antibodies indicate a high risk of scleroderma renal crisis: patients at risk learn home blood pressure monitoring, and any corticosteroid prescription requires specialist advice, because a prednisone dose above 15 mg daily in the preceding three months appears to promote crisis[3].

4.4 What a negative result does not exclude

In the Treatise: § 8.1, § 8.3, § 8.4 and § 9.4

Absence of anti-double-stranded DNA antibodies does not exclude systemic lupus erythematosus, nor does absence of anti-ENA antibodies[1]. An anti-ENA panel includes at least anti-Sm, anti-Ro60/SSA, anti-La/SSB and anti-U1-RNP antibodies; anti-Sm antibodies, although uncommon, are highly specific for lupus[1]. Anti-nucleosome antibodies are present in 10% of lupus cases without anti-double-stranded DNA antibodies; together with anti-ribosomal P protein, anti-Ku and anti-C1q antibodies, they are not tested routinely but may help when anti-double-stranded DNA testing is negative[1].

ANCA immunoassays can miss antibodies; with strong clinical suspicion, IIF or another confirmatory test supplements them as a second step[2]. In eosinophilic granulomatosis with polyangiitis (EGPA), anti-MPO ANCA are found in only one-third of cases[2]; cardiac involvement is associated with marked eosinophilia and absence of ANCA, and endomyocardial biopsy may establish the diagnosis, particularly in ANCA-negative patients whose cardiac involvement is early or predominant[10]. A negative ANCA therefore does not exclude cardiac vasculitis.

An initial negative assessment may simply be early. In systemic sclerosis, patients without ANA or without an identified specificity should be retested later, because antibodies may become positive or reveal a specificity subsequently[3]. In Sjögren syndrome, anti-SSA antibodies are present in only two-thirds of patients and, rarely, may exist without HEp-2 cell fluorescence; testing may then be requested despite negative screening[7].

In primary care, when Sjögren syndrome is suspected, the first step is ANA testing on Ro60/SSA-transfected cells, together with anti-SSA/Ro60 and anti-La/SSB testing; rheumatoid factor, positive in half of cases but without anti-cyclic citrullinated peptide antibodies, and protein electrophoresis for polyclonal hypergammaglobulinemia are added[7]. Negative results do not exclude the diagnosis, because 30% of patients have no detectable autoantibodies; the patient is then referred to a rheumatologist, an internist or a competence or reference center, and salivary gland biopsy is performed in an expert center[7].

4.5 Whether to repeat an autoantibody test

In the Treatise: § 8.1, § 8.9 and § 9.4

Most autoantibodies are diagnostic markers, not activity markers. In lupus, ANA and other nonspecific antibodies are not markers of disease activity and should not be routinely repeated[1]. The same rule applies in systemic sclerosis, apart from retesting at 6 to 12 months after an initial negative assessment or one without defined specificity[3]. A positive anti-SSA test is not repeated: it remains positive for life and its titer does not track activity[7].

A few antibodies are monitored at defined intervals. During lupus follow-up, repeating anti-double-stranded DNA antibodies more often than every 6 to 12 months is generally of no value[1]. Antiphospholipid antibodies may be repeated, particularly before a planned pregnancy, as may anti-SSA antibodies when previous testing was negative[1].

ANCA are often measured every 3 to 6 months during vasculitis follow-up. Their trajectory alone should not guide treatment but may prompt closer monitoring[2]. A rise in titer or reappearance of ANCA is insufficient to diagnose relapse; it requires closer monitoring, particularly with kidney involvement, and anti-MPO ANCA are less often associated with relapse than anti-PR3[2].

In primary care, a lupus follow-up request does not repeat ANA or other nonspecific antibodies[1]. It includes urine dipstick screening for proteinuria every 3 to 6 months, a complete blood count, creatinine, transaminases and alkaline phosphatase, C3 and possibly C4, whose normal concentrations do not exclude active disease, and anti-double-stranded DNA antibodies no more often than every 6 to 12 months[1]. In antiphospholipid syndrome, antibodies are rechecked annually during the first few years to establish persistence and then according to the course, with anti-double-stranded DNA and anti-ENA testing even without signs of systemic disease; carriers of persistent antibodies without thrombosis are reviewed at least annually[8]. Antiphospholipid antibod-

ies arising during an infection are usually transient and disappear within 8 to 10 weeks: this is the reason for retesting at 12 weeks[8].

4.6 Autoantibodies and the heart

In the Treatise: § 6.5, § 8.4 and § 8.9

Some autoantibodies act on the heart. According to the European working group on myocardial and pericardial diseases, detectable autoantibodies may sustain inflammation through immune complex formation and directly impair target-organ function; in the heart, this results in electrical disturbances, dysfunction or loss of cardiomyocytes and heart failure[10].

Anti-SSA antibodies provide the obstetric example. In women carrying them, the risk of fetal atrioventricular block is very low, below 2%, and the risk of neonatal skin involvement is 5%; this risk justifies preconception consultation and follow-up in an obstetric unit familiar with autoimmune diseases[7]. In adults, the 2025 European guideline notes, in relation to Sjögren syndrome, that anti-SSA antibodies may be found with unexplained heart block[11].

For rhythm, the relevant target is not the diagnostic target. Corrected QT interval (QTc) prolongation associated with anti-SSA antibodies appears specific to anti-Ro52 (anti-TRIM21), classified as anti-Ro/SSA in the QT literature, and dependent on their concentration, including in people without connective tissue disease[12]. Anti-Ro52 antibodies, without value for diagnosing Sjögren syndrome, therefore matter here; because "anti-SSA" results most often refer only to anti-Ro60[7], anti-Ro52 testing is requested by name from the laboratory when the question concerns rhythm. In a cohort of 7,339 US veterans, including 612 with anti-SSA antibodies, this positivity was associated with an approximately twofold adjusted risk of QTc above 500 ms[13]. The review authors advise repeated electrocardiograms and information on QT-prolonging medications for anti-SSA carriers, including antimalarials such as hydroxychloroquine: they inhibit the same potassium channel involved in repolarization, and their effect adds to that of the antibodies[12].

Antibodies directed against the heart itself require specialist assessment. The 2025 European myocarditis and pericarditis guideline accepts that testing may be useful in selected cases, depending on local laboratory availability: organ-specific anti-heart antibodies, anti-intercalated disc antibodies and non-organ-specific serum autoantibodies; at high titers, they may have adverse prognostic value[11]. In the data it cites, high-titer anti-heart antibodies and ANA were among the independent predictors of death and transplantation[11].

In primary care, preconception consultation for a woman with lupus reviews anti-SSA antibodies, one of its four essential areas alongside lupus, antiphospholipid antibodies and treatments[1]. In children of mothers with anti-SSA or anti-SSB antibodies, congenital atrioventricular block occurs in 0.7 to 2% of cases, usually between 16 and 26 weeks of gestation, and recurrence risk reaches 17 to 19% after a pregnancy complicated by block[7]. These figures vary by source and study population: the lupus protocol gives a risk of 1% and recurrence of 10 to 17%[1]. Fetal heart rhythm monitoring every two weeks during this interval, still often proposed, shows no abnormality in 99% of cases, and no curative treatment for block is validated[7]. Hydroxychloroquine is offered to every woman who has had a previous pregnancy complicated by block; without this history or another indication, it is not recommended, although it may be considered[7]. The 2020 American guideline goes further: it conditionally recommends hydroxychloroquine during pregnancy for every woman with anti-SSA

or anti-SSB antibodies, based on early and limited data[14]. The newborn has an electrocardiogram during the first three days of life[7].

Table 4.1. Interpreting an autoantibody result, situation by situation

Situation	What the result allows	What it does not allow
Positive ANA	Continue the investigation: titer, pattern, specificities[1]	Diagnose connective tissue disease without compatible clinical features[1]
Negative ANA on HEp-2 cells (titer below 1:80)	Make lupus extremely unlikely[1]	Exclude anti-SSA/Ro60 when Sjögren syndrome is suspected[7]
Positive anti-PR3 or anti-MPO ANCA with a suggestive presentation	Establish the diagnosis and treat, even without histology[2]	Overlook endocarditis, tuberculosis or levamisole[2]
Negative ANCA	Nothing definitive if suspicion is strong[2]	Exclude cardiac involvement in EGPA[10]
Antiphospholipid antibodies positive once	Retest after at least 12 weeks[6]	Describe positivity as persistent[6]

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PART II

Connective Tissue Diseases, Arthritis and Vasculitis

5

Systemic lupus erythematosus and antiphospholipid syndrome, including the catastrophic form

Chapter contents

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Lupus and antiphospholipid syndrome (APS) share antibodies, obstetric risk and a valvular lesion, Libman-Sacks endocarditis. Their laboratory assessment answers two distinct questions: whether the disease is present and which organ is involved. Autoantibodies address the first; they say almost nothing about the second.

5.1 Systemic lupus erythematosus

In the Treatise: § 8.1, § 8.1.4, § 8.1.8 and § 8.1.9

Systemic lupus erythematosus (SLE) is diagnosed through converging clinical and laboratory findings; autoantibodies alone do not establish it, and it is first suspected from compatible symptoms[1]. The first investigation is antinuclear antibody (ANA) testing by indirect immunofluorescence (IIF) on HEp-2 cells (a human cell line), the reference method. A negative result, with a titer below 1:80, makes the diagnosis extremely unlikely; positivity is poorly specific, because ANA also occur in other systemic diseases, liver diseases, hematologic conditions, viral infections, with certain medications and even in healthy individuals. The laboratory specifies the titer and pattern and may test for anti-double-stranded DNA and anti-extractable nuclear antigen (ENA) antibodies on its own initiative[1].

Immunoglobulin G (IgG) anti-double-stranded DNA antibodies are less often positive than ANA but are much more specific. The Farr assay remains the reference test, IIF on *Crithidia luciliae* is highly specific but poorly sensitive, and quantitative immunologic methods are more sensitive and less specific than Farr[1]. The ENA panel includes at least anti-Sm, anti-Ro60/SSA (Sjögren syndrome antigen A), anti-La/SSB (antigen B of the same syndrome) and anti-U1-RNP (U1 nuclear ribonucleoprotein). Absence of anti-double-stranded DNA or anti-ENA antibodies does not exclude the diagnosis. The essential assessment also includes total hemolytic complement activity (CH50), C_3 and C_4, a complete blood count with reticulocytes, assessment for proteinuria, leukocyturia and hematuria, and creatinine; protein electrophoresis and a direct Coombs test are part of the same nonexhaustive list[1].

Several tests are added according to the context. Anti-nucleosome, anti-ribosomal P protein, anti-Ku and anti-C1q antibodies are not tested routinely; they may help when anti-double-stranded DNA is negative, and anti-nucleosome antibodies are present in 10% of SLE cases without anti-double-stranded DNA[1]. Anemia prompts haptoglobin, lactate dehydrogenase (LDH), unconjugated bilirubin and a blood smear for schistocytes. Suspected macrophage activation syndrome prompts assessment for hypofibrinogenemia, hyperferritinemia, hypertriglyceridemia and a mixed pattern of hepatic injury. Suspected thrombotic thrombocytopenic purpura prompts measurement of the activity of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), a von Willebrand factor-cleaving protease, followed by anti-ADAMTS13 antibody testing if activity is below 10 IU/dL (10%)[1]. The differential diagnosis justifies human immunodeficiency virus (HIV), hepatitis C virus (HCV) and parvovirus B19 serology and anti-cyclic citrullinated peptide (anti-CCP) antibodies[1].

Specialist assessment is needed in four situations. Weakly positive anti-double-stranded DNA by a quantitative method in an uncertain presentation may warrant confirmation by Farr or *Crithidia* to avoid an incorrect diagnosis. Persistent hypocomplementemia during prolonged remission suggests a genetic deficiency, and profoundly low CH50 with normal C_3 and C_4 suggests deficiency of early components[1]. Interferon alpha assays and interferon scores

are used neither for diagnosis nor to guide treatment; persistent elevation during remission, outside infection, points toward a Mendelian interferonopathy. Before azathioprine, testing for thiopurine methyltransferase deficiency is described as nonroutine in the assessment, but appears in the pretreatment assessment for that drug in the same protocol's monitoring table[1].

Follow-up relies on proteinuria assessment, by dipstick or spot sample and quantified if positive, every 3 to 6 months, together with a complete blood count, creatinine, transaminases and alkaline phosphatase[1]. C3 and possibly C4 are interpreted cautiously because active disease can coexist with normal C3; repeating anti-double-stranded DNA more often than every 6 to 12 months is generally of no value. ANA are not markers of disease activity. The 2024 American College of Rheumatology (ACR) lupus nephritis guideline strongly recommends screening for proteinuria at least every 6 to 12 months in patients without known kidney involvement, or during an extrarenal flare; it also strongly recommends quantifying it at least every 3 months in nephritis without a complete renal response. During nephritis, complement and anti-double-stranded DNA are measured at each visit, no more often than monthly[2].

Assessment of cardiac and vascular involvement includes risk factors, lipid and glucose testing, a baseline electrocardiogram and echocardiogram, and systematic antiphospholipid antibody (aPL) testing[1]. A cerebral ischemic event prompts echocardiography to look for a thrombus or Libman-Sacks endocarditis. Two pitfalls deserve attention: anti-Ro52 antibodies are not anti-SSA but anti-TRIM21 (tripartite motif-containing protein 21), and isolated anti-DFS70 (dense fine speckled 70 kDa protein) antibodies occur in healthy individuals[1]. An isolated change in complement or anti-double-stranded DNA requires careful clinical and laboratory reassessment, but does not by itself mandate preemptive treatment without clinical manifestations[2].

In primary care, when lupus is suspected, the first assessment combines ANA, a complete blood count, creatinine and screening for proteinuria; if ANA are positive, the laboratory may add anti-double-stranded DNA and anti-ENA testing on its own initiative[1]. Diagnosis benefits from confirmation by a reference or competence center, or their network[1]. Proteinuria of at least 0.5 g/g or unexplained kidney dysfunction is an indication for prompt kidney biopsy[1,2]. Follow-up is shared: assessment every 6 months in quiescent disease, every 3 months in intermediate situations and monthly during active lupus or pregnancy, with urine dipstick testing at each consultation; any treatment change requires specialist assessment[1]. A blood hydroxychloroquine concentration is requested mainly during a flare or when adherence is uncertain. During azathioprine treatment, a complete blood count and transaminases are checked weekly for 8 weeks, monthly for 3 months, then every 3 months and 1 to 2 weeks after any dose change; the French protocol contraindicates combination with allopurinol or febuxostat (see 21.3)[1].

5.2 Planning pregnancy and the risk of congenital atrioventricular block

In the Treatise: § 8.9.1

All women with lupus are routinely tested for aPL because of the associated increase in obstetric morbidity[1]. The 2020 ACR reproductive health guideline strongly recommends testing for anti-Ro/SSA and anti-La/SSB once, before or early in pregnancy, in women with lupus or a related disease, Sjögren syndrome, systemic sclerosis or rheumatoid arthritis; it strongly recommends against repeating this testing during pregnancy[3]. It generally recommends aPL

testing in lupus and related conditions and when the history or signs are suggestive; elsewhere, the decision is made with the patient[3].

During pregnancy in lupus, laboratory monitoring is monthly: creatinine, proteinuria, complement, which rises physiologically, anti-double-stranded DNA, transaminases, platelets, hemoglobin and possibly LDH and haptoglobin, blood glucose and toxoplasmosis and rubella serology if negative[1]. The soluble fms-like tyrosine kinase-1 to placental growth factor ratio (sFlt-1/PlGF) helps assess preeclampsia risk in women with a high-risk pregnancy profile[1]. Before mycophenolate, cyclophosphamide or methotrexate, absence of pregnancy and effective contraception must be established (pretreatment assessment: see 21.1)[1].

Congenital atrioventricular block threatens the child of a mother with anti-SSA or anti-SSB antibodies. Depending on the cohort, it occurs in 0.7 to 2% of pregnancies without a prior history, usually between 16 and 26 weeks of gestation, and recurs in 10 to 19% of subsequent pregnancies after an affected child: the lupus protocol gives 1% and 10 to 17%[1], while the Sjögren syndrome protocol gives 0.7 to 2% and 17 to 19%[4]. For this risk, unlike for diagnosis, the lupus protocol includes both 52 and 60 kDa anti-SSA/Ro antibodies[1]. The 2020 ACR guideline gives approximately 2% without a prior history and 13 to 18% after a child with cutaneous or cardiac neonatal lupus, noting that low-titer antibodies probably do not carry the same risk[3]. Once performed, the assay is not repeated during pregnancy: these antibodies persist and their titers vary little[3]. Additional fetal ultrasound scans every two weeks between 16 and 26 weeks of gestation and weekly after a history of congenital atrioventricular block may be proposed, but their value is much debated[1]; they fall within specialist care.

In primary care, pregnancy is planned: contraception is discussed from the first visit and becomes essential during teratogenic treatment[1]. Preconception consultation includes rubella immunity and a review of aPL and anti-SSA antibodies; the French protocol permits repeat testing before a planned pregnancy[1]. Pregnancy is discouraged after a recent flare, with corticosteroid dependence above 10 mg daily, glomerular filtration rate below 40 mL/min/1.73 m^2, severe hypertension, inadequately controlled pulmonary hypertension or poorly tolerated valvular disease; it may be considered 12 months after remission of a severe flare, particularly a renal flare, and after 6 months of clinically inactive lupus[1]. A vitamin K antagonist, contraindicated from 6 weeks of gestation, is replaced by low-molecular-weight heparin as soon as pregnancy is diagnosed. Any abnormality during pregnancy requires prompt multidisciplinary discussion, usually in a specialized center[1].

5.3 Antiphospholipid syndrome

In the Treatise: § 8.5 and § 11.4

The diagnosis is considered after thrombosis or an obstetric complication, and sometimes with valvular involvement[5]; in lupus, aPL testing is routine (see 5.1). The essential assessment is a complete panel: lupus anticoagulant by coagulation tests, and IgG and immunoglobulin M (IgM) anticardiolipin (aCL) and anti-β2-glycoprotein I (anti-β2GPI) by immunologic tests[5]. Lupus anticoagulant is assessed in citrated plasma after double centrifugation, in three stages: screening, mixing and confirmation; the two recommended screening tests are the dilute Russell viper venom time and an activated partial thromboplastin time (aPTT) using a lupus anticoagulant-sensitive reagent[5]. The French protocol considers IgG or IgM aCL above 40 units or the 99th percentile, and IgG or IgM anti-β2GPI above the 99th percentile, to be significant when mea-

sured by standardized enzyme-linked immunosorbent assay (ELISA)[5]. The 40- and 80-unit thresholds proposed by the criteria apply to ELISA, not chemiluminescence[1], whose values, like those from multiplex bead assays, cannot be compared with ELISA values[5].

Persistence is documented by at least one antibody present on two occasions at least 12 weeks apart: infection-associated aPL are usually transient and disappear within 8 to 10 weeks[5]. Not all profiles carry the same risk: lupus anticoagulant, double or triple positivity or persistently high titers define a high thrombosis-risk profile; isolated low- or moderate-titer aCL or anti-β2GPI defines a low-risk profile[5]. Elevated C-reactive protein and fibrinogen may cause a false-positive lupus anticoagulant result, hence retesting well after the thrombosis, once any inflammatory syndrome has resolved; during pregnancy, elevated factor VIII may cause a false-negative result, and a negative test is repeated from the third month postpartum[5]. Rheumatoid factor, hypergammaglobulinemia or gammopathy may interfere with IgM aCL screening[5].

Interpretation during anticoagulant treatment requires specialist assessment. An anticoagulant may cause false-positive or false-negative lupus anticoagulant results: ideally performed off treatment, testing may be performed during vitamin K antagonist or heparin treatment according to agent-specific rules, but not during direct oral anticoagulant treatment (see 2.3); the prescriber states the anticoagulant, dose and administration time, on which test feasibility and interpretation depend[5]. aCL and anti-β2GPI assays, in contrast, are not affected by anticoagulants. Other tests exist, but their contribution to routine practice has not been demonstrated[5].

The main pitfall concerns the 2023 ACR and European Alliance of Associations for Rheumatology (EULAR) criteria: these are classification criteria intended for studies; their specificity reaches 99% with 84% sensitivity, compared with 86% and 99%, respectively, for the revised Sapporo criteria[6]. They include valvular disease among their six clinical domains, which is relevant to cardiologists. In the French protocol, a laboratory criterion persistent at 12 weeks and a clinical criterion no more than 5 years apart allow diagnosis; in rare situations, however, diagnosis may be established outside the criteria, and an infectious or malignant context may lead to its rejection in a patient who meets them[5].

In primary care, the risk of overdiagnosis requires prompt confirmation, sometimes urgently, by a reference or competence center[5]. All tests in the panel are ordered at the same time, informing the laboratory of current anticoagulant treatment, and any positive result is retested at least 12 weeks later[5]. Follow-up is shared between the expert center and primary care physician, with 1 to 4 consultations annually: creatinine, transaminases, a complete blood count with reticulocytes and proteinuria; anti-double-stranded DNA and anti-ENA even without signs of systemic disease; blood glucose and lipids annually; aPL annually during the first few years to confirm persistence[5]. During vitamin K antagonist treatment, capillary international normalized ratio (INR) self-testing is not recommended because its reagents may be overly sensitive to aPL, unless agreement with the laboratory has been demonstrated. Direct oral anticoagulants are usually discouraged in definite APS[5].

5.4 Catastrophic antiphospholipid syndrome

In the Treatise: § 8.5.3

The diagnosis is considered when at least three organs, systems or tissues are affected simultaneously or within less than one week. Preliminary classification criteria add histologic evidence of small-vessel occlusion and laboratory confirmation of aPL; kidney involvement is defined as a 50% rise in creatinine, severe hypertension above 180/100 mmHg or proteinuria above 500 mg per 24 hours[7]. The 2018 McMaster guideline conditionally suggests using these criteria for diagnosis, with very low certainty, without waiting for all criteria to be met before treating.

Lupus anticoagulant and aPL immunoassays are suggested to confirm diagnosis without delaying empiric treatment; samples are collected before plasma exchange or anticoagulation when possible[7]. Biopsy is suggested only in selected cases: a positive result confirms, but a negative result does not exclude. In a patient without known APS, laboratory confirmation under these criteria requires two positive tests at least 6 weeks apart; this interval should not defer treatment[7].

The main differential diagnosis is thrombotic thrombocytopenic purpura, with a platelet count below 100 × 10^9/L, microangiopathic hemolytic anemia with low haptoglobin, elevated LDH and schistocytes, and relatively preserved kidney function[8]. Plasma for ADAMTS13 is collected before any plasma exchange or blood product; with strong suspicion, plasma exchange and corticosteroids begin without waiting for the result. Activity below 10 IU/dL (10%) establishes thrombotic thrombocytopenic purpura; above 20 IU/dL (20%), other diagnoses are considered; between these values, clinical judgment decides. The seven-item clinical and laboratory PLASMIC score and the French score were developed in adults without comorbidities and are less reliable in pregnancy, cancer or sepsis[8].

The French protocol emphasizes not waiting for the criteria to be fulfilled before treating, and notes that skin biopsy, performed as soon as possible, is generally informative[5]. With unfractionated heparin, monitoring relies on anti-Xa activity rather than aPTT, which lupus anticoagulant may prolong spontaneously: adjusting heparin to aPTT is a common error causing underdosing, which may trigger or worsen the syndrome. Elevated troponin or N-terminal pro-B-type natriuretic peptide (NT-proBNP) requires urgent cardiac imaging[5].

In primary care, catastrophic syndrome should be suspected readily when there are signs of organ injury involving the heart, kidneys, central nervous system or gastrointestinal tract in a patient with strongly positive aPL, particularly lupus anticoagulant[1]. It often complicates infection, surgery or any interruption or change in anticoagulation, including a switch to a direct oral anticoagulant, particularly in triple-positive patients; cancer, estrogen-containing contraception, pregnancy and the postpartum period, and a lupus flare also increase risk[5]. This is an emergency requiring immediate advice from a reference or competence center[5]; mortality, estimated at 50% by the McMaster guideline[7], reached 37% of episodes in the international registry of 500 patients and 48% with lupus[9]. Microangiopathy is investigated through platelets, hemoglobin, haptoglobin, LDH, schistocytes and creatinine[8], without delaying treatment; samples for aPL and ADAMTS13 are collected before plasma exchange, anticoagulation or blood products[7,8].

5.5 Libman-Sacks nonbacterial endocarditis

In the Treatise: § 8.1.4

Nonbacterial endocarditis is suspected with systemic embolism in a predisposed setting: cancer, lupus or APS[10]. When all microbiological investigations are negative, the 2023 European guideline calls for systematic consideration of this diagnosis and testing for ANA and aPL, specifically IgG anticardiolipin and IgG and IgM anti-β2GPI. These antibodies may also be present in proven infective endocarditis: their positivity therefore never removes the need for blood cultures or prior infectious investigations[10].

Hypercoagulability markers, including lupus anticoagulant, anticardiolipin, anti-β2GPI or signs of disseminated intravascular coagulation, are nonspecific and occur in other patients with endocarditis and emboli[10]. Diagnosis is echocardiographic; compared with transesophageal imaging, transthoracic echocardiography has only 63% sensitivity for this lesion and confirmed the diagnosis in only 45% of patients in a recent registry[10]. Laboratory findings identify the underlying setting; they do not locate the vegetation.

The underlying setting is often dual. In this registry, cited by the European guideline, 41% of patients with nonbacterial endocarditis had cancer, 33% lupus and 36% APS, with 21% having both of the latter conditions; stroke was the most common presentation, in 60% of cases[10]. In lupus, echocardiography for cerebral ischemia and aPL testing form part of the cardiac assessment (see 5.1).

In primary care, baseline transthoracic echocardiography and aPL testing form part of the initial lupus assessment[1]. Known valvular disease requires regular echocardiographic monitoring[1]. If involvement is significant, the French protocol recommends antibiotic prophylaxis before any dental care, upper airway procedure or surgery[1]; the 2023 European guideline reserves it for high-risk patients, particularly those with a prosthetic valve or a history of endocarditis, before a high-risk dental procedure, and does not recommend it routinely for native valvular disease, whether rheumatic, degenerative or congenital, where it is considered case by case[10]. Systemic embolism, particularly an ischemic stroke, in a patient with lupus, aPL or cancer prompts echocardiography, with transesophageal imaging being more sensitive[10]. Fever in a patient with valvular disease prompts at least three sets of blood cultures before any antibiotic therapy: aPL positivity does not exclude infective endocarditis[10]. Anticoagulant treatment for nonbacterial endocarditis, to be considered in all patients according to bleeding risk, relies on heparin or a vitamin K antagonist; direct oral anticoagulants have no data in this indication[10].

Table 5.1. Laboratory assessment in lupus and antiphospholipid syndrome, tier by tier

Situation	Essential	Depending on the context	Specialist assessment
Suspected lupus	ANA by HEp-2 IIF, IgG anti-double-stranded DNA, ENA (Sm, Ro60, La, U1-RNP), CH50, C3, C4, complete blood count, urine tests, creatinine, aPL	Hemolysis tests, anti-nucleosome antibodies, ADAMTS13, HIV, HCV and B19 serology, anti-CCP	Farr or *Crithidia*, complement deficiency, interferon
Lupus follow-up	Proteinuria every 3 to 6 months, dipstick at every consultation, complete blood count, creatinine, transaminases, alkaline phosphatase	C3, C4; anti-double-stranded DNA generally no more often than every 6 to 12 months, at every consultation in nephritis (no more often than monthly); blood hydroxychloroquine concentration	Kidney biopsy if proteinuria ≥ 0.5 g/g or unexplained kidney dysfunction
Planned pregnancy	Anti-Ro/SSA and anti-La/SSB before or early in pregnancy, not repeated during pregnancy; aPL; monthly laboratory assessment during pregnancy	sFlt-1/PlGF in high-risk pregnancy	Closely spaced fetal ultrasound scans from 16 to 26 weeks of gestation, subject to discussion
Suspected APS	Lupus anticoagulant, IgG and IgM aCL and anti-β2GPI; retesting after at least 12 weeks	Lupus anticoagulant retested well after thrombosis, once inflammation has resolved, and from the third month postpartum if negative during pregnancy; during follow-up, aPL annually in the first few years, anti-double-stranded DNA and anti-ENA	Interpretation during anticoagulant treatment (see 2.3)
Catastrophic syndrome	aPL, sampled before plasma exchange or anticoagulation, without delaying treatment	Platelets, hemoglobin, haptoglobin, LDH, schistocytes, creatinine; troponin, NT-proBNP; anti-Xa with unfractionated heparin, not aPTT	ADAMTS13 before plasma exchange or blood products; biopsy in selected cases
Libman-Sacks endocarditis	Blood cultures; if negative, ANA, IgG aCL, IgG and IgM anti-β2GPI	—	Transesophageal echocardiography

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6

Systemic sclerosis, mixed connective tissue disease, Sjögren syndrome and inflammatory myopathies

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6.4 Inflammatory myopathies 46

These connective tissue diseases share antibodies that classify the disease and signal its complications without ever establishing them in an individual patient. The heart is affected by fibrosis, pulmonary vasculopathy, myocardial inflammation or, in the fetus, maternal antibodies. Cardiac laboratory testing therefore has a role of its own alongside the immunologic assessment.

6.1 Systemic sclerosis

In the Treatise: § 8.3 and § 11.2

When systemic sclerosis (SSc) is suspected, autoantibody testing and nailfold capillaroscopy are the first-line investigations[1]. More than 90% of patients have antinuclear antibodies (ANA) by indirect immunofluorescence (IIF) on HEp-2 cells (a human cell line), at a titer above 1:160 or 1:200, with two main patterns, centromere and nucleolar; in 20 to 30% of cases, no target antigen is identified. The main antibodies, usually mutually exclusive, are anticentromere, defined by the fluorescence pattern, anti-topoisomerase I (anti-Scl70) and anti-RNA polymerase III, the latter associated with a high risk of scleroderma renal crisis[1].

Other specificities are tested according to phenotype. Anti-U1-RNP (U1 nuclear ribonucleoprotein) antibodies are not specific to SSc because they occur in mixed connective tissue disease and other overlap syndromes; anti-PM-Scl (polymyositis-scleroderma) and anti-Ku suggest overlap with myositis, and a dedicated panel may reveal anti-fibrillarin or anti-Th/To[1]. These associations are neither automatic nor exclusive: a patient with anti-Scl70 may have no lung involvement, while one with anticentromere antibodies may have severe interstitial lung disease. If ANA or a specificity is absent initially, testing is repeated at 6 to 12 months; outside this situation, ANA are not a marker of disease activity[1].

The essential initial assessment includes a complete blood count with platelets, electrolytes, creatinine, uric acid, C-reactive protein (CRP), fasting blood glucose, calcium and phosphate, albumin and liver tests, creatine kinase (CK), urine dipstick testing, possibly supplemented by urine microscopy and culture and a urine protein-to-creatinine ratio, N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP), thyroid-stimulating hormone (TSH) and ferritin[1]. Reticulocytes, schistocytes, haptoglobin and lactate dehydrogenase (LDH) are added only if renal crisis is suspected. This also warrants unconjugated bilirubin, proteinuria and urine examination, because dipstick blood may reflect only hemoglobinuria from hemolysis; microscopic hematuria without hypertension prompts antineutrophil cytoplasmic antibody (ANCA) testing. In thrombotic microangiopathy, ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) may be measured to exclude a rare associated thrombotic thrombocytopenic purpura[1].

For the heart, beyond NT-proBNP in the initial and annual assessments, the French protocol requests natriuretic peptides when ventricular dysfunction or pulmonary arterial hypertension (PAH) is suspected, and troponin when coronary ischemia or myocarditis is suspected[1]. The 2024 British guideline goes further: annual screening for primary cardiac involvement, even when asymptomatic, using an electrocardiogram, echocardiogram, troponin I/T and NT-proBNP, or BNP with kidney involvement (Grade 2C)[2].

The same British guideline also calls for annual PAH screening (Grade 1B) using pulmonary function tests, echocardiography, NT-proBNP and, in adults with diffusing capacity for carbon monoxide below 60% predicted and disease

duration above 3 years, the DETECT study algorithm[2], of which uric acid is one component[1]. The 2022 European pulmonary hypertension guideline also recommends it (Class I, Level B) in adults with disease duration above 3 years, forced vital capacity of at least 40% and diffusing capacity below 60%[3]. The algorithm's first step includes three laboratory variables: anticentromere antibodies, NT-proBNP and uric acid. In the original study, the algorithm had 96% sensitivity and 98% negative predictive value, but 48% specificity and 35% positive predictive value: approximately two out of three catheterizations did not confirm PAH[4]. None of these assays diagnoses pulmonary hypertension, which is confirmed by right heart catheterization[1].

During follow-up, the complete blood count, electrolytes, creatinine, uric acid, CRP, albumin, liver tests, CK and urine dipstick are checked at each visit, at the clinically determined interval; blood glucose, calcium, protein electrophoresis, NT-proBNP, TSH, ferritin, folate and vitamin B12 are checked at least annually according to results and treatments[1]. In recent-onset diffuse disease or forms at risk of renal crisis, particularly with anti-RNA polymerase III antibodies, home blood pressure monitoring is recommended early in the disease[1]. Before autologous stem cell transplantation, the assessment includes NT-proBNP, high-sensitivity troponin, liver and kidney function and infection screening[2].

An unexpected anti-Scl70 result discordant with the clinical picture requires specialist assessment: in a US expert-center series, 52 patients with anti-Scl70 positivity from a commercial or local laboratory but without classifiable systemic sclerosis were retested by immunodiffusion; 48 were negative, and none of the 19 negative patients seen at least once during follow-up developed sufficient criteria to be classified as SSc[5]. Most results had come from a multiplex flow immunoassay; the series does not allow calculation of assay specificity[5]. Cancer is investigated when general health deteriorates or SSc develops after age 60, particularly in anti-RNA polymerase III-positive diffuse disease, where it is sometimes synchronous[1]. In children, a scleroderma-like condition prompts consideration of a genetic cause, particularly a laminopathy, STAT3 gain of function or an interferonopathy[1].

In primary care, with Raynaud phenomenon and puffy fingers or skin sclerosis, the practitioner requests ANA on HEp-2 cells and anticentromere, anti-topoisomerase I and anti-RNA polymerase III antibodies, then refers the patient to a specialist at an expert center for initial management[1]. Any new hypertension or acute kidney injury raises concern for renal crisis, which is normotensive in approximately 10% of cases: this is a hospital emergency, with urine dipstick, a complete blood count including schistocytes and platelets, creatinine and potassium obtained immediately[1]. In diffuse disease of less than 3 to 5 years' duration or with anti-RNA polymerase III antibodies, blood pressure is self-monitored, creatinine and urine dipstick are monitored regularly, and prednisone above 15 mg daily is contraindicated[1]; in adults, the 2024 British guideline calls for caution above 10 mg prednisolone equivalent, as well as with the calcineurin inhibitors cyclosporine and tacrolimus[2]. New dyspnea, anemia, episodes of faintness or a digital ulcer requires prompt consultation[1]. Electrocardiography, echocardiography and NT-proBNP are performed at least annually[1].

6.2 Mixed connective tissue disease (Sharp syndrome)

In the Treatise: § 11.1.1

The 2019 Japanese diagnostic criteria define mixed connective tissue disease by Raynaud phenomenon or puffy fingers, anti-U1-RNP positivity and either characteristic organ involvement, PAH, aseptic meningitis or trigeminal neuropathy, or overlap manifestations in at least two of the three lupus, scleroderma and myositis domains[6]. Anti-U1-RNP is therefore essential, but insufficient: without the clinical domains, it does not establish the diagnosis.

Depending on the context, laboratory findings contribute to the overlap domains: a white blood cell count ≤ 4×10^9/L or platelets ≤ 100×10^9/L count in the lupus domain, and elevated muscle enzymes in the myositis domain[6]. Either finding is sufficient to contribute to its domain; combining them is not required.

Specialist assessment is necessary when an antibody from another connective tissue disease is present. With anti-double-stranded DNA or anti-Sm, anti-topoisomerase I or anti-RNA polymerase III, anti-aminoacyl-tRNA synthetase or anti-MDA5 (melanoma differentiation-associated protein 5), mixed connective tissue disease should be diagnosed cautiously[6]. PAH is among the characteristic organ manifestations: together with Raynaud phenomenon or puffy fingers and anti-U1-RNP, it is sufficient for diagnosis even without overlap manifestations[6]. In children, finger edema, sclerodactyly or skin sclerosis more often belong to mixed connective tissue disease than SSc, and suspected SSc at this age requires advice within the reference and competence center network[1].

In primary care, mixed connective tissue disease is considered with Raynaud phenomenon or puffy fingers: the request combines ANA with anti-U1-RNP testing, whose positivity establishes the diagnosis only alongside the clinical domains[6]. The risk to monitor is PAH, a recognized complication[3]. Outside systemic sclerosis, the 2022 European pulmonary hypertension guideline does not endorse screening without suggestive symptoms; with symptoms, particularly dyspnea, echocardiography, BNP or NT-proBNP, pulmonary function tests or cardiopulmonary exercise testing should be considered (Class IIa, Level B)[3]. When the connective tissue disease has scleroderma features, annual PAH risk assessment may be considered (Class IIb, Level C)[3]. Any suspected connective tissue disease-associated PAH is confirmed by right heart catheterization; corticosteroid and cyclophosphamide immunosuppression may improve PAH in mixed connective tissue disease, whereas it is not recommended in systemic sclerosis[3].

6.3 Sjögren syndrome

In the Treatise: § 8.4 and § 8.9.1

The initial assessment of Sjögren syndrome combines routine laboratory tests, including a complete blood count, electrolytes, calcium, phosphate, creatinine, urine sediment examination, urine protein-to-creatinine ratio, liver tests, CRP, TSH and CK, with assessment of B-cell activity: rheumatoid factors, ANA with anti-SSA/Ro60 (Sjögren syndrome antigen A) and anti-SSB (Sjögren syndrome antigen B), electrophoresis and immunofixation, immunoglobulin concentrations, C_3 and C_4, and cryoglobulin[7]. Beta-2-microglobulin is optional. The differential diagnosis justifies hepatitis B and C and human immunodeficiency virus (HIV) serology, immunoglobulin G subclass 4 (IgG_4) and angiotensin-converting enzyme measurement. Investigation for another

autoimmune disease prompts myositis antibodies, anti-double-stranded DNA, anti-cyclic citrullinated peptide, antithyroid antibodies and ANCA[7].

Anti-SSA is the key diagnostic finding, but is present in only two out of three patients[7]. For diagnosis, only anti-Ro60 counts: isolated anti-Ro52, or anti-TRIM21 (tripartite motif-containing protein 21), occurs in healthy individuals, inflammatory myopathies and autoimmune liver diseases. Anti-SSA points toward two diseases, Sjögren syndrome and lupus. Anti-SSB never occurs in Sjögren syndrome without anti-SSA, and isolated anti-SSB is usually a false-positive result just above the threshold. With clinical suspicion and negative IIF, anti-Ro60 testing may still be requested because fluorescence is absent in rare cases. These antibodies remain positive for life and their titers do not track activity: testing is not repeated[7].

Follow-up is adapted to the initial phenotype. At each visit: a complete blood count, electrolytes, creatinine and glomerular filtration rate, CRP, urine protein-to-creatinine ratio, albumin, liver tests and CK, with electrophoresis and immunoglobulin G (IgG) measurement to screen for a monoclonal component[7]. Rheumatoid factor, C_3, C_4 and cryoglobulin are rechecked if cryoglobulin was positive or in clinical progression, vasculitis or glomerular involvement; LDH is checked if lymphoma is suspected. The interval is 12 to 24 months for nonsystemic forms without B-cell activity markers, 6 to 12 months with B-cell activity markers and no more than 6 months for systemic forms[7]. Viral serology and an interferon-gamma release assay precede any immunosuppressant or biologic therapy[7].

Anti-SSA carries a very low risk of fetal atrioventricular block, below 2%, and neonatal skin involvement in 5% of cases, warranting preconception consultation[7]. Before pregnancy, the protocol provides for anti-SSA/Ro60 and anti-Ro52 testing, both relevant to fetal risk (see 5.2), and an antiphospholipid panel if not previously performed; an initially negative anti-SSA may be retested for this purpose alone. The 2020 American guideline strongly recommends a single measurement before or early in pregnancy, without repetition during pregnancy[8]. During follow-up, electrocardiography and echocardiography are requested for cardiac symptoms, dyspnea or pain suggestive of pericarditis[7].

In primary care, with the triad of dryness, fatigue and pain, particularly in a woman around age 50, the primary care physician requests ANA on Ro60-transfected cells with anti-SSA/Ro60 and anti-SSB testing, rheumatoid factor, positive in half of cases, and protein electrophoresis to look for polyclonal hypergammaglobulinemia[7]. A negative assessment does not exclude the disease: 30% of patients have no detectable autoantibodies, and diagnosis relies on salivary gland biopsy performed in an expert center; the patient is referred to a rheumatologist, an internist or a competence or reference center[7]. Moderate or severe systemic activity, recurrent parotid enlargement, purpura, a monoclonal immunoglobulin or rheumatoid factor signal lymphoma risk[7]. Outside systemic disease, the primary care physician coordinates care with specialists; pregnancy in a woman with anti-SSA is followed in an obstetric unit familiar with autoimmune diseases[7].

6.4 Inflammatory myopathies

In the Treatise: § 8.8 and § 12.2

In suspected adult or juvenile dermatomyositis, at least one muscle enzyme among creatine kinase, aspartate aminotransferase, LDH and aldolase is elevated in 70 to 90% of patients; in practice, only CK is recommended, based on expert opinion, and a normal value does not exclude the diagnosis[9]. ANA by HEp-2 IIF are the essential first step; the pattern may be nuclear, cytoplasmic or both, and the laboratory specialist should know the clinical context. Dermatomyositis-specific antibodies, anti-Mi2, anti-SAE (SUMO1-activating enzyme), anti-TIF1-gamma (transcription intermediary factor 1 gamma), anti-NXP2 (nuclear matrix protein 2) and anti-MDA5, are routinely sought when dermatomyositis is suspected, even with negative ANA, because they define subgroups with different phenotypes and prognoses in adults and children[9].

Specialist assessment is needed when a result is weakly positive or discordant: because methods are not standardized, confirmation with a second technique may be justified[9]. An immunoblot result is interpreted alongside the clinical picture, and antibody titers are not used to monitor activity[10]. The 2016 French protocol noted that no study had validated serial specific antibody measurements[9].

Antisynthetase syndrome and immune-mediated necrotizing myopathies also put the heart at risk. In an Italian series of 43 patients with antisynthetase syndrome, 53% of whom had anti-Jo-1, myocarditis was diagnosed in 30%, at disease onset in 54% of these cases; these patients more often had fever and higher CRP, high-sensitivity troponin T and NT-proBNP[11]. In a Chinese series of 57 patients with necrotizing myopathy, 56% anti-SRP (signal recognition particle)-positive and 21% anti-HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase)-positive, cardiac involvement of varying severity was present in 53%[12].

In these myopathies, troponin is interpreted with a caveat: in adults, the 2022 British guideline favors troponin I over troponin T for screening and monitoring cardiac involvement (Grade 1B), because troponin T may be released by regenerating skeletal muscle[10]. The 2016 French protocol screens for cardiac involvement clinically and by electrocardiography; it considers pro-B-type natriuretic peptide (proBNP) and cardiac enzymes unvalidated for this screening, and notes that with very high CK, a simultaneous rise in cardiac enzymes may be nonspecific. A combination of findings leads to echocardiography, cardiac magnetic resonance imaging and Holter monitoring[9].

During dermatomyositis follow-up, the 2016 French protocol calls for CK and a complete blood count once or several times annually according to severity and treatment, repeated transaminase measurements during methotrexate treatment (pretreatment assessment: see 21.1), and fasting blood glucose, triglycerides and cholesterol annually[9]. Calcium and phosphate assessment with 25-OH vitamin D becomes annual with osteoporosis risk factors; when infection is suspected during immunosuppressive treatment, blood cultures, urine testing and serology are guided by the clinical context[9].

In inclusion body myositis, CK is normal or moderately elevated and stable, and does not measure treatment response[13]. Anti-cytosolic 5′-nucleotidase 1A (anti-cN1A) has 33 to 76% sensitivity depending on the method; a pooled analysis questioning its diagnostic usefulness found 46% sensitivity and 91% specificity. It is positive in a substantial proportion of patients with lupus or Sjögren syndrome: it supports but does not decide. No association with cancer has been found in patients carrying it[13]. Toxic myopathies, including

chloroquine myopathy, and genetic myopathies with vacuoles are among the disease's histologic mimics[13].

In primary care, with suggestive skin signs and proximal muscle weakness, the practitioner measures CK and requests ANA, then seeks prompt diagnostic confirmation by an experienced physician in the reference and competence center network; hospitalization is generally necessary to confirm diagnosis and start treatment[9]. Swallowing difficulties, interstitial lung disease, myocarditis, gastrointestinal vasculitis or severe skin ulceration require urgent care[9]. In adults, cancer risk is considered in everyone; screening is discussed particularly with late onset, male sex, dysphagia, skin necrosis or anti-TIF1-gamma or anti-NXP2 (Grade 1B)[10]. According to the same French protocol, after the initial assessment or a treatment change, the patient is seen monthly for 3 months, with transaminases during methotrexate treatment; the expert center sees the patient at least twice annually while disease remains active[9].

Table 6.1. Laboratory assessment in systemic sclerosis, mixed connective tissue disease, Sjögren syndrome and myopathies, tier by tier

Situation	Essential	Depending on the context	Specialist assessment or emergency
Suspected SSc	ANA, anticentromere, anti-Scl70, anti-RNA polymerase III; NT-proBNP, CK, urine tests	Hemolysis tests and ADAMTS13 if renal crisis; troponin if ischemia or myocarditis	Expert center from the outset; discordant anti-Scl70; pediatric genetics
SSc follow-up	Routine laboratory tests at each visit; annual NT-proBNP	Annual cardiac screening including troponin (British guideline)	New hypertension or acute kidney injury: hospital emergency; assessment before autologous stem cell transplantation
Mixed connective tissue disease	Anti-U1-RNP with clinical domains	White blood cells, platelets, muscle enzymes; echocardiography and NT-proBNP for dyspnea	Antibodies from another connective tissue disease; suspected PAH: right heart catheterization
Sjögren syndrome	Anti-SSA/Ro60, anti-SSB, rheumatoid factor, C3, C4, cryoglobulin, electrophoresis	LDH if lymphoma; beta-2-microglobulin	Negative antibodies: salivary gland biopsy in an expert center
Dermatomyositis	CK, ANA, specific antibodies	Troponin I in adults	Second method if discordant; high-risk features: urgent care
Inclusion body myositis	CK	Anti-cN1A, supportive rather than decisive	—

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7

Rheumatoid arthritis, spondyloarthritis and psoriatic arthritis

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In inflammatory rheumatic diseases, laboratory findings guide and classify; diagnosis remains clinical and radiologic, and a negative marker excludes nothing. The heart is relevant through cardiovascular risk and, in spondyloarthritis, through the aorta and aortic valve.

7.1 Rheumatoid arthritis

In the Treatise: § 8.2

Persistent synovitis of undetermined cause raises suspicion of rheumatoid arthritis (RA) and prompts specialist advice. In adults with suspected RA and synovitis on examination, the National Institute for Health and Care Excellence (NICE) guideline proposes rheumatoid factor (RF) testing; if negative, anti-cyclic citrullinated peptide (anti-CCP) testing is considered[1]. When ordered in primary care, these tests should not delay referral. Referral is urgent even with a normal acute-phase response and negative anti-CCP or RF if the small joints of the hands or feet are affected, more than one joint is involved or three months or more have elapsed between the first symptoms and the first consultation[1].

Once the diagnosis is established, anti-CCP is measured as soon as possible if not already done, with hand and foot radiographs to look for erosions[1]. Anti-CCP positivity or erosions signal increased risk of radiographic progression without necessarily predicting poorer function; they may favor remission over low disease activity as the target. A functional capacity measure, such as the Health Assessment Questionnaire (HAQ), provides a baseline for assessing treatment response[1].

In active RA, C-reactive protein (CRP) and a composite activity score, such as the 28-joint Disease Activity Score (DAS28), are measured together monthly in specialist care until the target is reached: remission (for example, DAS28 below 2.6) or, failing that, low disease activity (for example, DAS28 below 3.2)[1]. This monthly interval applies to active disease, not stable RA. The 2025 European recommendation calls for activity monitoring every 1 to 3 months during active disease, combining joint counts, inflammatory markers such as CRP and patient-reported data; treatment is adjusted if improvement is absent by 3 months at the latest or the target is not reached by 6 months, and monitoring becomes less frequent, for example every 6 months, once the target is sustained[2].

Under an interleukin-6 receptor inhibitor or Janus kinase (JAK) inhibitor, CRP and erythrocyte sedimentation rate (ESR) may fall or normalize independently of clinical improvement. Activity scores that weight them heavily should then be avoided, and the CRP response during infection may be blunted: a low CRP indicates neither remission nor absence of infection[2].

In primary care, RF, followed by anti-CCP if negative, and hand and foot radiographs are requested without delaying referral[1]. Suspected septic arthritis requires urgent medical and surgical care; signs of cervical myelopathy require urgent magnetic resonance imaging (MRI) and surgical advice[1]. Every patient, even at target, has an annual review covering activity, functional capacity, comorbidities (hypertension, ischemic heart disease, osteoporosis, depression) and complications (vasculitis and cervical spine, lung or eye involvement)[1]. Cardiovascular risk is assessed at least every five years and after any major change in disease-modifying treatment, according to national guidelines; it relies on nonfasting total and high-density lipoprotein (HDL) cholesterol, preferably measured during stable disease or remission, and the

calculated risk is multiplied by 1.5 unless the algorithm already incorporates this[3].

7.2 Axial spondyloarthritis and reactive arthritis

In the Treatise: § 8.6

Spondyloarthritis is excluded neither by a negative human leukocyte antigen B27 (HLA-B27) nor by normal CRP and ESR[4]. Positive HLA-B27 increases the likelihood of peripheral spondyloarthritis without proving it. When spine and sacroiliac joint MRI does not meet Assessment of SpondyloArthritis international Society (ASAS) and Outcome Measures in Rheumatology (OMERACT) criteria, axial spondyloarthritis is not excluded: HLA-B27 is requested if not already tested and, if positive, the diagnosis of nonradiographic axial spondyloarthritis rests on clinical findings[4].

With acute anterior uveitis, the ophthalmologist asks about joint pain that has previously prompted a consultation or back pain beginning before age 45 and lasting more than three months. If either is present, psoriasis prompts direct referral to a rheumatologist; without psoriasis, HLA-B27 is requested, with positivity leading to rheumatology referral[4].

During follow-up, the Ankylosing Spondylitis Disease Activity Score (ASDAS), preferably calculated with CRP, is the recommended instrument for measuring axial spondyloarthritis activity: it combines the patient's perspective with an objective inflammation measure[5]. Follow-up frequency is decided individually according to symptoms, severity and treatment. A biologic or JAK inhibitor is considered with ASDAS of at least 2.1 despite at least two nonsteroidal anti-inflammatory drugs (NSAIDs), together with elevated CRP, sacroiliac inflammation on MRI or radiographic sacroiliitis. Elevated CRP, attributed to the disease after other causes have been excluded, is then the strongest predictor of response, ahead of sacroiliac inflammation on MRI[5].

After a gastrointestinal infection, reactive arthritis is not diagnosed through infectious serology, which is not routinely requested[4]. As in any peripheral spondyloarthritis, positive HLA-B27 increases its likelihood, while negative HLA-B27 or normal CRP does not exclude it. In specialist care, validated criteria, including the French Society for Rheumatology criteria for reactive arthritis, may guide clinical judgment[4].

In primary care, back pain beginning before age 45 and lasting more than three months prompts rheumatology referral if at least four of the following nine criteria are also present: onset before age 35; waking during the second half of the night; buttock pain; improvement with movement; improvement within 48 hours of NSAIDs; a first-degree relative with spondyloarthritis; current or past arthritis; current or past enthesitis; current or past psoriasis. With exactly three criteria, HLA-B27 is requested and positivity prompts referral[4]. Symptoms of acute anterior uveitis require an ophthalmic examination the same day. Flares may be treated in primary care, with specialist advice if recurrent or persistent, during biologic or targeted treatment or with comorbidities; monitoring accounts for adverse effects of NSAIDs and disease-modifying treatments[4]. Cardiovascular risk is assessed at least every five years, without the RA-specific 1.5 multiplier[3].

7.3 Psoriatic arthritis

In the Treatise: § 8.6

Psoriatic arthritis belongs to the peripheral spondyloarthritis group: normal CRP or ESR does not exclude it, nor does negative HLA-B27[4]. HLA-B27 is requested in specialist care, where positivity increases the likelihood of peripheral spondyloarthritis without proving it. If recent-onset inflammatory arthritis instead suggests RA, the RA approach is followed: RF, then anti-CCP if negative[1,4].

Acute-phase reactants have prognostic value. In peripheral disease, elevated ESR or CRP is among the poor prognostic factors, alongside structural damage, dactylitis and nail involvement; in monoarthritis or oligoarthritis, it prompts rapid introduction of a conventional disease-modifying drug, as in polyarthritis, with methotrexate preferred for clinically significant skin involvement (pretreatment assessment: see 21.1)[6]. The strategy aims for at least a 50% reduction in activity within 3 months and the target within 6 months; otherwise, the conventional disease-modifying drug is not continued[6].

The 2023 European recommendation calls for consideration of skin, eye and gastrointestinal manifestations and comorbidities: obesity, metabolic syndrome, cardiovascular disease and depression[6]. It urges caution with JAK inhibitors from age 65, in current or long-term former smokers, with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, and with cancer or venous thrombosis risk factors[6]. For drug-specific pretreatment assessment and monitoring, see Chapter 21.

In primary care, recent-onset inflammatory arthritis suggestive of spondyloarthritis is referred urgently to a rheumatologist, unless RA, gout or acute calcium pyrophosphate arthritis is suspected[4]. Dactylitis prompts rheumatology referral; so does enthesitis without an apparent mechanical cause if persistent, at multiple sites or associated with nonmechanical back pain, uveitis, psoriasis, a gastrointestinal or genitourinary infection, inflammatory bowel disease or a first-degree relative with spondyloarthritis or psoriasis. No normal laboratory result removes the need for these referrals[4]. The rheumatologist follows musculoskeletal involvement, with a dermatologist if skin involvement is substantial[6]. Cardiovascular risk is assessed at least every five years and after any major change in disease-modifying treatment, using a nonfasting lipid panel[3].

Table 7.1. Laboratory assessment in inflammatory rheumatic diseases, tier by tier

Situation	Essential	Depending on the context	Specialist assessment
Synovitis, suspected RA	RF, without delaying referral	Anti-CCP if RF negative	Urgent referral according to clinical findings, even with normal tests
Diagnosed RA	Anti-CCP if not previously tested	—	Monthly CRP and DAS28 if RA is active
RA follow-up	—	CRP as part of activity assessment, every 1 to 3 months if RA is active; caution with an interleukin-6 receptor or JAK inhibitor	—
RA, spondyloarthritis, psoriatic arthritis: cardiovascular risk	Nonfasting total and HDL cholesterol at least every 5 years	—	—
Suspected spondyloarthritis	—	CRP, ESR, HLA-B27 (negative results do not exclude)	Interpretation integrated with MRI
Back pain before age 45, over 3 months, exactly 3 of the 9 NICE criteria	HLA-B27	—	Referral if positive
Acute anterior uveitis with back or joint pain, without psoriasis	HLA-B27	—	Referral if positive
Axial spondyloarthritis follow-up	—	CRP within ASDAS	Elevated CRP before a biologic or JAK inhibitor
Reactive arthritis	—	CRP, ESR, HLA-B27; no routine infectious serology	Validated criteria
Psoriatic arthritis	—	CRP, ESR (prognosis); RF and anti-CCP if RA suspected	HLA-B27

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8

Large- and medium-vessel vasculitis: giant cell arteritis, Takayasu arteritis, aortitis, polyarteritis nodosa, Kawasaki disease, Behçet disease, Cogan syndrome and relapsing polychondritis

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None of these diseases has a specific laboratory marker. Laboratory testing measures inflammation, excludes differential diagnoses and monitors treatment; diagnosis rests on clinical findings, imaging and sometimes histology. Laboratory evidence of inflammation is never the sole measure of activity.

8.1 Giant cell arteritis

In the Treatise: § 9.2 and § 20.5

The inflammatory response in giant cell arteritis (GCA) is almost universal, to the extent that its absence makes the diagnosis unlikely unless corticosteroid treatment has already begun[1]. At diagnosis, only C-reactive protein (CRP) is needed; other markers are investigated only if it is normal or nearly normal. Mean CRP is 94 ± 63 mg/L, but it is markedly lower in patients with an ischemic complication, averaging 35 versus 108 mg/L. No laboratory abnormality is specific: anicteric cholestasis, present in one-third of patients, has a low predictive value[1].

According to the French protocol, the differential workup includes antineutrophil cytoplasmic antibodies (ANCA) directed against myeloperoxidase (MPO) and proteinase 3 (PR3). In patients with joint manifestations, rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP) help exclude rheumatoid arthritis with rhizomelic onset, which is more common in older people[1]. Anemia of inflammation and thrombocytosis occur in half of cases; they accompany inflammation without pointing to the disease.

During follow-up, CRP is combined with a marker with slower kinetics; fibrinogen is preferred to the erythrocyte sedimentation rate (ESR), which is affected by anemia and hypergammaglobulinemia[1]. During tocilizumab treatment, interleukin-6 blockade rapidly normalizes CRP, ESR, fibrinogen and haptoglobin, making them uninterpretable for assessing activity and detecting infection: relapse is then assessed clinically and by imaging. During tocilizumab or methotrexate treatment (pretreatment workup: see 21.1), the complete blood count (CBC) and transaminases are checked every 1 to 2 weeks during the first month, then every 1 to 3 months, with creatinine during methotrexate treatment; the lipid profile is checked 8 to 12 weeks after starting tocilizumab[1]. This schedule comes from the GCA protocol; the general methotrexate rule appears in section 21.3. Alongside tocilizumab, the 2025 European recommendations (EULAR) include upadacitinib, a Janus kinase (JAK) inhibitor, as adjunctive treatment for GCA, particularly in relapse, refractory disease or increased risk of corticosteroid adverse effects (level of evidence 1)[2]; its laboratory monitoring follows that for JAK inhibitors (see 21.5).

In primary care, suspected GCA calls for immediate CRP testing; fibrinogen has replaced ESR as the marker with slower kinetics[1]. An ophthalmic sign requires corticosteroid treatment without delay: prednisone, 40 to 80 mg daily (0.7 to 1 mg/kg daily) according to the French protocol, or 40 to 60 mg daily according to the 2025 European recommendations[2], may be started urgently in primary care, with prompt referral to an internist or rheumatologist, ideally through a fast-track pathway; the European recommendations call for specialist referral within 24 hours for every suspected case of GCA[2]. Follow-up is shared between the primary care physician and specialist: visits every 1 to 3 months during the first three months, then every 3 to 6 months, with CRP and fibrinogen at least monthly[1]. Recurrent symptoms or rising inflammatory markers suggest relapse, except during tocilizumab treatment, when relapse is assessed mainly on clinical symptoms; in patients with documented vascular involvement, follow-up imaging may help assess activity. The primary care

physician screens for corticosteroid adverse effects: diabetes, hypertension and infections. The protocol specifies laboratory monitoring: before treatment, fasting venous glucose and glycated hemoglobin (HbA1c) in patients at risk; potassium after 1 to 2 weeks; glucose, preferably late in the morning, a few days after starting treatment and then at 1 month; HbA1c and a fasting lipid profile every 3 months[1]. This schedule is more intensive than that in section 21.2.

8.2 Takayasu arteritis

In the Treatise: § 9.2.4

There is neither a diagnostic laboratory marker nor a specific antibody for Takayasu arteritis[3]. Laboratory evidence of inflammation, including ESR, CRP, fibrinogen, orosomucoid or haptoglobin, is not always present; antinuclear antibodies (ANA) and rheumatoid factor are negative in the absence of associated connective tissue disease. Anti-endothelial cell antibodies are not specific. Pentraxin 3 has been described as an activity marker, but is not measured routinely[3].

Inflammatory markers poorly reflect activity: approximately 30% of patients may have active disease without elevated markers, while approximately 30% have elevated markers without clinical activity[3]. Activity is therefore assessed by combining clinical findings, imaging and laboratory results. The 2022 US aortic disease guideline recommends periodically assessing treatment efficacy in active GCA and Takayasu arteritis using CRP and ESR, imaging and symptoms (Class 2a, Level C-LD, indicating limited data)[4]. The 2025 European recommendations likewise base follow-up of GCA and Takayasu arteritis on symptoms, physical examination and inflammatory markers; in Takayasu arteritis, relapse is assessed primarily by imaging, together with clinical findings and laboratory results[2]. In children, ESR and then CRP are most often elevated, with the same uncertainty about their value as activity markers[3].

Activity criteria derived from a prospective National Institutes of Health series of 60 patients require the onset or worsening of at least two of four features: signs of vascular ischemia or inflammation, unexplained systemic symptoms, angiographic abnormalities and elevated inflammatory markers[3]. Laboratory findings represent only one of four criteria. Cytokines, pentraxin 3 or B-cell activating factor (BAFF) increase in active disease, but testing is not available routinely and their advantage over ESR, CRP and fibrinogen remains to be demonstrated.

In primary care, pain along the carotid artery, an absent pulse, a vascular bruit, limb claudication or unexplained hypertension in a young person suggests the disease; CRP and fibrinogen or ESR are requested at the outset because they will subsequently help monitor activity during treatment[3]. Diagnosis is confirmed in consultation with an expert physician on the basis of age, clinical findings and imaging. Ideally, follow-up alternates between visits to the primary care physician and to the vascular physician, internist or rheumatologist; weight and glucose are monitored during corticosteroid treatment. Even a moderate increase in an inflammatory marker during follow-up warrants further investigations for relapse. Blood pressure is measured in the limb with the highest reading to avoid underestimating hypertension distal to a stenosis[3].

8.3 Aortitis

In the Treatise: § 9.2.3 and § 20.5

Takayasu arteritis and GCA are the most common causes of aortitis; other known causes include immunoglobulin G4 (IgG4)-related disease, ANCA-associated vasculitis, sarcoidosis, Behçet disease and relapsing polychondritis (see 8.8), and many cases remain idiopathic[4]. Takayasu arteritis and GCA more often affect the thoracic aorta, whereas IgG4-related disease more often affects the abdominal aorta.

Infectious aortitis warrants specialist assessment: blood cultures and cultures of surgical specimens may be negative in a substantial proportion of patients, so antimicrobial selection is often empirical[4]. In active GCA and Takayasu arteritis, CRP and ESR are used for follow-up alongside imaging, but normal results do not exclude aortitis, particularly during tocilizumab treatment[1,4].

In GCA, the aorta and its branches are involved in approximately 40% of patients, often without symptoms at diagnosis, which explains the recommendation for large-vessel imaging at the outset[1]. During follow-up, persistent imaging abnormalities may reflect remodeling without activity; conversely, new or worsening lesions raise the possibility of active disease, whether or not inflammatory markers are elevated.

In primary care, no laboratory test alone can monitor aortitis: CRP and ESR complement imaging and symptoms. In GCA and Takayasu arteritis in remission with aortic involvement, the US guideline considers annual surveillance imaging with computed tomography (CT), magnetic resonance imaging or fluorodeoxyglucose positron emission tomography reasonable (Class 2a, Level C-EO, indicating expert opinion)[4]. In GCA, the primary care physician remains alert to late cardiovascular complications, including increased cardiovascular risk and aortic dilation, which may occur 5 to 10 years after diagnosis even when disease is no longer active[1]. In a patient with an aortic graft, fever or elevated CRP prompts investigation for graft infection: the initial workup includes basic laboratory tests, blood cultures and cross-sectional imaging, preferably CT angiography[4].

8.4 Polyarteritis nodosa

In the Treatise: § 9.3.2

Polyarteritis nodosa (PAN) is confirmed primarily by biopsy of an affected organ, which must not delay treatment when suspicion is high; angiographic microaneurysms may provide evidence in a suggestive setting[5]. Testing for PR3-ANCA and MPO-ANCA is essential: in a vasculitis setting, their specificity approaches 100%, and their presence points to ANCA-associated vasculitis rather than PAN (see 9.1)[5]. The organ assessment and pretreatment workup include a CBC, prothrombin time and activated partial thromboplastin time, CRP and fibrinogen, serum and urinary electrolytes, creatinine and estimated glomerular filtration rate (eGFR), urine dipstick, urine protein-to-creatinine ratio and testing for hematuria; liver tests, glucose, calcium and phosphate, protein electrophoresis, creatine kinase (CK), lactate dehydrogenase and a lipid profile. Waiting for results must not delay treatment initiation[5].

Hepatitis B virus (HBV) markers, including surface antigen (HBsAg), anti-HBs antibodies and anti-HBc antibodies directed against the nucleocapsid or core antigen, supplemented when needed by viral deoxyribonucleic acid (DNA) testing, identify HBV-associated PAN; human immunodeficiency virus

(HIV) and hepatitis C virus (HCV) serology, with HCV ribonucleic acid (RNA) testing if the HCV serology is positive or equivocal, investigate secondary disease. These serologic tests are essential before treatment (see 21.1)[5]. In an anti-HBc-positive patient, particularly one with chronic hepatitis B, the risk of viral reactivation during corticosteroid or immunosuppressive treatment requires virologic and liver test monitoring 1 month after treatment begins, then every 3 months, and hepatology advice on preemptive treatment[5]. Blood cultures in patients with fever or even routinely, and echocardiography for a previously unknown murmur, help exclude endocarditis. ANA, rheumatoid factor, cryoglobulin, complement and antiphospholipid testing are requested according to the findings. Hematologic evaluation includes investigation for myelodysplastic syndrome, which the protocol reserves mainly for suspected PAN[5].

For cardiac assessment, an electrocardiogram and transthoracic echocardiography are routine; troponin and a natriuretic peptide are reserved for suspected cardiac involvement[5]. Specialist assessment is required for juvenile-onset PAN with fever, livedo, stroke or gangrene, suggesting adenosine deaminase 2 (ADA2) deficiency; its enzymatic or genetic investigation is discussed with that deficiency (see 11.4).

In primary care, mononeuritis multiplex, necrotic purpura or kidney impairment with microscopic hematuria, together with elevated inflammatory markers, suggests necrotizing vasculitis; treatment should begin early, often urgently, and definitive diagnosis is established with a reference or competence center[5]. Between specialist visits, the primary care physician manages intercurrent conditions related to the disease and its treatments. During maintenance treatment, a CBC with platelets, electrolytes, creatinine and eGFR, glucose, CRP, urine dipstick and, in patients with kidney involvement, the urine protein-to-creatinine ratio are checked every 3 months, together with liver tests. After treatment is discontinued, monitoring takes place every 6 months for at least 2 years, then annually for at least 5 to 10 years, because relapse can occur late[5].

8.5 Kawasaki disease

In the Treatise: § 9.3.1

Kawasaki disease remains a clinical diagnosis with no pathognomonic test[6]. Nonspecific laboratory tests support diagnosis when suggestive but incomplete findings are present; clinical experience suggests that the disease is unlikely if ESR, CRP and platelets are normal after day 7[7]. Leukopenia with lymphocyte predominance points toward another diagnosis. Thrombocytosis develops during the second week; thrombocytopenia, which is rare, may indicate disseminated intravascular coagulation and is associated with coronary risk.

When incomplete disease is suspected, with fever for at least 5 days and 2 or 3 clinical criteria, or in an infant with unexplained fever for at least 7 days, the US algorithm, based on expert opinion in the absence of a diagnostic reference standard, starts with CRP and ESR[7]. If CRP is at least 30 mg/L (3.0 mg/dL in the US guideline) or ESR is at least 40 mm/h, treatment is indicated when at least three of the following laboratory abnormalities are present: anemia for age, platelets at least 450×10^9/L after day 7, albumin at most 30 g/L, elevated alanine aminotransferase (ALT), white blood cells at least 15×10^9/L and urine white blood cells at least 10 per high-power field. Treatment is also indicated

when echocardiography is positive. These criteria remain unchanged in the 2024 update[6].

During follow-up, CRP is the best marker of inflammation after treatment: intravenous immunoglobulin raises ESR, whose decline should not be used to judge response[7]. N-terminal pro-B-type natriuretic peptide (NT-proBNP) may increase, but has insufficient discriminatory power and no defined threshold. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) must now be included in the differential diagnosis, although its frequency has fallen markedly since 2022: thrombocytopenia, lymphopenia and elevated troponin or B-type natriuretic peptide (BNP) are more pronounced[6].

In primary care, time matters: diagnosis should be made within the first 10 days of fever, ideally around day 4 or 5 in complete disease and as early as possible in incomplete disease, because treatment within this window markedly reduces the risk of coronary dilation and aneurysms[6]. A child with fever for 5 days and suggestive findings, or an infant with unexplained fever for 7 days, therefore needs prompt specialist pediatric assessment, with CRP, ESR, a CBC, albumin, ALT, urine examination and echocardiography. In the absence of coronary involvement, the 2024 update provides for reassessment 1 to 2 weeks after discharge; the 4- to 6-week assessment is considered only if coronary imaging is inadequate or inflammatory markers remain abnormal at 1 to 2 weeks[6]. Discharge from cardiology follow-up occurs between 4 weeks and 1 year[6]. The 2017 guideline considers measuring blood pressure and obtaining a fasting lipid profile at least once reasonable, ideally at least a year after the episode; this can be done by the primary care physician (Class IIa, Level C)[7].

8.6 Behçet disease

In the Treatise: § 12.3

Behçet disease is diagnosed clinically, with no supportive laboratory criterion[8]. According to the national protocol, human leukocyte antigen B51 (HLA-B51) should not be used to confirm or exclude the diagnosis, and HLA typing for diagnostic purposes is discouraged; however, the protocol's introduction acknowledges that it may be useful in uncertain situations. Applying this exception is a specialist decision. Inflammatory markers are not always elevated; elevation is more common with vascular involvement or arthritis[8].

In children and young adults, venous thrombosis prompts investigation for inherited or acquired thrombophilia; unexplained thrombosis without another risk factor and with negative thrombophilia testing should raise suspicion for the disease[8]. The combination of deep venous thrombosis and pulmonary artery aneurysms, or Hughes-Stovin syndrome, carries a high risk of hemoptysis. Severe cardiovascular and pulmonary involvement requires an expert center.

There is no reliable laboratory marker of activity: CRP is insufficiently sensitive to reflect low-grade activity[8]. Severe, early-onset oral and genital aphthosis with predominantly gastrointestinal involvement and flares with markedly elevated CRP raises the possibility of dominantly inherited A20 haploinsufficiency and requires specialist assessment[8].

In primary care, the primary care physician has an essential role in first-line assessment[8]. Unexplained venous thrombosis in a young adult is particularly suggestive if proximal or atypical, involving the iliofemoral veins, vena cava, hepatic veins or cerebral veins; it is often accompanied by ele-

vated inflammatory markers. Serious visceral involvement, even if isolated and the initial manifestation, always requires expert assessment. Before anticoagulation for venous thrombosis, bleeding risk, particularly from associated arterial aneurysms, must be excluded, and anti-inflammatory treatment is decided with an expert center[8]. During follow-up, generally every 3 to 6 months, monthly initially in severe disease and at least annually in quiescent disease, CRP alone cannot assess activity: history and physical examination take precedence.

8.7 Cogan syndrome

In the Treatise: § 9.5.2

Cogan syndrome is a diagnosis of exclusion with no specific laboratory marker, in particular no autoantibody[9]. Approximately three-quarters of patients have elevated inflammatory markers. By definition, syphilis serology is negative: it is therefore essential before making the diagnosis. Depending on the presentation and manifestations outside the eyes or auditory system, immunologic testing with ANA, ANCA and complement investigates another systemic disease[9].

In isolated interstitial keratitis, bacterial, viral or parasitic infectious causes are excluded according to the setting, with corneal sampling if necessary[9]. Among bacterial causes, the protocol lists syphilis, tuberculosis, Lyme disease, leprosy, brucellosis, leptospirosis, chlamydial infection and Whipple disease; investigation is guided by the epidemiologic and clinical setting. Conversely, isolated sensorineural hearing loss with vertigo initially suggests labyrinthitis or autoimmune hearing loss.

During follow-up, monitoring includes inflammatory markers, whose normality does not exclude ongoing activity; additional investigations mainly seek cardiac and aortic involvement, which can be asymptomatic, as well as cochleovestibular and ocular involvement, while laboratory testing also detects treatment complications[9]. In children, elevated CRP or ESR accompanies most flares[9].

In primary care, a red, painful, tearing eye caused by interstitial keratitis, or sudden sensorineural hearing loss with spinning vertigo and tinnitus in a young adult, suggests the diagnosis; suspicion warrants urgent ophthalmic assessment[9]. Syphilis serology, essential before making the diagnosis, and CRP can be requested at this stage. Management is specialist-led in collaboration with the primary care physician, who should recognize situations requiring emergency assessment. During follow-up, inflammatory markers are monitored without taking normal results as reassurance; depending on treatment, a CBC, serum creatinine, transaminases, gamma-glutamyl transferase (gamma-GT) and alkaline phosphatase are added, and cardiovascular risk is monitored carefully. Ascending aortic involvement or aortic regurgitation always prompts investigation for infective endocarditis[9].

8.8 Relapsing polychondritis

In the Treatise: § 12.9

Relapsing polychondritis (RP) is suspected in chondritis: painful inflammation lasting more than one day of the auricular cartilage (sparing the lobule), the nasal bridge or the sternocostal cartilages[10]. The presentation is atypical in 40% of cases, with joint, respiratory, ear, nose and throat, ocular or cutaneous

manifestations, or even only prolonged fever or unexplained elevated inflammatory markers. Diagnosis is clinical and can be made with certainty only in the presence of chondritis; no laboratory test, including autoantibodies, establishes it. For cardiologists, valve disease predominates, in 6 to 27% of patients across series: mainly aortic regurgitation caused by dilation of the annulus and ascending aorta, which develops after several years, even without symptoms. Other manifestations include atrioventricular conduction disorders, pericarditis (3 to 6%), aortic aneurysms (4 to 6%) and deep venous thrombosis (4 to 10%)[10].

The initial workup includes standard laboratory tests, inflammatory markers, which are normal during 40% of flares, and immunologic testing: ANA and antibodies to extractable nuclear antigens (ENA), rheumatoid factor and anti-CCP, MPO-ANCA and PR3-ANCA[10]. These tests exclude differential diagnoses and investigate associated disease; they do not confirm RP. ANA and rheumatoid factor may be weakly positive; ANCA are absent. The principal differential diagnosis is granulomatosis with polyangiitis (GPA), from which RP is distinguished by negative ANCA, absence of pulmonary nodules and absence of kidney involvement; proliferative glomerulonephritis first suggests GPA. A baseline electrocardiogram and transthoracic echocardiography are routine, together with pulmonary function tests and dynamic CT of the neck and chest[10].

Depending on the setting, HLA-B27 typing is added, particularly for axial symptoms suggesting associated spondyloarthritis[10]. Another disease, usually autoimmune or inflammatory, accompanies RP in 20 to 30% of cases, including Sjögren syndrome, Hashimoto thyroiditis, lupus, antiphospholipid syndrome, rheumatoid arthritis, spondyloarthritis and inflammatory bowel disease; investigation for these conditions, at least clinically, guides testing. Ascending aortic involvement or new or worsening aortic or mitral regurgitation always requires investigation for infective endocarditis[10]. Testing for anti-cartilage, anti-type II collagen or anti-matrilin 1 antibodies is not useful.

The CBC deserves careful attention. Myelodysplastic syndrome accompanies RP in 6 to 11% of patients, mainly men older than 60, often with skin involvement, and worsens prognosis[10]. A persistent abnormality in a cell lineage, even isolated macrocytosis, prompts consideration of bone marrow aspiration with cytogenetic analysis in consultation with a hematologist. In men older than 50, atypical or treatment-resistant polychondritis with fever, neutrophilic dermatosis, pulmonary infiltrates, macrocytic anemia, myelodysplasia or monoclonal gammopathy prompts investigation for VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic): vacuoles in bone marrow precursors are suggestive, but their absence does not exclude it; diagnosis rests on a somatic UBA1 gene mutation identified in whole blood or bone marrow (see 11.5)[10]. RP associated with myelodysplasia can occur without a UBA1 mutation.

During follow-up, laboratory testing monitors any elevated inflammatory markers, whose normality does not exclude ongoing activity, and the CBC for myelodysplasia[10]. Depending on treatment, serum creatinine, transaminases, gamma-GT and alkaline phosphatase are added; glucose and a lipid profile are checked annually during corticosteroid or tocilizumab treatment. The protocol's authors do not recommend dapsone; if prescribed, glucose-6-phosphate dehydrogenase deficiency, which contraindicates its use because of a major hemolysis risk, is investigated before treatment. Cardiac, aortic and tracheal involvement, sometimes asymptomatic, is screened for clinically and by imag-

ing, including echocardiography, at a frequency determined by severity; less severe disease does not warrant routine annual structural imaging[10].

In primary care, management is preferably shared with a reference or competence center; the primary care physician provides local follow-up, essential for early recognition of flares and complications[10]. In chondritis, the initial workup includes a CBC, inflammatory markers, ANA, rheumatoid factor and ANCA; a photograph of the chondritis helps the specialist because the flare may subside within days. Laryngeal dyspnea or stridor, which may require emergency intervention, and sudden hearing loss, a treatment emergency, require immediate assessment. Visits range from monthly in severe active disease to every 3 months, then every 6 months in quiescence or even annually after several years of quiescence; the CBC retains a role in detecting myelodysplasia[10].

Table 8.1. The workup for large- and medium-vessel vasculitis and polychondritis, tier by tier

Situation	Essential	Depending on the context	Specialist assessment
Suspected GCA	CRP; MPO-ANCA and PR3-ANCA	Another marker if CRP is normal; RF and anti-CCP for arthritis	—
GCA follow-up	CRP and fibrinogen at least monthly; during corticosteroid treatment, potassium at 1 to 2 weeks, glucose at 1 month, HbA1c and lipids every 3 months	CBC, liver and kidney tests during treatment; lipids during tocilizumab treatment	Activity during tocilizumab treatment
Takayasu arteritis	CRP, fibrinogen or ESR at diagnosis	The same markers during follow-up, with clinical assessment and imaging	Pentraxin 3: not measured routinely
Aortitis	—	CRP and ESR with imaging; blood cultures if an aortic graft and fever are present	Infectious aortitis
PAN	PR3-ANCA and MPO-ANCA; inflammatory, kidney and urine testing; HBV, HCV and HIV serology	Blood cultures, directed immunologic testing; if anti-HBc positive, HBV DNA and liver tests during treatment	ADA2 for juvenile-onset disease
Incomplete Kawasaki disease	CRP, ESR	CBC, albumin, ALT, urine testing	Algorithm interpretation
Behçet disease	—	CRP; thrombophilia testing for thrombosis	HLA-B51 discouraged except for diagnostic uncertainty
Cogan syndrome	Syphilis serology	ANA, ANCA, complement; CRP	—
Polychondritis	CBC, inflammatory markers; ANA, ENA, RF, anti-CCP, ANCA	HLA-B27 for axial symptoms; investigation for endocarditis with aortic or valve involvement	Bone marrow aspiration and cytogenetics for a persistent cell lineage abnormality; VEXAS

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9

Small-vessel vasculitis, cryoglobulinemia and central nervous system vasculitis

Chapter contents

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Laboratory testing carries different weight in these three settings. In antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, the antibody underpins the diagnosis but not follow-up decisions. In cryoglobulinemia, sample collection is decisive. In primary central nervous system vasculitis, normal blood test results point toward the diagnosis.

9.1 ANCA-associated vasculitis: granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis

In the Treatise: § 9.4, § 9.4.1 and § 9.4.2

When findings suggest ANCA-associated vasculitis, the 2022 European recommendations call for first-line testing for ANCA directed against proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA) using a high-quality antigen-specific immunoassay (level 1a, grade A)[1]. The 2026 French protocol adopts this approach, without preliminary screening by indirect immunofluorescence (IIF)[2]. Other targets, including bactericidal permeability-increasing protein (BPI), elastase, cathepsin G and lactoferrin, have no clinical relevance and should not be tested. PR3-ANCA are present in most cases of granulomatosis with polyangiitis (GPA), including 60% of localized and 85% of systemic disease; MPO-ANCA occur in 60% of microscopic polyangiitis (MPA) and one-third of eosinophilic granulomatosis with polyangiitis (EGPA) cases[2].

Diagnosis is not based on serology alone: ANCA occur in other inflammatory diseases, infections or during drug exposure, and a small proportion of disease limited to the airways or kidneys is seronegative[1]. If the immunoassay is negative and suspicion is high, a second immunoassay or IIF is advised. Anti-glomerular basement membrane (anti-GBM) antibodies are tested for in pulmonary-renal syndrome[1] or rapidly progressive glomerulonephritis[2]. In severe disease, a rapid dot blot provides PR3-ANCA and MPO-ANCA results within hours; in a suggestive setting, positivity may be sufficient to begin treatment without histology[2].

The organ assessment and pretreatment workup include a complete blood count (CBC) with platelets, prothrombin time and activated partial thromboplastin time, C-reactive protein (CRP) and fibrinogen to investigate inflammation or hypereosinophilia; serum and urinary electrolytes, creatinine and estimated glomerular filtration rate (eGFR), urine dipstick, urine protein-to-creatinine ratio and testing for hematuria; liver tests, glucose, protein electrophoresis, creatine kinase (CK), lactate dehydrogenase and a lipid profile[2]. Testing also includes hepatitis B virus (HBV) serology, with surface antigen (HBsAg), anti-HBs and anti-HBc antibodies, human immunodeficiency virus (HIV) and hepatitis C virus (HCV) serology, with viral ribonucleic acid (RNA) testing if HCV serology is positive or equivocal, both to diagnose secondary disease and as pretreatment assessment (see 21.1 and 21.4); blood cultures in patients with fever or even routinely, and echocardiography for a previously unknown murmur, help exclude endocarditis[2]. Waiting for results does not delay treatment. In EGPA, etiologic investigation of hypereosinophilia distinguishes myeloid or lymphoid hypereosinophilic syndromes (see Chapter 14).

For cardiac assessment, an electrocardiogram and transthoracic echocardiography are routine; troponin, B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), or even cardiac magnetic resonance imaging, are added in EGPA or suspected cardiac involvement[2].

Magnetic resonance screening for asymptomatic involvement could lead to overtreatment. In EGPA, ANCA are present in only approximately 30% of patients at diagnosis, mainly MPO-ANCA, and cardiomyopathy is more common in ANCA-negative patients: their absence therefore does not exclude cardiac involvement[1]. In a cross-sectional study of 49 patients with EGPA, cardiac involvement was associated with ANCA negativity and higher eosinophil counts, 9.9 versus 3.7 × 10^9/L^3.

During follow-up, CRP is measured at each reassessment, together with creatinine, eGFR, urine protein-to-creatinine ratio and hematuria[2]. Persistently or newly elevated CRP prompts investigation for infection as well as activity. ANCA are often checked every 3 to 6 months; changes alone should not guide treatment but may prompt closer monitoring. MPO-ANCA negativity appears to have good negative predictive value for relapse, unlike PR3-ANCA negativity[2]. The European recommendations base treatment decisions on structured clinical assessment rather than ANCA or CD19+ B cells alone (level 1b, grade B)[1].

During rituximab treatment, serum immunoglobulins are measured before each course to detect secondary immunodeficiency (level 1b, grade B)[1]. The protocol's follow-up schedule includes CD19+ B-cell counts every 6 months during rituximab treatment, as well as CD4+ T-cell counts during cytotoxic immunosuppressive treatment; however, its rationale states that regular CD19+ typing should not be routine outside clinical trials. It is mainly useful in poorly controlled disease, where incomplete depletion (CD19+ > 0/mm^3) less than 6 months after the last infusion prompts investigation for anti-rituximab antibodies or underdosing[2]. Other urinary biomarkers, including CD163, monocyte chemoattractant protein 1 (MCP-1) and kidney injury molecule 1 (KIM-1), have not demonstrated utility. A kidney-related pitfall: persistence of low-level hematuria or proteinuria after a flare does not by itself warrant another biopsy; recurrent hematuria also requires exclusion of a urologic cause, including a urothelial tumor promoted by cyclophosphamide or smoking[2]. ANCA can accompany certain infections, including endocarditis, bartonellosis and tuberculosis, as well as inflammatory bowel disease; levamisole-adulterated cocaine often induces them, frequently with dual PR3 and MPO specificity[2].

In primary care, diagnosis is suspected from a combination of findings, some particularly suggestive: mononeuritis multiplex, necrotic purpura, crusting rhinitis, pulmonary nodules, refractory asthma or kidney impairment with microscopic hematuria; laboratory testing seeks elevated inflammatory markers, hypereosinophilia and ANCA[2]. Definitive diagnosis is established with a reference or competence center; treatment often needs to be prescribed urgently after discussion with that center, without waiting for nonessential tests. During induction, a CBC, electrolytes, creatinine and eGFR, glucose, CRP, urine dipstick and, in patients with kidney involvement, urine protein-to-creatinine ratio are checked before each cyclophosphamide or rituximab infusion, or monthly with other treatments, and liver tests are checked monthly. During maintenance treatment, these tests and liver tests are checked every 3 months, ANCA every 3 to 6 months and immunoglobulins every 6 months. After treatment is discontinued, monitoring takes place every 6 months for at least 2 years, then annually for at least 5 to 10 years, because relapse can occur late (see 21.7). Rising ANCA alone cannot establish relapse but requires closer monitoring, particularly after kidney involvement. After cyclophosphamide exposure, any episode of gross hematuria prompts investigation for urothelial cancer throughout life[2].

9.2 Cryoglobulinemia

In the Treatise: § 9.5.1

When cryoglobulinemic vasculitis is suspected, cryoglobulin detection, quantification and typing are essential, and the preanalytical phase determines the result[4]. Equipment is prewarmed to 37 °C and a transport device maintained at 37 °C is ready before venipuncture; the patient has avoided dietary fat for at least 4 to 6 hours; two or three 5 mL no-additive tubes without separator gel are required. When testing is performed by another laboratory, the collecting laboratory incubates the sample for at least 2 hours at 37 °C, then centrifuges and separates the serum; the serum can then travel at room temperature. If these conditions cannot be met, it is better not to collect the sample and to refer the patient to a laboratory that can meet them[4].

The sample is read after 7 days at +4 °C; testing is negative if no precipitate appears[4]. Routine repetition on three consecutive days is no longer performed, except when the setting is suggestive after an initial negative result. A positive or equivocal result is followed by quantification and identification of the cryoprecipitate. Most teams consider a concentration above 50 mg/L pathological; however, concentration and clinical findings do not strictly correlate, and a very low concentration is interpreted in light of suggestive symptoms. A 25% change from baseline is necessary to establish an increase or decrease[4].

Indirect findings help when detection is difficult: low C_4 with normal or slightly low C_3, and rheumatoid factor activity in mixed cryoglobulinemia, two abnormalities usually absent in type I[4]. Electrophoresis and immunofixation, which must be performed at 37 °C, show polyclonal hypergammaglobulinemia or a monoclonal immunoglobulin. The initial workup also includes a CBC, creatinine and eGFR, liver tests, CRP and fibrinogen, rheumatoid factor, C_3, C_4 and total hemolytic complement activity (CH_{50}), antinuclear antibodies (ANA), antibodies to extractable nuclear antigens (anti-ENA), ANCA, anti-liver-kidney microsomal (anti-LKM), anti-smooth muscle and antimitochondrial antibodies, HCV, HBV and HIV markers and immunoglobulin measurement; urinary tests include microscopy and culture, protein-to-creatinine and albumin-to-creatinine ratios, with urine immunofixation in type I[4]. In a patient with hepatitis C, HBV serology is essential: anti-HBc positivity, even without HBsAg, warrants preemptive treatment against HBV reactivation, particularly with rituximab treatment (see 21.1)[4].

Type I requires specialist assessment: bone marrow aspiration with flow cytometry, or even a bone marrow biopsy, and lymphocyte phenotyping to investigate a clone; type II calls for lymphocyte immunophenotyping[4]. Cardiac involvement is rare but increases mortality: microvascular involvement may cause severe heart failure; an electrocardiogram is part of the initial workup, and hypertension-related left ventricular hypertrophy is common. Myopericarditis is reported in only 4% of cases; cardiac evaluation includes NT-proBNP, an electrocardiogram, echocardiography and myocardial magnetic resonance imaging, which is particularly important before treatment, especially if high-dose corticosteroids are planned[4]. In a series of 7 cases with cardiac involvement, NT-proBNP and BNP were markedly elevated while troponin I remained negative: normal troponin does not exclude involvement[5]. In cryoglobulinemic glomerulonephritis, annual cardiac assessment is part of follow-up, particularly if eGFR is below 60 mL/min, because cardiovascular disease is the leading cause of death[4].

In primary care, the first-contact physician identifies findings warranting referral to an expert center[4]. Purpura, acral vascular symptoms, distal sen-

sory neuropathy, arthralgia, proteinuria or hematuria suggest the diagnosis, as do a monoclonal spike, rheumatoid factor or low C_4. A fluctuating erythrocyte sedimentation rate (ESR), spurious leukocytosis or thrombocytosis, or unexpected changes in total protein or gamma globulins sometimes reveal an unrecognized cryoglobulin. Stellate purpura progressing to necrosis often requires hospitalization. During follow-up, a urine dipstick is performed at each visit; cryoglobulin, C_4, rheumatoid factor, creatinine and eGFR, urine protein-to-creatinine ratio, hematuria on urine examination, CRP, calcium and a CBC are checked at 3 months, 6 months and then annually for 5 years; CRP is insufficiently sensitive to reflect low-grade activity, while calcium and the CBC screen for progression to lymphoma, which may occur late. A monoclonal spike is measured in serum maintained at 37 °C, with advance notification of the laboratory. After HCV cure, cryoglobulin is checked annually until it disappears[4].

9.3 Primary central nervous system vasculitis

In the Treatise: § 9.2.6, subsection "Primary central nervous system vasculitis"

There is no clinically useful laboratory marker for primary central nervous system vasculitis (PCNSV): normal blood test results in a suggestive clinical and imaging setting strengthen the hypothesis[6]. Inflammatory marker elevation is absent or modest, with CRP normal or only mildly elevated, often below 30 mg/L, unlike systemic vasculitis. The workup mainly excludes alternative diagnoses; the protocol's list is a minimum, to be adapted to the patient and epidemiologic setting.

Suggested blood and urine tests include a CBC, electrolytes, calcium, prothrombin time and activated partial thromboplastin time, creatinine, liver tests, CRP, fibrinogen, fasting glucose, glycated hemoglobin (HbA1c), a lipid profile including lipoprotein(a), ANA, anti-ENA and anti-double-stranded DNA antibodies, PR3-ANCA and MPO-ANCA, complement, rheumatoid factor, antiphospholipid testing, angiotensin-converting enzyme, protein electrophoresis and lactate dehydrogenase[6]. Additional tests include blood cultures, syphilis, HIV, hepatitis B and C and Lyme serology, an interferon-gamma release assay or tuberculin skin test, urine microscopy and culture, testing for proteinuria and toxicology screening.

Cerebrospinal fluid (CSF) is analyzed in a specialist setting: protein, glucose with blood glucose, cell counts, oligoclonal bands and immunoglobulin G (IgG) index, cytopathology, bacterial and mycobacterial cultures and varicella-zoster virus polymerase chain reaction (PCR)[6]. Abnormalities, including pleocytosis above 4 cells/mm³ or protein above 0.4 g/L, are common but nonspecific and only moderately sensitive; pleocytosis of 5 to 10 cells/mm³ should not be overinterpreted, particularly after a stroke. Normal CSF does not exclude the diagnosis. Pleocytosis above 500 cells/mm³, exceptional in PCNSV, prompts investigation for infectious or autoimmune meningoencephalitis and lymphoma; increased interleukin-10 favors lymphoma[6].

Optional tests require specialist assessment guided by suggestive findings: CK, cryoglobulin, JAK2 mutation, a paroxysmal nocturnal hemoglobinuria clone, ADAMTS13 protease activity (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), onconeural and anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies, immunoglobulin subclasses, homocysteine and genetic tests, including NOTCH3, HTRA1, COL4A1/A2, TREX1, mitochondrial genetics and adenosine deaminase 2 deficiency[6]. Other

biomarkers, including cytokines, remain under evaluation; testing is not routine and is the responsibility of expert physicians.

The heart is included in the initial workup: in stroke, transthoracic or transesophageal echocardiography and imaging of the supra-aortic vessels and aortic arch investigate an embolic source, including endocarditis, myxoma, intracardiac thrombus or atheroma[6]. There is no laboratory follow-up specific to PCNSV; laboratory testing monitors treatment. Lumbar puncture is not routinely repeated but may be considered if relapse is suspected; a new stroke requires a new cardiovascular workup[6].

In primary care, unusual headache, rapidly progressive cognitive impairment, a neurologic deficit or a seizure calls for immediate referral to the nearest hospital with appropriate facilities, even if imaging is available in the community, because diagnostic management is urgent[6]. During follow-up, the primary care physician coordinates with the neurologist-internist team and contacts them for any episode suggestive of activity. Community laboratory testing monitors treatment: during cyclophosphamide treatment, a CBC, platelets, creatinine and testing for hematuria at a minimum before each infusion and every 2 weeks during the first 3 months, then monthly if treatment is continued orally; neutrophils below 1.5×10^9/L on the scheduled pulse date prompt a 25% dose reduction or even postponement of the infusion; during methotrexate treatment (pretreatment workup: see 21.1), the protocol considers weekly testing for 1 month, monthly for 3 months, then every 3 months acceptable (general rule: see 21.3); at the start of corticosteroid treatment, glucose, potassium and blood pressure. During immunosuppressive treatment, a central neurologic manifestation first raises suspicion of infection[6].

Table 9.1. The workup for ANCA-associated vasculitis, cryoglobulinemia and PCNSV, tier by tier

Situation	Essential	Depending on the context	Specialist assessment
Suspected ANCA-associated vasculitis	PR3-ANCA and MPO-ANCA by immunoassay; CBC, CRP; kidney and urine tests; HBV, HCV and HIV serology; blood cultures; electrocardiogram and echocardiography	Second immunoassay or IIF; anti-GBM for pulmonary-renal syndrome or rapidly progressive glomerulonephritis; troponin and BNP for EGPA or suspected cardiac involvement	Hypereosinophilia workup (EGPA)
ANCA-associated vasculitis follow-up	CRP and kidney tests at each reassessment; immunoglobulins before each rituximab course; CBC and glucose before each infusion or monthly during induction; liver tests monthly during induction; these tests every 3 months during maintenance	ANCA every 3 to 6 months, without standalone decision-making value	CD19+ and anti-rituximab antibodies for poorly controlled disease
Suspected cryoglobulinemia	Collection and transport at 37 °C; detection (read at +4 °C after 7 days), quantification, typing; rheumatoid factor, C3, C4; autoantibodies; HCV, HBV, HIV	Repeat testing if the first result is negative and the setting suggestive; urine immunofixation (type I); NT-proBNP for cardiac assessment, particularly before treatment	Investigation for a clone (type I, type II)
Cryoglobulinemia follow-up	Urine dipstick at each visit; cryoglobulin, C4, rheumatoid factor, kidney tests, CRP, CBC and calcium at 3 and 6 months, then annually for 5 years	Monoclonal spike in serum at 37 °C; annual cryoglobulin after HCV cure	Annual cardiac assessment for glomerulonephritis
Suspected PCNSV	Minimum exclusion workup: CBC, CRP, kidney and liver tests, autoantibodies, ANCA, antiphospholipid testing, serology, tuberculosis, toxicology	Cardiovascular assessment for stroke	CSF; optional tests, genetics
PCNSV follow-up	Laboratory monitoring of treatment	Lumbar puncture if relapse is suspected	Any suspected relapse

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PART III

Autoinflammatory, Infiltrative and Rare Diseases

10

Still disease, macrophage activation syndrome and hemophagocytic lymphohistiocytosis

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Ferritin links these diseases but distinguishes them poorly. Marked hyperferritinemia points to Still disease or macrophage activation syndrome, but no isolated result establishes the diagnosis: the overall pattern, particularly its day-to-day changes, is decisive. Cardiac involvement includes pericarditis, sometimes tamponade and myocarditis, and circulatory failure during the cytokine storm.

10.1 Still disease

In the Treatise: § 10.2, § 10.2.1 and § 13.8.11

Adult-onset Still disease (AOSD) is suspected in fever, rash, arthralgia or arthritis and marked laboratory evidence of inflammation: elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), with neutrophilic leukocytosis[1]. The 2024 recommendations of the European Alliance of Associations for Rheumatology and the Paediatric Rheumatology European Society (EULAR/PReS) bring systemic juvenile idiopathic arthritis and adult-onset disease together under the single name Still disease. They emphasize that no clinical or laboratory finding is specific on its own and that infections, cancers, other immune-mediated diseases and monogenic autoinflammatory diseases must be excluded; in adults, they mention VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) and clonal hematopoiesis[1].

The initial workup proposed by the 2017 French National Diagnostic and Care Protocol (PNDS) includes, as first-line tests, a complete blood count (CBC) with platelets and blood smear, prothrombin time and activated partial thromboplastin time (aPTT), electrolytes, urea and creatinine, transaminases, alkaline phosphatase, gamma-glutamyl transferase and bilirubin, lactate dehydrogenase (LDH), ferritin and its glycosylated fraction, creatine kinase, protein electrophoresis and CRP[2]. Additional tests include blood cultures, urine microscopy and culture, human immunodeficiency virus (HIV), hepatitis B and C, Epstein-Barr virus and cytomegalovirus serology, then antinuclear antibodies (ANA), anti-double-stranded DNA and anti-extractable nuclear antigen antibodies, complement, rheumatoid factor, anti-cyclic citrullinated peptide antibodies and antineutrophil cytoplasmic antibodies (ANCA)[2].

Ferritin is useful diagnostically only when very high: the PNDS cites a proposed threshold of 4,000 ng/mL and notes that concentrations of 10,000 ng/mL or higher sometimes indicate hemophagocytosis or severe hepatocellular injury. According to the same text, an increase above four times normal occurs in only 67% of patients, with a specificity of 85%[2]. A glycosylated ferritin fraction below 20% is suggestive but not always present. The 2024 recommendations add that interleukin-18 (IL-18) and S100 proteins, including calprotectin, strongly support diagnosis and should be measured if available (level of evidence 4, grade C); they specify that no threshold is agreed upon or validated and that these assays remain restricted to tertiary centers[1].

As second-line investigations according to the setting, the PNDS adds fibrinogen, D-dimer and fibrin degradation products if disseminated intravascular coagulation is suspected, triglycerides and bone marrow aspiration if macrophage activation syndrome is suspected, immunofixation, free light chains and beta-2-microglobulin, directed infectious investigations and a bone marrow core biopsy if hematologic malignancy is suspected[2]. Joint aspiration is indicated for arthritis and lymph node biopsy for asymmetric or indurated lymphadenopathy[2].

Follow-up depends on severity and treatment. As guidance, the PNDS proposes a monthly CBC for three months, then every three months; transam-

inases at the same intervals during methotrexate (pretreatment workup: see 21.1), tocilizumab, anakinra or nonsteroidal anti-inflammatory drug treatment; and electrolytes with creatinine every three months during the first year, then every six months; during corticosteroid treatment, fasting glucose and glycated hemoglobin every three months, vitamin D, calcium and albumin, and an annual lipid profile[2]. The 2017 PNDS considered the usefulness of ferritin during follow-up unproven; conversely, the 2024 recommendations call for regular measurement in every patient, and daily or even twice-daily measurement when macrophage activation is suspected or the patient is at risk[1].

The most common cardiac manifestation is pericarditis, sometimes the presenting feature, which can progress to tamponade; myocardial involvement is not exceptional[2]. No specific laboratory test identifies it; the Treatise highlights pericardial effusion in a febrile young adult with very high ferritin as a warning sign. A pitfall: canakinumab or tocilizumab may blunt or delay fever and the rise in ferritin[1].

In primary care, the primary care physician has a role in suspecting the diagnosis; suspected disease is preferably referred to a reference center or, failing that, a hospital emergency department, and the French long-term illness coverage application follows specialist advice[2]. In shared follow-up, the physician attends to vaccinations and treatment tolerability. Stable disease is reviewed once or twice a year and at least every six months during biologic treatment; in remission, a reference or competence center reassesses the patient at least every two years[2]. A flare differing from previous flares through cytopenias, hypertriglyceridemia, hypofibrinogenemia or hyperferritinemia raises concern for macrophage activation, as do transaminases above ten times normal: management is then urgent in a specialist setting[2]. Difficult-to-treat disease, severe macrophage activation and lung involvement are followed with an expert center[1].

10.2 Macrophage activation syndrome

In the Treatise: § 10.2 and § 10.3.5

Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) are two systemic hyperinflammatory syndromes grouped as HLH/MAS by the 2022 EULAR and American College of Rheumatology (EULAR/ACR) points to consider; MAS denotes the secondary form occurring in rheumatic diseases[3]. The syndrome is suspected in unexplained or unusually severe abnormalities, especially in combination: persistent fever, rising ferritin, cytopenias, liver involvement, coagulopathy, splenomegaly and neurologic findings[3]. In Still disease, the 2024 recommendations identify persistent fever, splenomegaly, high or rising ferritin, inappropriately low cell counts, abnormal liver tests, intravascular coagulation activation and high or rising triglycerides (level 2a, grade B)[1]. In validation, the 2016 EULAR/ACR/PRINTO (Paediatric Rheumatology International Trials Organisation) criteria for MAS complicating systemic juvenile idiopathic arthritis had a sensitivity of 0.73 and a specificity of 0.99; these are classification criteria designed for study enrollment and developed in childhood disease[4].

The essential workup includes ferritin, to be measured in every patient with a hyperinflammatory syndrome (level 1A) and repeated if normal when suspicion persists (level 5D). Routine assessment includes a CBC with differential, liver tests, fibrinogen, D-dimer, LDH and CRP[3]. The text cautions that ferritin is sensitive but thresholds differ across populations, from 500 to 2,000 ng/mL

in pediatric studies and often above 10,000 ng/mL in adults, and that iron overload, cancer or hepatitis also raise it[3].

Specialized biomarkers, including soluble interleukin-2 receptor (soluble CD25), CD163, neopterin, IL-18, interferon-gamma and C-X-C motif chemokine ligand 9 (CXCL9), assist diagnosis and are interpreted with a specialist when available (level 4C)[3]. Results often return too late for the initial decision and are rarely available outside university centers. Bone marrow aspiration is reserved for suspected MAS or the hematologic differential diagnosis; absence of hemophagocytosis must not delay management when the presentation is compatible[2]. The points to consider encourage investigation for cancer, particularly lymphoma, in every patient, especially adults, in whom it accounts for almost half of cases; histologic evidence is sought before corticosteroids if possible, because they may obscure it, and a triggering infection is investigated broadly[3].

Initial monitoring may be daily for inflammatory markers, ferritin and CRP, and for organ injury markers, including a CBC, fibrinogen and alanine aminotransferase; specialized biomarkers are checked less frequently than ferritin and CRP, and CXCL9 is particularly useful during interferon-gamma blockade[3]. The graded statement sets a minimum: organ injury markers at least daily and inflammatory markers at least twice weekly (level 2B)[3]. Lack of response to initial treatment requires diagnostic reassessment. The main pitfall is seeking a threshold: no isolated finding is specific, and the overall pattern, interpreted dynamically, matters[1]. For cardiac involvement, the Treatise relates circulatory failure and myocardial dysfunction to cytokine exposure rather than primary structural injury.

In primary care, the points to consider also address first-contact physicians[3]. In persistent fever with cytopenias, liver involvement or elevated ferritin, the community laboratory rapidly provides initial triage: ferritin, a CBC with differential, liver tests, fibrinogen, D-dimer, LDH and CRP[3], to which the Still disease PNDS adds triglycerides[2]. Normal ferritin does not settle the issue if suspicion persists: it is measured again[3]. In Still disease, MAS requires urgent specialist management, possibly in intensive care, and investigation for infection, particularly Epstein-Barr virus viral load, is part of diagnosis[2]. In the series analyzed by the points to consider, more than one-third of children with HLH/MAS and almost half of adults with MAS required intensive care[3].

10.3 Familial hemophagocytic lymphohistiocytosis and NLRC4 syndrome

In the Treatise: § 10.3.5 and § 13.8.19

A genetic cause is suspected with young age, family history, consanguinity or prominent neurologic involvement[3]. Cytotoxicity defects mainly present in infants and young children; adult forms exist, but a clinically useful genetic finding is rare in adults. The points to consider support early genetic testing in children and high-risk adults, preferably using a multigene panel or exome or genome sequencing rather than gene-by-gene testing, always with genetic counseling and a decision made with a specialist (levels 3B to 5D)[3].

The susceptibility gene table lists PRF1, UNC13D, STX11 and STXBP2 for impaired granule-mediated cytotoxicity and states that it is not exhaustive[3]. Functional investigations, including perforin expression by flow cytometry, natural killer (NK) cell function and CD107a mobilization, require specialized laboratories; according to the same table, NK function should remain abnormal even in remission. A positive functional test or known family history allows

targeted single-gene sequencing[3]. Selection of a genetic test incorporates age, clinical presentation and laboratory and functional test results and is decided with a specialist (level 4C)[3].

The NLRC4 inflammasome-associated syndrome, called NLRC4-MAS or autoinflammation with infantile enterocolitis, appears in the same table among disorders of inflammasome regulation, with early onset and enterocolitis; the specialized test that points toward it is chronically very high serum IL-18[3]. The Treatise identifies free IL-18 as a biomarker discriminating this mechanism from familial hemophagocytic lymphohistiocytosis due to cytotoxicity defects; total and free fractions and assay methods are not interchangeable, and no universal threshold is proposed.

Follow-up is the same as for MAS, with particular attention to the central nervous system: neurologic involvement should be investigated in every patient, and an assessment is indicated in patients younger than one year, with a known genetic form of hemophagocytic lymphohistiocytosis or with neurologic findings, without delaying treatment[3]. Early recognition of familial disease may expedite allogeneic hematopoietic stem cell transplantation and allow consideration of transplantation in an affected but still asymptomatic sibling[3].

In primary care, familial disease or an NLRC4-associated syndrome can be suspected but not confirmed. Persistent fever with cytopenias, liver involvement, coagulopathy or high and rising ferritin prompts the core MAS laboratory workup and rapid assessment, especially in a young patient or with family history, consanguinity or neurologic findings[3]. Central nervous system involvement, liver failure or multiorgan failure worsens prognosis and requires urgent care; these patients need continuous monitoring, sometimes in intensive care[3]. Specialized markers, such as soluble CD25 or IL-18, are interpreted with a specialist in these diseases; the decision to perform genetic testing is made with that specialist, and genetic counseling is offered before any test[3].

Table 10.1. The workup for Still disease, MAS and hemophagocytic lymphohistiocytosis, tier by tier

Situation	Essential	Depending on the context	Specialist assessment
Suspected Still disease	CBC and blood smear, prothrombin time, aPTT, CRP, LDH, ferritin and glycosylated ferritin, CK, protein electrophoresis, liver and kidney tests; blood cultures, urine microscopy and culture, HIV, HBV, HCV, EBV and CMV serology; ANA, anti-DNA, anti-ENA, complement, RF, anti-CCP, ANCA	Other serology, viral PCR, tuberculosis testing	IL-18 and S100 proteins if available
Suspected MAS	Repeated ferritin, CBC, liver tests, fibrinogen, D-dimer, LDH, CRP, triglycerides; investigation for a triggering infection, including EBV viral load, and cancer, particularly lymphoma	—	Soluble CD25, CXCL9, IL-18; bone marrow aspiration
Suspected familial disease or NLRC4	The same core workup	—	Genetic panel, perforin, NK function, CD107a, IL-18

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11

Periodic fevers and monogenic diseases: FMF, MKD, CAPS, TRAPS, interferonopathies, DADA2 and VEXAS

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These diseases are recognized clinically and confirmed genetically; routine laboratory testing identifies none of them specifically. It measures inflammation between attacks as well as during them, monitors kidney function for amyloidosis and supports treatment monitoring. Cardiac involvement occurs through pericarditis, AA amyloidosis (amyloid A protein amyloidosis), vasculopathy or thrombosis, and rarely through primary cardiac disease.

11.1 Familial Mediterranean fever

In the Treatise: § 10.3.1 and § 7.3.4

Familial Mediterranean fever (FMF) is suspected in brief, recurrent febrile attacks with serositis, including peritonitis, pleuritis or pericarditis, particularly in a patient of Mediterranean origin. An autosomal recessive disease, it involves two pathogenic variants in the MEFV gene[1]. The 2022 French National Diagnostic and Care Protocol (PNDS) considers genetic testing necessary for confirmation. Homozygous or compound heterozygous genotypes combining the exon 10 variants p.Met694Val, p.Met694Ile, p.Met680Ile and p.Val726Ala confirm diagnosis; other findings are difficult to interpret and expert center advice is strongly recommended[1]. The 2024 update of the European Alliance of Associations for Rheumatology (EULAR) recommendations, endorsed by the Paediatric Rheumatology European Society (PReS), emphasizes that FMF clinical assessment and genetics require expertise[2].

The PNDS identifies three genetic pitfalls. Routine analysis covers exon 10 only, and full sequencing can be requested only by an expert center. A single pathogenic variant, particularly p.Met694Val, may accompany a typical phenotype without identification of a second variant: the genotype is termed inconclusive. Finally, some variants are no longer considered pathogenic, the most common being p.Glu148Gln[1]. Genetic findings must always be assessed against the clinical presentation.

According to the PNDS, annual follow-up of uncomplicated FMF includes inflammatory markers, kidney tests and liver tests[1]. In children, annual C-reactive protein (CRP) testing appears necessary, with paired CRP and serum amyloid A protein (SAA) testing once initially to check that the two markers do not diverge. In adults, CRP alone is sufficient if testing has excluded discordance between the markers, namely low CRP despite high SAA; otherwise, CRP and SAA are monitored together. During colchicine treatment, a CBC, creatinine, liver tests and creatine kinase (CK) are added[1]. During dose escalation in active disease, the 2016 EULAR recommendations call for CRP, SAA or both at least every three months[3].

The 2024 update calls for regular monitoring of response, toxicity and adherence, more frequently at diagnosis and while disease remains uncontrolled (level 5)[2]. If liver enzymes exceed twice normal, the colchicine dose is reduced and the cause investigated. In patients with kidney impairment, toxicity risk is high: toxicity signs and CK are monitored closely and the dose reduced[2]. The PNDS includes CK in the annual tolerability workup; the European recommendations emphasize its importance when kidney function declines.

AA amyloidosis determines prognosis. The PNDS screens for it at least annually using creatinine and proteinuria, initially by dipstick and then by the urine protein-to-creatinine ratio; persistent proteinuria or unexplained kidney impairment requires histologic evidence, first from minor salivary glands, abdominal fat or gastrointestinal mucosa, then from the kidney[1]. Once amyloidosis is established, treatment aims for complete control of laboratory inflammation, measured by SAA or, if unavailable, CRP (level 3)[2]; the 2016 rec-

ommendations targeted SAA below 10 mg/L and considered CRP an imperfect substitute[3]. However, in the UK national center cohort, mortality risk remained higher with SAA of 4 to 9 mg/L than below 4 mg/L (see 13.3).

Regarding cardiac involvement, the 2016 recommendations note that the heart is rarely affected by FMF-associated AA amyloidosis[3]. The Treatise reports clinical pericarditis in 0.7 to 1.4% of patients, with subclinical pericardial involvement detected by echocardiography in up to approximately 27%.

In primary care, uncomplicated, well-controlled FMF is reviewed once or twice a year; follow-up can be provided by the primary care physician, with contact with a reference or competence center at least every two years in adults and annually in children[1]. CRP is measured outside attacks, at least ten days after the last attack ends, and should remain below the laboratory's upper limit of normal. An inadequate response to colchicine is determined by a specialist physician or in a national multidisciplinary case discussion, and only after adherence has been confirmed[1]. Colchicine must not be combined with macrolides, such as erythromycin, clarithromycin and josamycin, or pristinamycin, which the PNDS recommends writing on every prescription[1]. The PNDS lists cyclosporine, tacrolimus, azole antifungals, certain antiretrovirals such as ritonavir, verapamil, diltiazem, amiodarone, statins, digoxin, ranolazine and grapefruit juice among agents interacting with colchicine through P-glycoprotein (P-gp, or the ABCB1 transporter) or cytochrome P450 3A4 (CYP3A4). The PNDS strictly contraindicates these combinations in kidney or liver impairment; outside these situations, if a combination is unavoidable, the colchicine dose and duration of coadministration are reduced as much as possible and overdose symptoms monitored: diarrhea, vomiting, muscle weakness and tingling in the fingers and toes[1]. The French Summary of Product Characteristics (SmPC) of colchicine classifies these interactions differently: combination with macrolides other than spiramycin and with pristinamycin is contraindicated; combination with verapamil, cyclosporine, telaprevir, ritonavir-boosted protease inhibitors, azole antifungals (itraconazole, ketoconazole, voriconazole, posaconazole) or strong CYP3A4 inhibitors is not recommended; statins call for clinical and laboratory monitoring as a precaution for use, particularly at the start of coadministration; colchicine itself is contraindicated in severe kidney impairment (creatinine clearance below 30 mL/min) and severe liver impairment[4].

11.2 Mevalonate kinase deficiency, TRAPS and CAPS

In the Treatise: § 10.3.4, § 10.3.2 and § 10.3.3

Mevalonate kinase deficiency (MKD) generally begins during the first year of life: febrile attacks lasting four to six days with abdominal pain, vomiting, diarrhea, cervical lymphadenopathy, aphthae or rash; vaccination-triggered attacks point toward this diagnosis[5]. It is an autosomal recessive disease caused by loss-of-function mutations in the MVK gene[5]. Its most severe form, mevalonic aciduria, includes cognitive involvement and may be complicated by macrophage activation syndrome[5].

The confirmatory test is MVK gene analysis, to be performed in every suspected patient regardless of clinical score results (level B), with genetic counseling for the patient and family[6]. The 2021 EULAR/American College of Rheumatology (ACR) points to consider generally recommend next-generation sequencing rather than a gene-by-gene approach[5]. If genetics is negative or inconclusive despite a suggestive presentation, the 2024 revision of the SHARE (Single Hub and Access point for pediatric Rheumatology in

Europe) recommendations proposes testing for MVK deletions or duplications and assessing other laboratory findings against the clinical presentation[6].

During attacks, white blood cells, erythrocyte sedimentation rate (ESR), CRP and SAA confirm inflammation without being diagnostic; they fluctuate and may normalize between attacks (level A)[6]. Urinary mevalonic acid is elevated mainly during attacks. The 2024 revision states that a normal concentration does not exclude MKD, and urinary mevalonic acid testing is not a mandatory prerequisite for genetic testing; however, its commentary gives a negative predictive value of 98%, whereas its recommendation table describes this negative predictive value as low[6]. Enzyme activity measurement is reserved for severe phenotypes when the result may change a decision, particularly bone marrow transplantation (level B).

Immunoglobulin D (IgD) measurement is not recommended: its diagnostic value is negligible, and the former name hyper-IgD syndrome does not justify it (level B)[6]. During follow-up, the 2021 points to consider monitor inflammation through neutrophilia, CRP and ESR, and through SAA and S100 proteins if available. They recommend assessing proteinuria every six months in all interleukin-1-mediated autoinflammatory diseases, particularly with a family history of amyloidosis[5]. The Treatise describes MKD as having the least prominent cardiovascular impact in this group.

The same points to consider cover two autosomal dominant diseases: tumor necrosis factor receptor-associated periodic syndrome (TRAPS), caused by TNFRSF1A mutations, and cryopyrin-associated periodic syndromes (CAPS), caused by gain-of-function NLRP3 mutations[5]. Confirmation is genetic, generally by next-generation sequencing. Mutations may be familial, de novo or somatic; in CAPS, somatic mutations occur particularly in severe disease and may require deep sequencing. In TRAPS, a common population variant of uncertain significance, such as R121Q, formerly R92Q, is not considered pathogenic[5]. Laboratory follow-up is the same as in MKD: neutrophilia, CRP and ESR, SAA and S100 proteins if available, and proteinuria every six months[5].

In primary care, MKD follow-up is coordinated by a hospital physician with the primary care physician and a reference or competence center; the center reviews the patient every six months during biologic treatment and annually if disease is well controlled without biologic treatment[7]. The 2015 PNDS provides for a CBC, CRP and SAA at least annually, more often during treatment adjustment; liver tests, kidney function and a urine dipstick every six months; urine protein-to-creatinine ratio annually; and cholesterol and triglycerides every six months during anti-interleukin-1 treatment[7]. Significant proteinuria, hematuria or kidney impairment prompts consideration of kidney biopsy[7].

11.3 Type I interferonopathies

In the Treatise: § 12.7

The 2021 EULAR/ACR points to consider address three interferonopathies: CANDLE/PRAAS (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, or proteasome-associated autoinflammatory syndrome), STING-associated vasculopathy with onset in infancy (SAVI) and Aicardi-Goutières syndrome (AGS)[8]. These are suspected in unexplained early-onset systemic inflammation with vasculopathic skin lesions, chilblains or acral ischemia, early interstitial lung disease suggesting SAVI, panniculitis suggesting CANDLE/PRAAS or early neurologic involvement suggesting AGS.

A chronically elevated blood interferon signature is common to all three diseases and should be measured repeatedly to establish chronicity[8]. It is not required for diagnosis: it may be negative in mild disease, during corticosteroid treatment and in some patients with AGS. In the absence of internationally standardized methods and reference values, it is interpreted using laboratory-specific standards. CRP and ESR are elevated in CANDLE/PRAAS and SAVI, rarely in AGS[8]. Confirmation is genetic, using next-generation sequencing rather than gene-by-gene testing; large deletions may escape exome sequencing, and a patient with a suggestive phenotype but no molecular diagnosis is referred to an expert center[8].

The initial workup includes a CBC with differential, transaminases, which can also increase because of myositis, and a minimum immune assessment: infection history, lymphocyte subsets and immunoglobulins[8]. Autoimmunity is investigated regularly: antinuclear antibodies (ANA) have been found in up to 62.5% of SAVI, 42% of CANDLE/PRAAS and 23% of AGS cases, antineutrophil cytoplasmic antibodies (ANCA) in up to 71% of SAVI cases and antiphospholipid antibodies in all three diseases. Urinalysis is recommended, with kidney involvement mainly reported in AGS and SAVI[8].

During Janus kinase (JAK) inhibitor treatment, BK viral load in blood and urine and kidney function are checked before initiation and at every visit; kidney ultrasound and a urine protein- or albumin-to-creatinine ratio are obtained before treatment[8]. During baricitinib treatment, monitoring for thrombocytosis, leukopenia and infections is advised in AGS. This monitoring applies to these diseases and does not automatically extend to all JAK inhibitor prescriptions.

Regarding cardiac involvement, pulmonary hypertension, potentially severe and probably underdiagnosed, is investigated regularly by echocardiography in CANDLE/PRAAS and AGS; certain AGS genotypes confer a risk of infantile hypertrophic cardiomyopathy and valve calcification[8]. The metabolic syndrome in CANDLE/PRAAS warrants dedicated screening.

In primary care, follow-up is multidisciplinary, and patients with inactive disease are reassessed every three months for disease activity and treatment toxicity[8]. ESR, CRP, a CBC with differential and urinalysis are checked at every visit; during JAK inhibitor treatment, liver tests, kidney function and BK viral load in blood and urine are added[8]. In CANDLE/PRAAS, blood pressure is measured at every visit, lipids and glucose are checked every 12 to 36 months and echocardiography is repeated every 6 to 12 months; in AGS, echocardiography is performed every 1 to 2 years; signs of pulmonary hypertension prompt cardiology or pulmonology advice[8]. Live vaccines are avoided during JAK inhibitor or other immunosuppressive treatment, and treatment is not interrupted without a specific contraindication[8].

11.4 Adenosine deaminase 2 deficiency

In the Treatise: § 12.6

Deficiency of adenosine deaminase 2 (DADA2) is suspected in children with recurrent fever, livedo, early strokes, cytopenias or immunodeficiency. The 2023 international consensus also proposes investigation in childhood, adult or familial polyarteritis nodosa, Sneddon syndrome, inflammatory livedo racemosa and suggestive unexplained autoinflammatory syndromes[9]. The Treatise highlights coronary aneurysms in children mimicking Kawasaki disease.

Diagnosis rests on nearly absent blood adenosine deaminase 2 (ADA2) enzyme activity or biallelic pathogenic or likely pathogenic ADA2 variants

(level 2, grade B); both methods are combined if possible (level 5, grade D)[9]. Normal ADA2 activity excludes the diagnosis. Conversely, failure to identify a variant by sequencing does not necessarily exclude it. A nonconfirmatory genotype, consisting of a single variant or variants of uncertain significance, calls for enzyme activity measurement or other genetic tests; a monoallelic variant defines a carrier[9].

The recommended initial workup includes a CBC with differential and reticulocytes, ESR and CRP, liver and kidney function, urinalysis, immunoglobulins A, M and G (IgA, IgM and IgG), T, B and natural killer (NK) cell subsets and plasma ADA2 activity (level 5, grade D)[9]. An electrocardiogram is among baseline investigations. Depending on the affected organs, bone marrow aspiration and core biopsy with histology and flow cytometry, an autoantibody profile, vaccine responses and echocardiography are added[9].

Controlled disease is reviewed at least every three to six months with physical examination and routine laboratory tests: a CBC with differential, ESR, CRP, liver and kidney function[9]. Tuberculosis screening is required before anti-tumor necrosis factor (anti-TNF) treatment; drug concentrations and anti-drug antibodies may be monitored, for example every 6 to 12 months (level 5, grade D)[9]. The 2022 EULAR infection recommendations prefer an interferon-gamma release assay to a tuberculin skin test when available and call for determination of hepatitis B virus status before disease-modifying treatment[10].

Screening should be considered in all siblings of a confirmed case, symptomatic relatives and any relative being considered as a stem cell donor, with genetic counseling (level 5, grade D)[9]. After allogeneic transplantation, ADA2 activity may help confirm efficacy. A treatment pitfall relevant to cardiologists: antiplatelet agents, anticoagulants and antithrombotics should be avoided to prevent intracranial hemorrhage (expert opinion, level 5, grade D)[9].

In primary care, the 2023 consensus assigns follow-up to a multidisciplinary team and experienced clinicians, at least every three to six months when disease is controlled, with an examination and routine laboratory tests at every visit[9]. The community physician attends to vaccinations: inactivated vaccines and boosters are recommended in patients not receiving immunoglobulin replacement, while live vaccines are generally contraindicated during immunosuppressive treatment (level 5, grade D)[9]. A cardiologist or primary care physician who identifies a history of DADA2 does not independently start an antiplatelet agent, anticoagulant or antithrombotic: the consensus discourages them to prevent hemorrhagic stroke and does not propose routine use (expert opinion, level 5, grade D)[9]; an apparently compelling indication is discussed with the expert team following the patient. Acute stroke in a patient with confirmed or suspected disease is managed with neuroprotective measures, and anti-TNF treatment is considered to prevent recurrence (level 5, grade D)[9].

11.5 VEXAS syndrome

In the Treatise: § 12.5 and § 10.1

VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic), described in 2020, is an acquired autoinflammatory disease mainly affecting older men, caused by somatic mutations at codon p.Met41 of the X-linked UBA1 gene[11]. It is suspected in late-onset refractory inflammation with fever, chondritis, neutrophilic dermatosis, lung involvement or vasculitis, associated with macrocytic anemia, thrombocytopenia and bone marrow

dysplasia[11]. The 2024 EULAR/PReS recommendations call for consideration of VEXAS, together with clonal hematopoiesis, in adult-onset Still disease[12].

In the original series, all patients had markedly elevated acute-phase reactants and did not respond to disease-modifying treatments; bone marrow showed vacuoles restricted to myeloid and erythroid precursors[11]. The mutation was present in blood myeloid cells, including granulocytes and monocytes, and in bone marrow progenitors, but not lymphocytes or fibroblasts: testing is therefore performed on blood or bone marrow, and the somatic variant is mosaic[11]. Vacuoles are suggestive but not confirmatory; the somatic variant establishes the diagnosis.

The cardiovascular burden is primarily thrombotic. In a cohort of 119 patients, thrombosis occurred in 49% and venous thrombosis in 41%; almost two-thirds of venous thromboses were unprovoked, 41% recurred and 20% occurred during anticoagulation[13]. Cardiac and pulmonary inflammatory manifestations were associated with time to venous thrombosis, and the authors propose thromboprophylaxis in high-risk situations. In France, a VEXAS-specific PNDS has been hosted by the French National Authority for Health (HAS) since October 2026[14]; laboratory follow-up, allele fraction and bone marrow assessment are addressed by that protocol and the hematologist.

In primary care, the physician's first task is to suspect the disease: an unexplained autoinflammatory syndrome responsive to but dependent on corticosteroids, with elevated CRP and macrocytic anemia without vitamin B9 or B12 deficiency, with or without thrombocytopenia, in a man older than 50[14]. In an isolated first unprovoked thrombosis after age 50 without systemic inflammation, neutrophilic dermatosis, chondritis or macrocytic anemia, UBA1 mutation testing has a low yield[14]. Follow-up combines a reference or competence center with the primary care physician: every 1 to 3 months during active disease or treatment initiation and every six months during stable disease, with a CBC, CRP, creatinine, transaminases, gamma-glutamyl transferase and alkaline phosphatase and a review of vaccination status[14]. The primary care physician monitors the CBC and CRP, screens for infectious and thrombotic complications and coordinates follow-up with the hematologist and internist[14].

Table 11.1. The workup for periodic fevers and monogenic diseases, disease by disease

Disease	Confirmation	Laboratory follow-up	Pitfall
FMF	MEFV, interpreted at an expert center	CRP outside attacks, SAA if the markers diverge, creatinine and proteinuria at least annually; CBC, liver tests and CK during colchicine treatment	p.Glu148Gln nonpathogenic; CK particularly with reduced kidney function; colchicine: no macrolides or pristinamycin; P-gp- or CYP3A4-interacting drugs contraindicated by the PNDS in kidney or liver impairment (SmPC categories: see 11.1)
MKD	MVK; deletions if negative	CBC, CRP and SAA at least annually; liver and kidney tests and urine dipstick every 6 months; proteinuria every 6 months (EULAR/ACR 2021), urine protein-to-creatinine ratio at least annually (PNDS 2015)	IgD not recommended
TRAPS, CAPS	TNFRSF1A, NLRP3, by next-generation sequencing; deep sequencing for severe CAPS	Neutrophilia, CRP, ESR, SAA and S100 if available; proteinuria every 6 months	R121Q (formerly R92Q) nonpathogenic; somatic mutation possible in CAPS
Interferonopathies	Next-generation sequencing	CBC, transaminases, urine, autoantibodies; BK virus and kidney tests during JAK inhibitor treatment	Interferon signature may be negative
DADA2	ADA2 activity and ADA2 gene	CBC, ESR, CRP, liver and kidney tests every 3 to 6 months	Antithrombotics to be avoided
VEXAS	Somatic UBA1, blood or bone marrow	CBC, CRP, creatinine, liver tests; every 1 to 3 months if active, every 6 months if stable	Thrombosis despite anticoagulation

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12

Sarcoidosis, IgG4-related disease and Erdheim-Chester disease

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Three infiltrative diseases, three diagnoses that rest more on imaging and tissue than on blood. Laboratory testing investigates other organ involvement, prepares for and monitors treatment, and guards against false reassurance from a normal marker. Cardiac involvement occurs through granulomas, fibroinflammatory sheathing or histiocytic infiltration.

12.1 Sarcoidosis

In the Treatise: § 7.2, § 7.2.6.1 and § 11.5

According to the Treatise, cardiac sarcoidosis is suspected in unexplained high-grade atrioventricular block in a patient younger than 60, ventricular tachycardia or nonischemic cardiomyopathy. No blood test establishes the diagnosis. The 2024 American Heart Association (AHA) statement reproduces the 2016 Japanese criteria, in which elevated angiotensin-converting enzyme or serum lysozyme and elevated soluble interleukin-2 receptor are among five characteristic findings, alongside imaging and bronchoalveolar lavage[1]. It also notes that desmoplakin variant-related cardiomyopathy may mimic myocarditis, with elevated troponin and imaging resembling cardiac sarcoidosis[1].

The initial workup for any sarcoidosis follows the 2020 American Thoracic Society (ATS) guideline, whose recommendations all rest on very low-quality evidence[2]. It recommends baseline serum calcium in patients without signs of hypercalcemia (strong recommendation). It suggests creatinine in patients without known kidney involvement, alkaline phosphatase in those without known liver involvement and a CBC (conditional recommendations). It makes no recommendation for or against transaminase screening[2].

If evaluation of vitamin D metabolism is considered necessary, for example before supplementation, the ATS suggests measuring both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (conditional recommendation)[2]. This is not routine testing. During follow-up, the same guideline text considers annual creatinine common practice in patients without prior kidney involvement and proposes annual calcium and liver screening even if the initial workup was normal[2]. These schedules appear in a best-practice table rather than a graded recommendation.

Before treatment, the table in the 2024 AHA statement specifies the workup[1]. Before methotrexate (pretreatment workup: see 21.1), the statement calls for exclusion of tuberculosis, screening for hepatitis B and C and human immunodeficiency virus (HIV), a chest radiograph, a CBC and liver tests, creatinine monitoring and updated vaccinations. Before infliximab, adalimumab or rituximab, the same workup is supplemented with creatinine and left ventricular ejection fraction. Before azathioprine, the statement proposes considering thiopurine testing[1]; in practice, this means testing for thiopurine methyltransferase (TPMT), or possibly NUDT15, deficiency (see 21.3).

During methotrexate treatment, a CBC, liver tests and creatinine are checked every 2 to 4 weeks during the first three months, every 8 to 12 weeks from months three to six, then every 12 weeks; azathioprine follows the same schedule for the CBC and liver tests; during anti-tumor necrosis factor (anti-TNF) treatment, the CBC and liver tests are checked every 1 to 3 months, together with ejection fraction and signs of heart failure[1]. These table statements have neither a class nor an evidence level. The same table notes that infliximab and adalimumab can worsen preexisting heart failure and advises avoiding them in decompensated heart failure or severe left ventricular dysfunction: the pretreatment ejection fraction therefore informs prescribing[1].

In primary care, in patients without known kidney, liver or calcium abnormalities, outpatient follow-up includes annual calcium, creatinine and alkaline phosphatase: almost one in four patients develops new organ involvement within three years, often without symptoms[2]. The ATS suggests a baseline electrocardiogram in patients without cardiac findings (conditional recommendation). No subsequent cardiac investigation is routine, but chest pain, palpitations, presyncope or syncope, sustained bradycardia or tachycardia, dyspnea disproportionate to lung involvement or a newly abnormal tracing prompts investigation[2]. During methotrexate, azathioprine or anti-TNF treatment, community laboratory monitoring follows the AHA statement schedules; during anti-TNF treatment, signs of heart failure and ejection fraction are also monitored, and these drugs are avoided in decompensated heart failure or severe left ventricular dysfunction[1].

12.2 IgG4-related disease

In the Treatise: § 12.1

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is considered in aortitis, periaortitis, retroperitoneal fibrosis or coronary periarteritis. The 2025 French National Diagnostic and Care Protocol (PNDS) emphasizes that, unlike giant cell arteritis, Takayasu arteritis or infectious aortitis, IgG4-related aortitis is accompanied by little or no inflammatory marker elevation[3]. Pericoronary involvement is rare and severe, and is more common in younger patients. Aortitis with aneurysm or ischemic complications and coronary involvement are among urgent situations requiring prompt treatment[3].

No laboratory marker is specific[3]. Protein electrophoresis may show polyclonal hypergammaglobulinemia with beta-gamma bridging, but normal gamma globulins exclude nothing. The historical serum IgG4 threshold of 1.35 g/L is replaced by the upper limit of normal of the assay used. Sensitivity of an elevation is only 70%, and almost 30% of patients have normal concentrations, particularly in localized disease such as retroperitoneal fibrosis. Even above five times normal, positive predictive value is only 75%. The IgG4-to-immunoglobulin G (IgG) ratio performs no better[3]. In a review of 42 cases of IgG4-related coronary periarteritis, the ten cases with isolated coronary involvement had markedly lower IgG4 than those with other organs also involved (medians 2.61 and 13.55 g/L), as in other single-organ presentations[4].

IgG4 also increases in atopy, eosinophilic asthma, eosinophilic granulomatosis with polyangiitis, certain cancers and certain infections[3]. Reduced complement, including total hemolytic activity (CH_{50}), C_3 or C_4, occurs particularly in tubulointerstitial nephritis. Eosinophilia is found in almost 30% of patients; hypereosinophilia above 3×10^9/L (3,000/mm³) is an exclusion item in the 2019 ACR/EULAR (American College of Rheumatology and European League Against Rheumatism) classification criteria, but should not exclude the diagnosis in an individual patient[3].

The initial extent-of-disease workup includes at least a CBC, C-reactive protein (CRP), electrolytes, creatinine and creatinine clearance, liver tests, protein electrophoresis, IgG4, total immunoglobulin E (IgE) and complement C_3, C_4 and CH_{50}[3]. Suggested testing before each follow-up visit combines a CBC, electrolytes, creatinine, urine microscopy and culture, urine protein-to-creatinine ratio, liver tests, CRP and IgG4. C_3 and C_4 are monitored if low at diagnosis[3].

During anti-CD20 or anti-CD19 treatment, lymphocyte immunophenotyping is performed at six months and one year, or before each maintenance infusion, and quantitative immunoglobulins are measured, for example an-

nually; fasting glucose, glycated hemoglobin (HbA1c) and a lipid profile are monitored in pancreatic involvement or corticosteroid treatment[3]. The one-month workup does not require systematic reassessment of IgG4 or complement, which normalize later. A major pitfall: an isolated IgG4 increase without clinical, other laboratory or imaging progression is not an indication to restart or intensify treatment; it prompts closer monitoring[3].

In primary care, IgG4-RD progresses slowly and follow-up is usually outpatient[3]. Initial symptoms are often seen by the primary care physician; unexplained polyclonal hypergammaglobulinemia or complement consumption should raise suspicion[3]. The PNDS recommends clinical and laboratory reassessment one month after starting treatment, then every three to six months during the first year, every six months during the next two years, when relapse is most common, then annually in the absence of suggestive findings; each visit repeats the PNDS follow-up workup[3]. The following are considered urgent because they require prompt treatment: pancreaticobiliary involvement with jaundice, tubulointerstitial nephritis with kidney impairment, retroperitoneal fibrosis with urinary obstruction, symptomatic pachymeningitis, orbital involvement with optic nerve compression, aortitis with aneurysm or ischemic complications and coronary involvement[3].

12.3 Erdheim-Chester disease

In the Treatise: § 12.8

Erdheim-Chester disease is a rare histiocytosis recognized as a neoplasm since the discovery of recurrent activating mutations in the mitogen-activated protein kinase (MAP kinase) pathway; the 2020 consensus lists central diabetes insipidus, restrictive pericarditis, perirenal fibrosis and sclerotic bone lesions as typical findings and emphasizes that histologic diagnosis is often difficult[5]. The IgG4-RD PNDS lists it among the differential diagnoses of periaortitis[3].

No blood test confirms it. Biopsy and tissue genotyping require specialist assessment. In a prospective cohort of 60 patients, BRAF V600E was found in 51% of 57 biopsies, with other MAP kinase pathway abnormalities in a few patients; identifying them improves diagnosis and opens access to targeted treatment[6]. A biopsy without BRAF V600E therefore does not exclude disease: almost one in two biopsies lacked the mutation in this series.

The heart is involved in almost one in two patients. In a French single-center retrospective cohort of 200 patients assessed by cardiac magnetic resonance imaging, cardiac involvement occurred in 48%; it was associated with BRAF V600E, with cardiac involvement in 67% of mutation-positive patients versus 21% of mutation-negative patients (odds ratio 7.4), but not with reduced survival[7]. Significant atherosclerotic coronary disease was recorded in 23%. Tissue genotype therefore also helps guide cardiac assessment.

Plasma chromogranin A has been proposed as a marker of cardiovascular involvement: in two cohorts, it was higher than in controls, distinguished cardiovascular involvement and, in four patients followed over time, changed alongside pro-B-type natriuretic peptide (proBNP) during treatment[8]. This is exploratory work, without a threshold or recommendation.

In primary care, Erdheim-Chester disease is more readily suspected than proven, and both diagnosis and treatment require multidisciplinary collaboration[9]. The 2014 consensus calls for initial investigation of kidney impairment, cytopenias, inflammation and endocrinopathy (Grade C1): a CBC with differential, a comprehensive metabolic panel, erythrocyte sedimentation rate

(ESR), CRP, urine osmolality and morning cortisol, thyroid-stimulating hormone (TSH) and free thyroxine, prolactin, testosterone in men, luteinizing and follicle-stimulating hormones, vitamin B12 and thiamine[9]. No serum biomarker is specific; CRP, elevated in 80% of patients at diagnosis, may help monitor treatment (Grade D1)[9]. A change in kidney function prompts earlier imaging of the affected organ (Grade C2)[9].

Table 12.1. The workup for sarcoidosis, IgG4-RD and Erdheim-Chester disease, tier by tier

Disease	Essential	Depending on the context	Specialist assessment
Sarcoidosis	Calcium; creatinine, alkaline phosphatase, CBC (conditional)	25-hydroxyvitamin D and 1,25-dihydroxyvitamin D before supplementation if assessment is needed; workup before immunosuppressive treatment	TPMT, or possibly NUDT15, before azathioprine
IgG4-RD	CBC, CRP, electrolytes, creatinine, liver tests, electrophoresis, IgG4, IgE, C3, C4, CH50	B-cell immunophenotyping and immunoglobulins during anti-CD20 treatment; glucose, HbA1c, lipids	—
Erdheim-Chester disease	Initial workup: CBC, creatinine, CRP, ESR, endocrine assessment (2014 consensus)	Chromogranin A (exploratory)	Biopsy, BRAF V600E and MAP kinase pathway

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13

AL, ATTR and AA amyloidosis and Fabry disease

Chapter contents

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In infiltrative heart disease, laboratory testing determines the sequence of investigations: investigate a clone first, then interpret the image. Immunoglobulin light chain (AL) amyloidosis mistaken for transthyretin (ATTR) amyloidosis goes without urgent hematologic treatment. Fabry disease, a nonimmune storage cardiomyopathy, is also confirmed by laboratory testing, both enzymatic and genetic.

13.1 AL amyloidosis

In the Treatise: § 7.3.2, § 7.3.6 and § 7.3.7

Cardiac amyloidosis is suspected in the presence of red flags classified as clinical, electrocardiographic, echocardiographic and laboratory findings by the 2021 European Society of Cardiology (ESC) position statement. Laboratory red flags include even modest proteinuria, kidney impairment, N-terminal pro-B-type natriuretic peptide (NT-proBNP) disproportionate to the degree of heart failure and persistently elevated troponin[1]. For cardiac AL amyloidosis, the 2022 ESC cardio-oncology guideline specifies that NT-proBNP disproportionate to ventricular function is generally above 300 pg/mL in the absence of kidney impairment or atrial fibrillation (ungraded statement)[2]. Any suspicion of cardiac amyloidosis requires investigation for a monoclonal protein before any conclusion.

The essential workup combines three tests: serum protein electrophoresis with immunofixation, urine protein electrophoresis with immunofixation and serum free light chain (sFLC) measurement with the kappa-to-lambda ratio. Their combination achieves 99% sensitivity for the AL amyloidosis precursor[1]. The 2026 American Society of Hematology (ASH) guideline recommends the same trio whenever cardiac amyloidosis is suspected (strong recommendation, moderate certainty)[3]. The 2026 ESC heart failure guideline recommends an initial workup combining serum and urine immunofixation, sFLC and bone scintigraphy in heart failure with suspected amyloidosis (Class I, Level B)[4]. Electrophoresis is always performed with immunofixation; electrophoresis alone is insufficient. The normal ratio is 0.26 to 1.65 with the Freelite assay and 0.53 to 1.51 with the N Latex assay[1].

Kidney impairment complicates interpretation. With the Freelite assay and negative immunofixations, a ratio up to 2.0 for an estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73 m² or lower, or 3.1 in dialysis, can usually be considered normal; this adjustment does not apply to N Latex, and higher values require hematology advice[1]. The 2023 French National Diagnostic and Care Protocol (PNDS) for AL amyloidosis specifies that Freelite, N Latex and Sebia assays are not interchangeable, follow-up should use the same assay and preferably the same laboratory, and urinary free light chain measurement has no practical value[5].

Evidence is histologic and typing is essential: direct immunofluorescence or immunohistochemistry with at least anti-kappa, anti-lambda, anti-serum amyloid A protein and anti-transthyretin antibodies, and proteomics by mass spectrometry in difficult cases[5]. A monoclonal abnormality does not prove AL amyloidosis: ATTR amyloidosis with monoclonal gammopathy of undetermined significance, AL amyloidosis or a combination is possible, and histology with typing resolves the question[1]. This is not rare: in the cohort establishing noninvasive diagnosis of cardiac ATTR amyloidosis, 19% of patients with this amyloidosis, whose median age was 75, had a detectable monoclonal protein, a proportion the authors partly attributed to referral bias; 99% of AL amyloidosis cases had one[6]. If hereditary amyloidosis is suspected and typing does

not confirm AL, the PNDS calls for testing for mutations in fibrinogen Aα, transthyretin, lysozyme, apolipoproteins A1, A2, C2 and C3 and gelsolin[5].

According to the PNDS, assessment of confirmed AL amyloidosis characterizes the clone: sFLC, electrophoresis with immunofixation, bone marrow aspiration with or without biopsy and immunophenotyping, bone marrow cytogenetics including at least t(11;14), 1q gain, del(17p) and t(4;14); blood immunophenotyping for a B-cell clone, and MYD88 and TP53 mutations for a lymphoplasmacytic clone[5]. It assesses organ involvement: troponin and B-type natriuretic peptide (BNP) or NT-proBNP, a CBC with platelets and blood smear, creatinine, total protein, albumin, electrolytes, 24-hour urine protein and urine protein-to-creatinine ratio, liver tests, prothrombin time and activated partial thromboplastin time, fibrinogen as appropriate, factor X, ferritin for occult gastrointestinal bleeding, thyroid-stimulating hormone (TSH), lactate dehydrogenase (LDH) and uric acid[5].

Cardiac prognosis is staged using the European modification of the Mayo Clinic classification: stage I if NT-proBNP and high-sensitivity troponin are normal, stage II if either is elevated, stage III if both are elevated, with NT-proBNP above 332 pg/mL and troponin above its threshold, IIIA while NT-proBNP remains below 8,500 pg/mL and IIIB above that value[5]. The troponin threshold depends on the assay: the PNDS text uses 50 ng/L for high-sensitivity troponin, while its appendix uses 0.035 µg/L for conventional troponin T and 0.070 µg/L, or 70 ng/L, for high-sensitivity troponin T[5]. Hematologic response is assessed using the monoclonal light chain and the difference between involved and uninvolved light chains (dFLC), measured at least every cycle and weekly in stage IIIB; complete response requires negative serum and urine immunofixations[5]. In cardiac involvement, sFLC, NT-proBNP and troponin are measured monthly, and sFLC are monitored long term even after complete response[7].

In primary care, monoclonal gammopathy of undetermined significance is common in older people and often inconsequential; nevertheless, it should raise consideration of AL amyloidosis[5]. In every patient with monoclonal gammopathy, the PNDS emphasizes the value of creatinine and proteinuria, calls for routine albuminuria screening and notes that routine NT-proBNP has been proposed when sFLC are elevated[5]. The 2026 British Society for Haematology guideline goes further: urine protein-to-creatinine and albumin-to-creatinine ratios and NT-proBNP are added to the standard workup for every monoclonal gammopathy of undetermined significance at diagnosis and every reassessment (Grade 1A), with troponin considered if NT-proBNP is abnormal[8]. Unexplained NT-proBNP above 332 pg/mL, or a rising value, strongly suggests cardiac amyloidosis, while accounting for atrial fibrillation, kidney impairment or advanced age, which also raise it; falling albumin or rising alkaline phosphatase is investigated if persistent (Grade 1A). A pitfall: AL amyloidosis may occur with a minimal or even absent increase in clonal light chains (Grade 1A)[8]. In unexplained proteinuria, ASH suggests the same trio as in cardiac disease (conditional recommendation, low certainty)[3]. Excess monoclonal light chains, proteinuria, elevated NT-proBNP or a suggestive finding such as thickened walls with low voltage or periorbital bruising warrants referral without delay: prognosis is much better if treatment precedes symptomatic cardiac involvement or severe kidney impairment[5]. After treatment, sFLC monitoring continues indefinitely, generally every three months, with the same assay[5].

13.2 Transthyretin amyloidosis

In the Treatise: § 7.3.3, § 7.3.6 and § 7.3.7

According to the Treatise, wild-type or hereditary ATTR amyloidosis is considered in older patients with heart failure with preserved ejection fraction and thickened walls, bilateral carpal tunnel syndrome or low-flow aortic stenosis. Diagnosis without biopsy requires three conditions: a typical echocardiographic or magnetic resonance appearance, grade 2 or 3 myocardial uptake on bone scintigraphy with tomography and exclusion of a clonal dyscrasia by all three laboratory tests[1].

If any of these tests is abnormal, scintigraphy should not be used to establish ATTR diagnosis[1]. If scintigraphy shows uptake and a clonal test is abnormal, histology with typing is required, usually by endomyocardial biopsy. If scintigraphy shows no uptake and the clonal workup is negative, amyloidosis is unlikely, but persistent suspicion warrants magnetic resonance imaging followed by biopsy because some hereditary variants do not take up the tracer. Grade 1 uptake does not allow noninvasive diagnosis[1]. The AL amyloidosis PNDS notes that strongly positive scintigraphy favors ATTR without entirely excluding AL[5].

Once cardiac ATTR is confirmed, transthyretin (TTR) genetic counseling and testing are recommended to distinguish wild-type from hereditary disease, including in older patients[1]. Relatives are tested with genetic counseling. The 2021 position statement discourages testing minors; the 2021 cardiac amyloidosis PNDS reserves genetic counseling for adults, often between 40 and 50 years old and at least ten years before the age at onset of the youngest affected family member, with specific rules for certain variants[1,7].

In asymptomatic carriers, the initial cardiac assessment includes a complete laboratory workup with NT-proBNP and troponin; elevated troponin may be the first laboratory sign of infiltration[7]. Carriers are reassessed every two to three years before the predicted age of symptom onset, then annually. Patients with cardiac ATTR are followed at least every six months with cardiac biomarkers[7]; the ESC position statement describes the same schedule as a common approach while acknowledging that no study has established optimal follow-up[1].

Prognosis is staged using the National Amyloidosis Centre score, based on NT-proBNP above 3,000 pg/mL and eGFR below 45 mL/min/1.73 m²; the Mayo Clinic score specific to wild-type disease uses troponin T above 50 ng/L (0.05 ng/mL) and NT-proBNP above 3,000 pg/mL[1]. During follow-up, an NT-proBNP increase of more than 30% or more than 700 pg/mL indicates progression and is independently associated with mortality; a relative 30% increase in high-sensitivity troponin also indicates progression, and the prognostic value of troponin, well established in wild-type disease, remains to be demonstrated in hereditary disease[9]. A pitfall: kidney impairment also raises NT-proBNP[8]; the National Amyloidosis Centre score combines both parameters.

In primary care, the primary care physician and treating cardiologist follow the patient with the reference center; cardiac ATTR is reviewed at least every six months in specialist care with cardiac biomarkers, with annual echocardiography and Holter monitoring[7]. Between specialist visits, the physician watches for breathlessness, weight gain, edema, fatigue, arrhythmias, malnutrition and gastrointestinal symptoms and contacts the reference center for any acute amyloidosis-related problem[7]. In asymptomatic carriers of a transthyretin variant, unexplained weight loss, malnutrition, gastrointestinal

symptoms, carpal tunnel syndrome or lumbar spinal stenosis prompts referral to the reference center as soon as possible; the primary care physician also informs the family of the value of voluntary genetic counseling[7]. Positive scintigraphy is never interpreted without the complete clonal workup[1].

13.3 AA amyloidosis

In the Treatise: § 7.3.4

AA amyloidosis, involving amyloid A protein, complicates inadequately controlled chronic inflammatory diseases; its precursor is serum amyloid A protein (SAA). In the UK national center cohort of 374 patients, kidney involvement predominated: 97% had proteinuria above 500 mg daily or creatinine above 133 µmol/L, or both, at diagnosis[10]. Heart failure attributable to amyloidosis occurred in only one patient, and signs of cardiac infiltration in two of 224 assessed by echocardiography.

Diagnosis is tissue-based: elevated SAA does not prove amyloidosis, and deposit typing, with the PNDS panel including anti-SAA antibody, confirms the AA type[5]. As the kidney is the most affected organ, creatinine and proteinuria are used to assess and monitor its course[10]. In the same cohort, alkaline phosphatase above 1.5 times the upper limit of normal also occurred in patients without liver deposits; this elevation may reflect inflammation itself.

Serial SAA is the marker of control and prognosis. In this cohort, samples were scheduled monthly. Mortality risk was almost 18 times lower with SAA below 4 mg/L than with SAA of at least 155 mg/L, and SAA of 4 to 9 mg/L, often considered normal, already increased that risk fourfold[10]. Deposits regressed with a median SAA of 7 mg/L and progressed with a median of 54 mg/L. These are cohort associations, not diagnostic thresholds or validated targets for every patient. For familial Mediterranean fever, see 11.1.

In primary care, in familial Mediterranean fever (FMF), creatinine and proteinuria, initially by dipstick and then by urine protein-to-creatinine ratio, are checked at least annually[11]; in interleukin-1-mediated autoinflammatory diseases, the 2021 European Alliance of Associations for Rheumatology and American College of Rheumatology (EULAR/ACR) points to consider call for proteinuria testing every six months, particularly with a family history of amyloidosis[12]. Persistent proteinuria or unexplained kidney impairment calls for histologic evidence, initially from minor salivary glands, abdominal fat or gastrointestinal mucosa, with the kidney as second-line sampling[11]. Once amyloidosis is confirmed, the FMF PNDS calls for checking at least once that C-reactive protein (CRP) and SAA are both normal, as SAA may remain elevated despite low CRP[11].

13.4 Fabry disease

In the Treatise: § 7.4.1 and § 13.8.12

Fabry disease, an X-linked alpha-galactosidase A deficiency, is considered in unexplained left ventricular hypertrophy, particularly in a young man or a female relative, with acroparesthesias, angiokeratomas, cornea verticillata, proteinuria or hearing loss, according to the Treatise. Confirmation is performed in a specialized laboratory[13]. In men and boys, diagnosis initially rests on deficient alpha-galactosidase A activity in leukocytes or a dried blood spot: undetectable activity or below 3% in classic disease and residual activity of 1 to 20% in later-onset disease, particularly the cardiac form. Assay yield depends on the referral setting: among men referred for hypertrophic cardiomyopathy,

low plasma alpha-galactosidase A activity was found in 5 of 79 men (6.3%) diagnosed at age 40 or older versus 1 of 74 (1.4%) before age 40; all carried a gene mutation[14].

GLA gene analysis is essential for confirmation in men and women; it helps characterize the disease, conduct family investigation and assess amenability to chaperone treatment[13]. It must include testing for large deletions and copy number variations, which Sanger sequencing does not detect[15]. Variant pathogenicity is interpreted by a laboratory or reference center. The 2021 PNDS considers the variants p.Arg118Cys, p.Ala143Thr and p.Asp313Tyr benign: they do not confirm the diagnosis, and the PNDS notes that the list of nonpathogenic variants may change as knowledge advances[13]. A variant of uncertain significance is discussed in a multidisciplinary meeting with the reference center[13].

In women, diagnosis rests on GLA sequencing: enzyme activity may be normal because of preferential inactivation of the X chromosome carrying the variant[13]. An initial plasma globotriaosylsphingosine (lyso-Gb3) measurement is recommended to characterize disease and help interpret the variant, but may be normal in some heterozygous women. Children in known affected families may benefit from early screening if their families request it[13].

According to the PNDS, the initial workup and follow-up, at least annually in men and every two years in women, include creatinine, eGFR, urine albumin-to-creatinine and protein-to-creatinine ratios, electrolytes, troponin, NT-proBNP or BNP and plasma lyso-Gb3[13]. Fasting glucose and a lipid profile are part of the initial workup and are repeated only as needed; a CBC and calcium and phosphate tests belong to the initial workup. Kidney and cardiac monitoring becomes more frequent in advanced visceral involvement.

During enzyme replacement therapy, annual anti-agalsidase antibody measurement is desirable, more frequently with hypersensitivity reactions, with investigation of antibody type and neutralizing activity[13]. Cardiac assessment in adult men, including troponin, is annual from age 20 to 25 in classic disease and 30 to 35 in later-onset disease; in women, it is annual or every two years from age 25, or 35 to 40 for a late-onset variant[13].

In primary care, the primary care physician may play a decisive role by suspecting disease and referring to a reference or competence center, where enzyme testing and genotyping are performed[13]. A family history of death before 50, strokes, rhythm or conduction disorders, kidney impairment or dialysis should raise suspicion. The primary care physician contributes to screening and local follow-up, particularly monitoring specific treatment, and alerts the reference team to deterioration, complications or adverse effects[13]. Center assessments are annual in hemizygous men and every two years in heterozygous women; during enzyme replacement therapy, hospital visits occur every two weeks for the first three to four months, then annually; during chaperone treatment, every three to six months during the first year, then annually[13].

Table 13.1. The workup for amyloidosis and Fabry disease, tier by tier

Situation	Essential	Depending on the context	Specialist assessment
Monoclonal gammopathy followed in primary care	Creatinine, urine protein-to-creatinine and albumin-to-creatinine ratios, NT-proBNP, at diagnosis and every reassessment	Troponin if NT-proBNP is abnormal	Hematology assessment for excess light chains, proteinuria or elevated NT-proBNP
Suspected cardiac amyloidosis	Serum and urine immunofixation, sFLC and ratio	eGFR to interpret the ratio	Biopsy and typing
Confirmed AL	sFLC, dFLC, troponin, NT-proBNP, kidney and liver tests, coagulation testing including factor X	Ferritin, TSH, LDH, uric acid	Bone marrow aspiration, cytogenetics, MYD88
Confirmed ATTR	TTR genetic testing; NT-proBNP, troponin, eGFR	Assessment of relatives carrying a variant	Family genetic counseling
AA	Creatinine, proteinuria, serial SAA	—	Deposit typing
Fabry	Enzyme activity in men; GLA for confirmation in men and women, including large deletions; kidney tests, troponin, natriuretic peptide, lyso-Gb3, annually in men and every two years in women	Glucose and lipids during follow-up	Variant interpretation; anti-agalsidase antibodies

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14

Hypereosinophilic syndromes and Löffler syndrome

Chapter contents

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Persistent hypereosinophilia is first approached as an etiologic puzzle, and cardiac involvement is investigated at the outset, even without symptoms. The workup follows a sequential logic: drug-related and parasitic causes first, a common core workup next, and clonal and lymphocytic investigations only when supported by findings. In an organ-threatening emergency, treatment never waits for the workup.

14.1 Persistent hypereosinophilia: the etiologic workup

In the Treatise: § 6.3.1 and § 9.4.2

The 2023 French guidelines define hypereosinophilia (HE) as eosinophils above 1.5 × 10^9/L on two occasions one month apart and/or tissue eosinophilia; between 0.5 and 1.5 × 10^9/L, the term is eosinophilia[1]. Hypereosinophilic syndrome (HES) is diagnosed whenever HE causes organ involvement, whatever the mechanism, including parasitic infection. In severe involvement requiring urgent treatment, the one-month interval is no longer required[1].

The first step investigates a causative drug and infection. Human immunodeficiency virus (HIV) serology is performed routinely; human T-lymphotropic virus type 1 (HTLV-1) serology is proposed for patients from or with a history of travel to endemic areas, including Japan, the Caribbean and sub-Saharan Africa[1]. After tropical travel, even in the distant past, strongyloidiasis, filariasis and schistosomiasis are considered first, with infectious disease advice[1].

For unexplained persistent HE above 1.5 × 10^9/L, the core workup includes a CBC, electrolytes and creatinine, a complete liver panel, lactate dehydrogenase (LDH) and creatine kinase (CK), calcium and phosphate, troponin and B-type natriuretic peptide (BNP), serum protein electrophoresis, serum tryptase, vitamin B12, total immunoglobulin E (IgE), C-reactive protein (CRP), HIV serology, toxocariasis serology and stool examination for parasites, using the Baermann method if strongyloidiasis is suspected[1]. Other parasite serology and HTLV-1 testing are requested according to the setting. CT of the chest, abdomen and pelvis is added; an electrocardiogram and echocardiography complete the core workup as soon as HE persists without a cause[1]. Regardless of cause, cardiac involvement is investigated at the outset, even without symptoms (see 14.3)[1]; troponin belongs to the core workup without requiring suspicion of cardiac disease.

Each result guides investigation without settling the diagnosis. Elevated CRP suggests a solid tumor, lymphoma, vasculitis or certain HES complications, including myocarditis and thrombosis; the principal HES forms, FIP1L1::PDGFRA-associated clonal HES and lymphocytic HES, do not raise CRP outside these complications[1]. Elevated tryptase suggests mastocytosis or clonal disease; combined elevation of vitamin B12 and tryptase suggests clonal eosinophilia. Polyclonal hypergammaglobulinemia suggests immunoglobulin G4 (IgG4)-related disease, angioimmunoblastic T-cell lymphoma or chronic parasitic infection; elevated IgE, of limited specificity, suggests a reactive cause[1].

Antineutrophil cytoplasmic antibodies (ANCA) are tested for in inflammatory or joint manifestations suggesting vasculitis[1]. In eosinophilic granulomatosis with polyangiitis, they are present in only approximately 30% of patients, and asthma does not distinguish this vasculitis from HES: a negative ANCA result does not resolve the question[1]. T-cell phenotyping, T-cell clonality and FIP1L1::PDGFRA testing are not first-line investigations[1].

In primary care, the French guidelines are intended to guide primary care physicians and nonspecialists from the initial workup through follow-up[1].

First-line core tests are requested from the laboratory, together with CT of the chest, abdomen and pelvis; toxocariasis serology is performed in every patient above 1.5 × 10^9/L, whether symptomatic or not[1]. A very high eosinophil count, above 10 × 10^9/L for example, does not by itself require emergency treatment in the absence of clinical manifestations. Conversely, any organ-threatening involvement is urgent: myocarditis, intracardiac thrombus with embolism, coronary spasm, acute heart failure, severe acute asthma, hypoxemic lung involvement, cerebral infarcts or arterial or venous thrombosis[1]. Etiologic investigation is also urgent but never delays treatment.

14.2 Clonal and lymphocytic forms

In the Treatise: § 6.3.1

Clonal disease is suggested by hepatomegaly, splenomegaly, cytopenia, thrombocytosis, erythrocytosis, monocytosis, basophilia, elevated vitamin B12 or tryptase, or failure of eosinophils to normalize with corticosteroids[1]. Endomyocardial fibrosis, bilateral watershed cerebral infarcts, lymphomatoid papulosis and mucosal ulcerations strongly suggest FIP1L1::PDGFRA-associated chronic eosinophilic leukemia, which has a marked male predominance. Their presence requires comprehensive but sequential clonal investigation[1].

The first test detects the FIP1L1::PDGFRA transcript in blood using nested reverse-transcription polymerase chain reaction (RT-PCR) or quantitative real-time PCR, which are more sensitive than fluorescence in situ hybridization (FISH); FISH remains useful in rare atypical translocations in which PCR is falsely negative[1]. Erythrocytosis or thrombocytosis prompts blood testing for JAK2 V617F, CALR and MPL mutations; neutrophilia or basophilia prompts BCR::ABL1 transcript testing[1].

If blood molecular testing is negative, bone marrow aspiration with karyotyping and FISH for PDGFRA, PDGFRB, FGFR1 or ABL1 rearrangements is recommended[1]. Elevated tryptase with negative FIP1L1::PDGFRA prompts investigation for the KIT D816V mutation in bone marrow and abnormal mast cells; however, elevated tryptase may accompany FIP1L1::PDGFRA-positive disease. A next-generation sequencing panel may be considered when clonal suspicion is high; mutations associated with myeloid neoplasms have been reported in up to 30% of unexplained HE, but their prognostic impact in HES is not established[1]. Without clonal findings, bone marrow aspiration and core biopsy are not mandatory.

The lymphocytic form is screened for by flow cytometry, ideally by an experienced operator. The abnormal populations considered are CD3− CD4+ lymphocytes above 0.5% of lymphocytes, CD3+ CD4+ CD7− above 6 to 8% before age 60 and 10% thereafter, or double-negative T cells bearing the αβ T-cell receptor (TCRαβ+) above 1.5%[1]. T-cell clonality testing may lack sensitivity if the population is below 10% of lymphocytes; on its own, without an abnormal phenotype, it is insufficient for diagnosis[1].

Follow-up of controlled HES generally includes two specialist visits per year and a CBC every three months, more often if needed[1]. After starting imatinib in FIP1L1::PDGFRA-positive disease, the CBC is checked weekly until normalization, then every three months with electrolytes and liver tests; the transcript is checked three months after initiation, then every six months for two years, then annually[1]. After discontinuation, molecular monitoring is every three months during the first year, then every six months, even without HE. These schedules apply to this form, not all HE.

In primary care, the FIP1L1::PDGFRA transcript is not requested as a first-line test: without findings suggesting chronic eosinophilic leukemia, fewer than 2% of almost 6,700 requests sent to three university hospitals were positive, according to the authors' unpublished data, and testing should be restricted[1]. Follow-up is coordinated by a hospital physician; while the CBC remains controlled, invasive or expensive tests are not repeated[1]. Imatinib toxicity is mainly hepatic, muscular and hematologic; during hydroxyurea treatment, clinical and laboratory monitoring may be every two weeks for two months, monthly for three months, then every three months[1].

14.3 The heart: eosinophilic myocarditis and Löffler endocarditis

In the Treatise: § 6.3.1, § 13.8.5 and § 9.4.2

Severe cardiac involvement determines prognosis alongside clonal forms: the French guidelines consider only these two situations truly threatening[1]. Cardiac involvement may initially be asymptomatic and can lead to embolism or endomyocardial fibrosis; it should therefore be investigated routinely and promptly, including in children[1]. The Treatise describes the spectrum of lesions, from acute necrotizing myocarditis to Löffler fibroplastic mural endocarditis, then restrictive endomyocardial fibrosis with intracardiac thrombus.

In untreated patients or those with a partial response whose HE exceeds 1.5×10^9/L, troponin, BNP and echocardiography are repeated even without symptoms: at short intervals during the first months, then less often, for example annually[1]. In FIP1L1::PDGFRA-positive disease, cardiac and brain magnetic resonance imaging is proposed at the outset, even with normal troponin, BNP and echocardiography[1]. In specific cardiac involvement, troponin is measured 48 hours after starting imatinib because of a theoretical risk of early worsening through eosinophil lysis; measurement is performed in hospital if heart disease is severe, and an increase prompts a short corticosteroid course, for example 1 mg/kg/day for 5 to 7 days[1].

Markers do not settle the diagnosis. Blood eosinophilia, present in the great majority of patients with eosinophilic myocarditis, may be absent initially and never develop in some[2]; the 2025 European Society of Cardiology (ESC) guideline specifies that it is absent in up to 25%, contributing to underdiagnosis[3]. CRP, erythrocyte sedimentation rate, CK and troponin are often elevated, but normal results do not exclude myocarditis and these markers are nonspecific, as are natriuretic peptides[2]. According to ESC 2025, diagnosis rests on endomyocardial biopsy or magnetic resonance-proven myocarditis with characteristic findings combined with blood eosinophilia; causes, including hypersensitivity, eosinophilic granulomatosis with polyangiitis, HES, parasitic infections and cancers, are investigated routinely[3]. In focal disease, a negative biopsy may reflect sampling error and should be repeated when suspicion is high[2].

In an emergency, including myocarditis, respiratory distress, neurologic involvement or thrombosis, corticosteroids are the initial treatment regardless of cause, except severe strongyloidiasis, and must never await the etiologic workup[1]. Unless contraindicated, preemptive ivermectin is recommended to prevent severe strongyloidiasis during corticosteroid treatment; *Strongyloides* testing does not delay treatment. The Treatise also recalls the drug hypersensitivity form, whose first treatment is withdrawal of the drug.

In primary care, troponin and BNP are part of the initial workup for any unexplained HE, and repeat testing in uncontrolled disease, together with

echocardiography, follows the French guideline schedule[1]. Eosinophilic myocarditis often has a fulminant presentation with an abrupt fall in ejection fraction, a high risk of malignant arrhythmias and thromboembolic complications related to ventricular thrombi[3]: its signs, like those of coronary spasm or acute heart failure, require emergency care, and treatment does not await the etiologic workup[1]. In reactive disease, management includes treatment of the underlying disease or withdrawal of the causative drug[1]; ESC 2025 places hypersensitivity and allergic reactions first among the causes to investigate in eosinophilic myocarditis[3].

Table 14.1. The hypereosinophilia workup, tier by tier

Situation	Essential	Depending on the context	Specialist assessment
Unexplained persistent HE > 1.5 × 10^9/L	CBC, electrolytes, creatinine, liver tests, LDH, CK, calcium, phosphate, troponin, BNP, electrophoresis, tryptase, B12, IgE, CRP, HIV, *Toxocara*, stool; ECG, echocardiography	HTLV-1 and other serology according to exposure; ANCA if vasculitis is suspected	—
Clonal findings	—	—	Blood FIP1L1::PDGFRA; JAK2, CALR, MPL; BCR::ABL1; bone marrow aspiration, karyotype, FISH; KIT D816V; next-generation sequencing panel
Suspected lymphocytic form	—	—	T-cell phenotyping, T-cell clonality
Follow-up	CBC every three months if controlled; repeated troponin, BNP and echocardiography if HE is uncontrolled	FIP1L1::PDGFRA transcript during imatinib treatment	—

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PART IV

Cardiac Involvement

15

The etiologic workup of myocarditis, including hypersensitivity and DRESS

Chapter contents

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In myocarditis, laboratory testing does not establish the diagnosis: it measures injury, inflammation and their consequences, then points toward a cause. Imaging and, in severe forms, endomyocardial biopsy are decisive. The workup therefore has two stages: a core assessment for every patient and targeted tests justified by a specific hypothesis.

15.1 The core assessment in suspected myocarditis

In the Treatise: § 6.2.8, § 5.1.1 and § 20.6

The 2025 European guideline brings myocarditis and pericarditis together under the term inflammatory myopericardial syndrome (IMPS). For every patient with suspected disease, it recommends a comprehensive clinical evaluation including the history, examination, chest radiograph, electrocardiogram (ECG), echocardiography and laboratory markers (Class I, Level C)[1]. These markers are high-sensitivity (hs) troponin, C-reactive protein (CRP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP)[1]. History taking is as much a part of the workup as laboratory testing: recent viral infection, toxic exposures, medications, a family history of cardiomyopathy or sudden death, and known inflammatory or autoimmune disease[1].

The basic laboratory workup, detailed in the same document, includes markers of myocardial injury (high-sensitivity troponin T or I), systemic inflammation (CRP, erythrocyte sedimentation rate and white blood cells) and heart failure (NT-proBNP)[1]. It also includes a complete blood count with an eosinophil count, renal function and electrolytes (sodium, potassium and creatinine), thyroid function (thyroid-stimulating hormone, TSH) and liver tests (lactate dehydrogenase, aspartate and alanine aminotransferases)[1]. The eosinophil count is no minor detail: on its own, it opens an entire branch of the etiologic workup (see 15.3).

Each marker has its own scope. CRP is elevated in up to 80% of acute myocarditis cases, but a normal result does not exclude the diagnosis[1]. Troponin most often reflects cardiomyocyte necrosis; its initial level helps assess severity. Natriuretic peptide should be measured on admission and may be repeated at discharge and during outpatient follow-up to estimate the risk of events[1]. None of these markers is specific: they indicate injury and inflammation, not their cause.

What the workup should not contain is stated just as clearly. Routine viral serology is not recommended to investigate a viral cause (Class III, Level C), with exceptions for hepatitis C, human immunodeficiency virus (HIV) and Lyme disease[1]. The guideline extends the exception to suspected bacterial infections (*Borrelia*, rickettsiae) and *Trypanosoma cruzi*[1]. Positive viral serology does not prove myocardial infection[1]. When the clinical context suggests an acute coronary syndrome, coronary angiography or coronary CT angiography precedes the conclusion (Class I, Level C)[1].

In primary care, the guideline provides a specific algorithm for patients seen in the outpatient setting. The first-line assessment is the same as in the hospital, with laboratory testing that includes troponin, NT-proBNP, CRP and a differential white blood cell count (Class I)[1]. An elevated troponin prompts hospital referral[1]. Hospitalization is recommended for intermediate- or high-risk myocarditis (Class I, Level C); high-risk features include acute heart failure or shock, cardiac arrest or syncope, sustained ventricular arrhythmia, high-grade atrioventricular block, a newly reduced ejection fraction below 40% and extensive late gadolinium enhancement on magnetic resonance imaging[1]. After discharge, follow-up combines clinical examination and ECG, with tro-

ponin and CRP within the first month and again at 3 to 6 months; repetition at 12 months and beyond is decided case by case[1]. In uncomplicated cases, follow-up at 6, 12 and 24 months is sufficient[1].

15.2 Identifying a cause: systemic disease, infection and genetics

In the Treatise: § 6.3, § 6.3.3 and § 13.8

The search for systemic disease starts with the history and examination. The 2025 guideline lists features that should raise suspicion of an autoimmune rheumatic disease: family history, prolonged low-grade fever, joint symptoms, dry eyes and mouth, headache, lymphadenopathy, Raynaud phenomenon, rash, oral and genital ulcers, venous thrombosis, recurrent pregnancy loss, lymphopenia and chronically elevated creatine kinase (CK) and other inflammatory markers[1]. This combination of findings, rather than a routine panel, prompts testing for autoantibodies associated with the suspected disease (see Chapters 5 to 9). Immune checkpoint inhibitor myocarditis has its own workup (see Chapter 19).

A few associations deserve attention because they guide testing. In lupus, the diagnosis of myocardial involvement relies on disease-specific laboratory markers and imaging[1]. Antiphospholipid syndrome is identified by anticardiolipin antibodies, anti-β2-glycoprotein I antibodies and lupus anticoagulant, and myocardial involvement may be microthrombotic rather than inflammatory[1]. In Sjögren syndrome, anti-Ro/SSA antibodies (Sjögren syndrome antigen A) may be found in unexplained heart block[1]. In eosinophilic granulomatosis with polyangiitis, cardiac involvement predominantly affects patients without antineutrophil cytoplasmic antibodies (ANCA) and with marked eosinophilia[1].

Infectious testing remains targeted. Apart from HIV and hepatitis C, serology is ordered only in the presence of an exposure or a suggestive presentation: Lyme carditis (see Chapter 18) or Chagas disease in a person exposed in an endemic area[1]. In chronic Chagas disease, the guideline favors combining two serologic tests using different antigens; polymerase chain reaction (PCR) is the most sensitive test for acute infection[1]. Useful viral testing is performed on tissue: PCR on endomyocardial biopsy, paired with blood PCR to rule out contamination, with a threshold of more than 500 copies per microgram of DNA used for virus-related inflammation[1].

All matters involving histology and research markers require specialist assessment. Endomyocardial biopsy is recommended in high-risk myocarditis, in hemodynamic instability or in intermediate-risk myocarditis that does not respond to treatment, to determine the histologic type and look for a viral genome (Class I, Level C)[1]. It is assessed on three levels. Histology and immunohistology each require at least three samples; a threshold of at least 14 leukocytes per mm^2, including at least 7 CD3+ T lymphocytes, has been used to define myocarditis, although cardiac pathologists now debate it[1]. Molecular testing uses quantitative PCR primarily to detect enteroviruses, parvovirus B19, human herpesvirus 6 (HHV-6) and Epstein-Barr virus (EBV), as well as *Borrelia* and *Trypanosoma cruzi*, in an accredited laboratory[1]. This, rather than serology, identifies the virus: viral serology agrees with myocardial PCR in only about 4% of patients[1]. Anti-heart autoantibodies, either organ-specific or directed against intercalated disks, may help in selected cases depending on local availability; high titers may carry an adverse prognosis[1]. Tumor necrosis

factor alpha and interleukins 1β, 6 and 17A may be informative in particular circumstances; the other biomarkers studied in small cohorts are not used routinely[1].

Genetics now has a place in the workup. Genetic testing should be considered in definite myocarditis or pericarditis when there is a family history of inflammatory myopericardial syndrome or cardiomyopathy, severe ventricular arrhythmia, marked late gadolinium enhancement or persistent ventricular dysfunction, recurrent myocarditis or persistently elevated troponin (Class IIa, Level B)[1]. In a meta-analysis cited by the guideline, the prevalence of pathogenic or likely pathogenic variants was 4.2% in uncomplicated myocarditis and 22% in complicated myocarditis in adults[1].

In primary care, the search for a cause starts with the history taken during the basic assessment: recent upper respiratory or gastrointestinal infection, toxic exposures, recreational drugs and medications, recurrent symptoms, a family history of myopericarditis, cardiomyopathy or sudden death, and known inflammatory or autoimmune disease[1]. Basic laboratory testing combines high-sensitivity troponin, CRP, erythrocyte sedimentation rate, a complete blood count with eosinophils, NT-proBNP, creatinine and electrolytes, TSH and liver tests including lactate dehydrogenase[1]. Other tests, guided by clinical suspicion and ordered when they will change management, form part of the advanced evaluation, usually after admission[1]. High-risk or complicated cases require multidisciplinary discussion at a referral center (Class I, Level C), involving a rheumatologist or clinical immunologist, an infectious disease specialist and a geneticist as appropriate[1].

15.3 Eosinophilic myocarditis

In the Treatise: § 6.3.1 and § 13.8.5

This diagnosis should be considered in myocarditis that is often fulminant, with an abrupt fall in ejection fraction, malignant arrhythmias or an intraventricular thrombus[1]. It may also present as restrictive cardiomyopathy (Löffler endocarditis). A review of published, histologically proven cases involving 179 patients reported in-hospital mortality of 22%, highest in the hypersensitivity form (36%); that form accounted for 34% of cases, while approximately one-third remained idiopathic or undetermined[2]. The authors acknowledge that publication bias may have overestimated mortality[2].

A complete blood count with an eosinophil count is essential, but it is not sufficient: peripheral eosinophilia is absent in up to 25% of patients, contributing to underdiagnosis[1]. The diagnosis rests either on endomyocardial biopsy showing an eosinophilic infiltrate or on myocarditis demonstrated by magnetic resonance imaging together with blood eosinophilia[1]. A normal eosinophil count therefore does not settle the question when the presentation is suggestive.

A search for causes is required in every case, and the guideline lists them: hypersensitivity and allergic reactions, immune diseases, particularly eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome and its myeloproliferative variant, parasitic infections and cancers[1]. The history should seek features of granulomatosis or hypereosinophilic syndrome: asthma, sinusitis and characteristic skin lesions[1]. Laboratory details for these causes (ANCA, testing for the FIP1L1::PDGFRA fusion transcript and parasitic investigations) are covered in Chapters 9 and 14.

The workup has therapeutic consequences. Each cause has its own treatment: cyclophosphamide or interleukin-5 inhibitors in granulomatosis, ima-

tinib in the PDGFRA-associated variant and albendazole in *Toxocara canis* infection; in the hypersensitivity form, the first step is to remove the presumed cause of eosinophilia[1]. Intracavitary thrombi are reported in 12% of cases, prompting consideration of anticoagulation in the acute phase[1].

In primary care, eosinophilia found on a complete blood count in a patient with cardiac signs calls for the approach used in any suspected myocarditis: troponin, NT-proBNP, CRP and ECG, with hospital referral if troponin is elevated[1]. Conversely, a normal blood eosinophil count is not reassuring in a suggestive presentation, since eosinophilia is absent in up to one-quarter of patients[1]. The etiologic investigation (ANCA, parasitic infections and hypereosinophilic syndrome) is conducted with specialists in the underlying disease; their collaboration is considered important for establishing the diagnosis and planning treatment[1].

15.4 Drug hypersensitivity and DRESS

In the Treatise: § 6.3.1, § 13.8.5 and § 13.12.4

Drug reaction with eosinophilia and systemic symptoms (DRESS) combines an infiltrated rash with facial edema, lymphadenopathy, fever, organ involvement and hematologic abnormalities, particularly eosinophilia[3]. The liver and kidneys are most often affected; the lungs, heart and nervous system may also be involved[3]. The 2025 European guideline notes that drug-induced myocarditis may occur as part of DRESS and that clozapine is among the leading implicated drugs[1].

The basic workup is addressed by an international Delphi consensus for adults, published in 2024 and based on the opinions of 54 experts rather than trials[3]. It is essential in every suspected case: complete blood count with differential and platelets, creatinine, urea and estimated glomerular filtration rate (eGFR), urine sediment, liver tests, ECG and serum viral loads by PCR for EBV, cytomegalovirus (CMV) and HHV-6[3]. The same tests are used to grade severity. A factor V level below 50% classifies liver involvement as severe; hematologically, pancytopenia or hemophagocytosis has the same significance[3].

Cardiac assessment is guided by the clinical presentation. The consensus reserves natriuretic peptide, troponin T and transthoracic echocardiography for patients with suspected cardiac involvement; routine troponin testing in all patients did not achieve expert agreement[3]. The consensus immediately adds a warning: cardiac involvement in DRESS may be clinically silent during the acute phase[3]. ECG, however, is performed in all patients[3].

Virology is the most debated issue. The consensus places serum PCR for EBV, CMV and HHV-6 in the basic workup for every suspected case, alongside the complete blood count; it asks that this recommendation be read and interpreted according to the clinician's available resources, with divergent opinions partly reflecting unequal regional access to these tests[3]. Viral replication is not required for diagnosis, and the therapeutic implications of a positive PCR remain highly debated[3]. Human herpesvirus 7 (HHV-7) PCR is only an option when another reactivation has already been confirmed; testing for herpes simplex viruses 1 and 2 and parvovirus B19 is not recommended[3]. A high CMV viral load may prompt consideration of antiviral treatment[3].

Depending on the context, additional tests include prothrombin time, with or without factor V, in severe disease or organ involvement, and hepatitis serology. The panel rejected screening everyone for hepatitis A, B and C; it accepted such screening in liver involvement and endorsed hepatitis B and C screening before systemic treatment[3]. HIV serology was not endorsed[3]. Testing for

thymus and activation-regulated chemokine (TARC), or CCL17 (C-C motif chemokine ligand 17), did not achieve consensus[3].

The broad outlines of follow-up are defined. Visits start within the first month after discharge and continue throughout the first 6 months[3]. Blood tests follow the initial organ involvement; convalescence is the time to screen for autoantibodies and thyroid dysfunction[3]. For cardiac involvement, drug-induced myocarditis is treated by drug withdrawal and corticosteroids[1].

In primary care, the first step in suspected DRESS is immediate withdrawal of the implicated drug or drugs, endorsed by the consensus for all patients[3]. DRESS is severe in the presence of major cytopenia, including hemoglobin below 7 g/dL, pancytopenia, signs of hemophagocytosis, severe renal failure or rapidly progressive oligoanuria, liver enzymes above 15 times the upper limit of normal or factor V below 50%[3]. Any involvement of another organ, regardless of its intensity, also makes it severe[3]. Cardiac involvement therefore classifies DRESS as severe on its own. Between specialist reviews, monitoring prolonged corticosteroid therapy includes screening for adverse effects, and psychological support should be actively offered[3].

15.5 Giant cell myocarditis and biopsy

In the Treatise: § 6.3.2 and § 13.12.3

Giant cell myocarditis is suspected in acute myocarditis complicated by refractory heart failure or shock, ventricular arrhythmia or atrioventricular block[1]. In a Finnish study cited by the guideline, 25% of people younger than 55 with clinically idiopathic heart block had giant cell myocarditis or cardiac sarcoidosis on biopsy[1]. No blood test establishes this diagnosis.

Endomyocardial biopsy is the reference test. Its sensitivity is 68% with the first sampling and reaches 93% when the procedure is repeated up to three times; a nondiagnostic biopsy therefore does not exclude the disease, and repeat sampling should be considered when suspicion is high[1]. Intravenous corticosteroids given before sampling may reduce its yield[1]. Organization matters as much as the procedure: the guideline asks specialist centers to agree on providing histology results within no more than 3 days, ideally within 8 hours[1]. The laboratory workup for this form of myocarditis is limited to the core assessment (see 15.1) and the workup for immunosuppressive treatments (see Chapter 21).

Troponin has a particular interpretation here, described in a narrative review of 25 published cases[4]. During immunosuppression, troponin that plateaued at an elevated level or rose again prompted repeat biopsy and reconsideration of treatment, or heralded relapse. During relapses, it was elevated but lower than during the first episode; in some patients with histologic healing, it remained above normal after discharge. The authors found no relationship between its level and the extent of injury and considered their laboratory data inconclusive[4]. In these reports, a troponin level lower than on admission did not exclude relapse, and persistent elevation alone did not demonstrate active disease.

In primary care, giant cell myocarditis cannot be confirmed, but its presentation can be recognized: unexplained heart failure of less than two weeks' duration, with a normal-sized or dilated left ventricle, accompanied by new ventricular arrhythmia, second- or third-degree atrioventricular block or failure to respond to standard treatment within one to two weeks; endomyocardial biopsy is then recommended (Class I, Level C)[1]. Acute heart failure, sustained

ventricular arrhythmia and high-grade block are high-risk criteria, and hospitalization is recommended (Class I, Level C); complicated cases require a tertiary referral center[1]. The disease often progresses rapidly, with death or transplantation in approximately 85% by 3 years, and immunosuppression begins as soon as the disease is suspected[1]. During follow-up, stopping or reducing immunosuppression carries a risk of recurrence up to 8 years after diagnosis[1].

Table 15.1. The etiologic workup of myocarditis, tier by tier

Situation	Essential	Depending on the context	Specialist assessment
Suspected myocarditis	hs troponin, CRP, NT-proBNP, complete blood count with eosinophils, creatinine and electrolytes, TSH, liver tests	HIV and hepatitis C serology; Lyme and Chagas testing based on exposure	Biopsy with viral PCR; anti-heart autoantibodies; genetics
Eosinophilic myocarditis	Complete blood count with eosinophils	Search for causes: ANCA, parasitic infections, hematologic disease	Biopsy; FIP1L1::PDGFRA
DRESS	Complete blood count and platelets, creatinine, urea, eGFR, urine sediment, liver tests, ECG; serum PCR for EBV, CMV and HHV-6, interpreted according to available resources	Prothrombin time, with or without factor V; hepatitis testing; autoantibodies and thyroid assessment during convalescence; troponin T, natriuretic peptide and echocardiography if cardiac involvement is suspected	HHV-7 PCR

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16

The workup of pericarditis

Chapter contents

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Most cases of pericarditis are viral or idiopathic and resolve; laboratory testing primarily serves to triage patients, not to look for a cause in everyone. It takes on a different role in recurrence, a large effusion or systemic disease. C-reactive protein has a central place: it supports the diagnosis of recurrence and guides treatment duration.

16.1 The first episode: core assessment and triage

In the Treatise: § 5.1 and § 5.1.1

The initial evaluation is the same as for myocarditis: history, examination, chest radiograph, electrocardiogram, echocardiography and laboratory markers, recommended for all patients (Class I, Level C)[1]. The expected markers are high-sensitivity (hs) troponin, C-reactive protein (CRP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP); the basic workup also includes a complete blood count with eosinophils, creatinine and electrolytes, thyroid-stimulating hormone (TSH) and liver tests[1]. In developed countries, the cause is idiopathic or viral in 50% of hospitalized cases and more than 80% of outpatient cases[1].

CRP is elevated in up to 80% of pericarditis cases; it contributes to diagnosis and serves as a marker of activity to guide the duration of anti-inflammatory treatment, but a normal result does not exclude the diagnosis[1]. The so-called noninflammatory phenotype, with no or only a small increase in CRP, accounts for 10 to 20% of pericarditis cases[1]. In autoimmune diseases with a type I interferon signature, CRP is an unreliable marker of inflammation[1].

Troponin is measured because pericarditis is accompanied by myocardial involvement in 10 to 15% of cases; this is termed myopericarditis, with consequences for monitoring and return to sports[2]. The 2025 French National Diagnostic and Care Protocol (PNDS) specifies that there is no troponin threshold. It warns against the opposite excess: diagnosing myopericarditis on the basis of a minimal increase in high-sensitivity troponin, which may accompany uncomplicated pericarditis[2].

Not everyone needs an etiologic investigation. Patients with a high-risk criterion are hospitalized (Class I, Level B) and investigated for a cause[1]. These criteria are fever above 38 °C, effusive-constrictive pericarditis, failure of nonsteroidal anti-inflammatory drugs, incessant pericarditis, an effusion greater than 20 mm at end-diastole, tamponade and extensive pericardial enhancement on magnetic resonance imaging[1]. With no high-risk criterion and a good response to treatment, the patient is followed as an outpatient without an etiologic investigation[1].

The main pitfall is viral serology. It is not recommended routinely (Class III, Level C), except for hepatitis C, human immunodeficiency virus (HIV) and Lyme disease[1]. In endemic regions, tuberculosis accounts for approximately 70% of pericarditis cases, particularly in patients with HIV[1]; the patient's geographic origin is therefore part of the reasoning. Hospitalization is also recommended for intermediate- or high-risk myocarditis (Class I, Level C), directing the workup toward Chapter 15 once troponin indicates myocardial involvement[1].

In primary care, triage comes first: approximately one-quarter of acute pericarditis cases have a poor prognostic factor and require hospital care; the others can be treated as outpatients if they respond well[1]. The initial workup includes CRP and troponin (Class I)[1]. Response is assessed after 1 to 2 weeks; fever above 38 °C, signs of tamponade, failure of anti-inflammatory drugs or an effusion greater than 20 mm prompt hospitalization[1]. An elevated troponin

raises the question of myopericarditis, with its consequences: prolonged rest, hospitalization for monitoring and delayed return to sports[2]. The initial treatment dose is maintained until symptoms resolve and CRP normalizes, then tapered; monitoring includes a complete blood count, creatinine, creatine kinase, transaminases and CRP[1]. After recovery, troponin and CRP are checked within the first month and again at 3 to 6 months[1].

16.2 Recurrent pericarditis

In the Treatise: § 5.2, § 5.5 and § 13.8.11

Recurrence is diagnosed when at least one new episode of pericarditis occurs after a symptom-free interval of at least 4 to 6 weeks[3]. Recurrence usually occurs within 18 months of the initial episode and complicates 15 to 30% of first episodes; the proportion may reach 50% after a first recurrence when the initial episode was inadequately treated, with overly rapid tapering, without colchicine or with corticosteroids[1]. Laboratory testing provides evidence that the PNDS describes as very important: elevated inflammatory markers, particularly CRP[3].

The absence of an inflammatory response or an atypical presentation should prompt reconsideration of the diagnosis and expert consultation[3]. The opposite pitfall is common: chest pain with a modest CRP elevation, often in a viral context, without true recurrence. The PNDS then advises gathering the evidence, seeking specialist advice and, if necessary, obtaining cardiac magnetic resonance imaging (MRI)[2]. In the noninflammatory phenotype, the European guideline notes that patients are often difficult to treat and that the mechanism remains unknown[1].

Causes to rule out with an expert center are autoimmune diseases (lupus, Sjögren syndrome and rheumatoid arthritis), certain autoinflammatory diseases and, in prolonged cases, tuberculosis, cancer, the aftermath of myocardial infarction or cardiac surgery, and medications[3]. The PNDS also lists hypothyroidism, uremia, vaccines, chimeric antigen receptor T cells (CAR-T cells) and immune checkpoint inhibitors among the causes[2]. Idiopathic cases, presumed postviral, account for 80 to 90% of cases in industrialized countries[2]. An autoimmune phenotype combines subacute episodes, a moderate increase in inflammatory proteins and frequent autoantibodies, including antinuclear, anti-heart and anti-intercalated disk antibodies[2].

Genetics requires specialist assessment and is rarely requested. The PNDS does not recommend first-line targeted testing in sporadic, isolated cases; it reserves testing for syndromic presentations, a phenotype strongly suggestive of an autoinflammatory disease and a first-degree family history[2]. In 128 patients, sequencing of MEFV, TNFRSF1A, MVK and NLRP3 did not establish any diagnosis of monogenic disease[2]. Testing for TNFRSF1A variants, particularly R121Q, formerly R92Q, has no value: its prevalence in recurrent pericarditis does not differ from that in the general population[2]. The European guideline proposes considering testing for refractory inflammatory recurrence, particularly when refractory to colchicine and anti-interleukin-1 agents (Class IIa, Level B)[1]. These diseases are covered in Chapter 11.

Laboratory follow-up is detailed in the PNDS, which suggests, as a guide, weekly testing until inflammation normalizes, then monthly for 6 months, then every 3 to 6 months[2]. The minimum panel includes a complete blood count and platelets, electrolytes and creatinine, CRP and fibrinogen, transaminases, alkaline phosphatase and gamma-glutamyl transferase, prothrombin time, bilirubin and fasting glucose during corticosteroid therapy[2]. Troponin

and NT-proBNP are added initially if previously positive and, every quarter, protein electrophoresis and, during corticosteroid therapy, a lipid panel and glycated hemoglobin (HbA1c)[2].

In primary care, the treating physician is on the front line in recognizing recurrence: chest pain, signs of a new effusion, electrocardiographic changes and elevated CRP; the patient is then referred promptly so treatment can begin as early as possible[3]. The physician alerts the specialist to an incomplete treatment response, corticosteroid dependence, intolerance of or contraindications to standard treatment, poor adherence, a cause not yet investigated or extrapericardial involvement (arthralgia, rash or persistent fever)[3]. During colchicine treatment, the physician monitors gastrointestinal tolerability, adjusts the dose to renal function and checks for interactions[3]. Colchicine must not be combined with macrolides, such as erythromycin, clarithromycin and josamycin, or pristinamycin; cyclosporine, tacrolimus, azole antifungals, certain antiretrovirals such as ritonavir, verapamil, diltiazem, amiodarone, statins, digoxin, ranolazine and grapefruit juice, which interact with it through P-glycoprotein (P-gp) or cytochrome P450 3A4 (CYP3A4), carry a risk of colchicine overdose: if an otherwise permissible combination cannot be avoided, the dose and duration are reduced and signs of overdose are monitored[2]. The PNDS for familial Mediterranean fever strictly contraindicates these combinations in renal or hepatic impairment[4]. The French Summary of Product Characteristics (SmPC) also contraindicates colchicine itself in severe renal impairment (creatinine clearance below 30 mL/min) or severe hepatic impairment; for several of these drugs (macrolides, pristinamycin, cyclosporine, verapamil, ritonavir-boosted protease inhibitors, azole antifungals and statins), it specifies whether the combination is contraindicated, not recommended or subject to precautions for use (see 11.1)[5]. The same SmPC contraindicates colchicine for idiopathic acute pericarditis, first episode or recurrence, occurring during pregnancy, because of the required combination with conventional anti-inflammatory drugs[5]. The frequency of consultations is not standardized; the recurrent pericarditis PNDS suggests, as a guide, twice-monthly visits during the three months after diagnosis or a recurrence, then quarterly visits[2].

16.3 Pericarditis in systemic diseases and after cardiac injury

In the Treatise: § 5.1, § 5.3 and § 8.1

Pericarditis is the most common cardiac manifestation of lupus, reported in approximately 25% of patients; tamponade occurs in fewer than 2% of cases[1]. In rheumatoid arthritis, pericardial involvement is found in up to 50% of patients at autopsy, often with pleuritis[1]. In Sjögren syndrome, it is reported in fewer than one-third of cases[1]. The workup is then that of the underlying disease (see Chapters 5 to 7), including its activity biomarkers.

CRP is an imperfect guide in this setting. In connective tissue disease, the PNDS notes that a minimally inflammatory presentation points toward treatment of the underlying disease if there is evidence of systemic disease activity or if the effusion is symptomatic or recent[2]. The risk of constriction is intermediate after immune-mediated pericarditis, at 2 to 5%, compared with less than 1% after viral or idiopathic pericarditis[1]. Constrictive pericarditis classically presents as isolated right heart failure, with a normal or nearly normal natriuretic peptide level[1]: a low NT-proBNP does not exclude it. Long-term follow-up is recommended for incessant or recurrent pericarditis (Class I, Level C)[1].

Post-cardiac injury syndromes include Dressler syndrome after myocardial infarction, postpericardiotomy syndrome and post-traumatic pericarditis, increasingly of iatrogenic origin[1]. Dressler syndrome now occurs after fewer than 1% of myocardial infarctions, typically 1 to 2 weeks later[1]. Any post-cardiac injury syndrome requires at least two of five diagnostic criteria: (1) fever without another cause, (2) pericardial or pleuritic pain, (3) a friction rub, (4) pericardial effusion and/or (5) pleural effusion with elevated CRP[2]. After myocardial infarction, an effusion greater than 10 mm should prompt investigation for subacute rupture[1].

In primary care, pericarditis in a patient with lupus, Sjögren syndrome or rheumatoid arthritis should not be presumed viral: these causes are ruled out in collaboration with expert centers, and the treating physician contributes by collecting the personal and family history and extracardiac findings[3]. Extrapericardial involvement (arthralgia, rash or persistent fever) or an unexplored cause prompts the physician to alert the specialist[3]. In patients with lupus, ibuprofen is contraindicated if a flare is suspected, because of the risk of aseptic meningitis[2]. After myocardial infarction, high-dose aspirin is the first-choice anti-inflammatory agent, as it is in patients already receiving an antiplatelet drug (Class I, Level C); every post-cardiac injury syndrome warrants careful follow-up to detect progression to constriction (Class IIa, Level C)[1].

16.4 Pericardial effusion and tamponade

In the Treatise: § 5.4.1, § 5.4.9 and § 14.3.2

A large effusion changes the logic of the workup. In large series, causes are idiopathic in up to 50%, neoplastic in 10 to 32%, infectious in 15 to 30%, iatrogenic in 15 to 20% and related to connective tissue disease in 5 to 15%; tuberculosis predominates, accounting for more than 60%, in endemic countries[1]. An effusion is associated with a known or previously unrecognized condition, such as hypothyroidism, in up to 60% of cases, particularly when moderate or large[1]; TSH is part of the workup.

CRP determines treatment. In the absence of elevated CRP and imaging evidence of pericardial inflammation, anti-inflammatory treatment is not recommended[1]. Follow-up of an asymptomatic effusion that is at least moderate is based on symptoms, echocardiography and CRP, with assessment every 6 months being reasonable, ideally at a specialist center[1]. A minimal, idiopathic and asymptomatic effusion requires no specific monitoring, and patients with normal CRP need not restrict physical activity[1].

Tamponade is a clinical diagnosis confirmed by echocardiography; neither CRP nor an immunologic test establishes it[1]. Drainage, preferably by image-guided pericardiocentesis, must be performed without delay in an unstable patient[1]; no sampling should postpone it. Common causes are cancer, iatrogenic injury and trauma, pericarditis and tuberculosis; connective tissue diseases, uremia and bacterial infection are less common[1].

Pericardiocentesis is recommended in tamponade, suspected bacterial or neoplastic pericarditis, or a moderate to large effusion that remains symptomatic despite treatment (Class I, Level C)[1]. Fluid is sent for pathologic and microbiologic examination, including bacterial, fungal and tuberculosis testing[1]. A low pericardial-to-serum glucose ratio, averaging 0.3, and a neutrophil-rich cell count, averaging 92%, distinguish purulent disease from tuberculous disease (ratio 0.7, 50% neutrophils) and neoplastic disease (ratio 0.8, 55% neutrophils)[1].

Tuberculosis has its own markers, which require specialist assessment. In a meta-analysis, adenosine deaminase (ADA) had 90% sensitivity and 86% specificity[1]. The Xpert MTB/RIF test is highly specific, at 100%, but has 64% sensitivity in fluid and 78% in biopsy specimens[1]. Unstimulated interferon gamma in pericardial fluid reaches 97% sensitivity and 99% specificity[1]. Culture has low sensitivity, 53 to 75%, and takes more than 3 weeks[1]. The tuberculin skin test and interferon-gamma release assays have limited value[1].

In primary care, useful laboratory tests in a patient with pericardial effusion are CRP, which determines anti-inflammatory treatment, and TSH[1]. An asymptomatic effusion that is at least moderate is followed through symptoms, echocardiography and CRP, reasonably every 6 months, ideally at a specialist center; patients should seek care if dyspnea, fatigue or chest pain develops[1]. An effusion greater than 20 mm or signs of tamponade are high-risk criteria requiring hospitalization[1]. An effusion that remains symptomatic despite treatment, or suspected bacterial or neoplastic pericarditis, prompts referral for pericardiocentesis[1].

Table 16.1. The workup of pericarditis, tier by tier

Situation	Essential	Depending on the context	Specialist assessment
First episode	hs troponin, CRP, NT-proBNP, complete blood count, creatinine and electrolytes, TSH, liver tests	Search for a cause if a high-risk criterion is present; HIV, hepatitis C and Lyme serology	—
Recurrence	CRP with each episode	Autoantibodies for the suspected disease	Genetics of recurrent fevers
Effusion, tamponade	First-episode workup, CRP	TSH; pathologic and microbiologic fluid analysis	ADA, interferon gamma, Xpert on fluid or biopsy specimens

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17

Heart failure and pulmonary hypertension: the immune contribution

Chapter contents

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Heart failure and pulmonary hypertension each have a standard workup defined by general guidelines. An immune cause is not found by chance: it is sought only when a clinical, electrical or imaging clue raises the question. Standard laboratory testing helps confirm the syndrome and identify comorbidities; immune testing requires a hypothesis.

17.1 Heart failure: the standard workup

In the Treatise: § 13.6.4 and § 13.6.5

Natriuretic peptide measurement is recommended in suspected heart failure, interpreted according to age, obesity and other factors that affect its level (Class I, Level C)[1]. The 2026 European guideline recalls the single rule-out thresholds adopted in 2021: N-terminal pro-B-type natriuretic peptide (NT-proBNP) below 125 pg/mL or B-type natriuretic peptide (BNP) below 35 pg/mL[1]. However, the level depends strongly on age, and the guideline refers to age-adjusted NT-proBNP thresholds[1]. In outpatients, heart failure is likely from 125 pg/mL before age 50, 250 pg/mL between 50 and 75 and 500 pg/mL over 75; data are lacking for age-adjusted BNP thresholds[1]. In patients with heart failure, an NT-proBNP above 2,000 pg/mL is associated with a twofold higher risk of early heart failure hospitalization: specialist assessment should be prompt and echocardiography preferably performed within two weeks[1].

A comorbidity workup is recommended (Class I, Level C): complete blood count, renal function including estimated glomerular filtration rate and urine albumin-to-creatinine ratio, electrolytes, liver tests, thyroid function, glycated hemoglobin (HbA1c), lipids and iron status including transferrin saturation and ferritin[1]. The urine albumin-to-creatinine ratio has been added to the initial workup alongside the filtration rate. Severe albuminuria may be present despite a filtration rate of at least 90 mL/min/1.73 m² and carries strong independent prognostic value[1].

Natriuretic peptide must be interpreted in context (see Chapter 3). Many situations raise its level, including advanced age, atrial fibrillation, renal dysfunction, myocarditis and pulmonary hypertension; renal dysfunction raises NT-proBNP but does not justify disregarding the test[1]. Others lower it: obesity, African ancestry, constrictive pericarditis and several heart failure treatments; with sacubitril-valsartan, BNP may rise because neprilysin contributes to its degradation, whereas NT-proBNP is not distorted by this mechanism and falls as with other treatments[1]. A low peptide level therefore does not by itself rule out heart failure with preserved ejection fraction in a person with obesity. Nor does it rule out pericardial constriction, whose typical presentation combines right heart failure with a normal or nearly normal peptide level (see Chapter 16)[2].

Iron status has its own rule. The classic definition of iron deficiency, ferritin below 100 ng/mL or between 100 and 299 ng/mL with transferrin saturation below 20%, is the definition used in almost all recent trials of intravenous iron[1]. The 2026 guideline instead favors transferrin saturation below 20%. The former definition includes patients who are probably not iron deficient, and ferritin is highly sensitive to inflammation and oxidative stress[1]. This point is all the more important because ferritin rises with any inflammatory response (see Chapter 3). Iron deficiency should be sought routinely among noncardiovascular comorbidities, and iron status is included in follow-up testing when considered useful[1].

In primary care, the guideline provides a specific algorithm for outpatients[1]. In the presence of suggestive symptoms, natriuretic peptide is measured at once, alongside an electrocardiogram and a comorbidity workup[1]. An NT-proBNP above 2,000 pg/mL accelerates echocardiography and specialist assessment[1]. In symptomatic patients without recent decompensation, follow-up focuses on symptoms, adherence, arrhythmias and the electrocardiogram; echocardiography and laboratory tests, including a complete blood count, electrolytes, iron status and liver, renal and thyroid function, are added when considered useful[1]. Persistently elevated natriuretic peptides are among the criteria that should prompt timely referral to an advanced heart failure center[1].

17.2 When to look for an immune cause

In the Treatise: § 13.6, § 13.8 and § 13.9

The 2026 guideline calls for a multimodal etiologic assessment to identify a treatable cause[1]. In suspected cardiac amyloidosis, the initial workup combines serum and urine immunofixation, serum free light chain measurement and bone scintigraphy (Class I, Level B)[1]. In suspected cardiac sarcoidosis, 18F-fluorodeoxyglucose positron emission tomography should be considered (Class IIa, Level C)[1]. Endomyocardial biopsy should be considered in rapidly progressive heart failure despite treatment, or when other investigations suggest myocardial inflammation, infiltration or storage disease that no other method identifies (Class IIa, Level C)[1].

For the tests specific to each of the other causes, the 2026 guideline refers to its supplementary data. The causes table in the 2021 European guideline provides them. For autoimmune disease, it lists antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA) and rheumatology consultation[3]. For sarcoidosis, it adds serum angiotensin-converting enzyme (ACE) to imaging and biopsy[3]. For infection, it lists serology for human immunodeficiency virus (HIV), Lyme disease and Chagas disease; for Fabry disease, α-galactosidase A; for endomyocardial fibrosis with eosinophilia, biopsy[3].

This table is not a panel to order for everyone: it pairs each cause with its presentations, and those presentations prompt the test. Features that should raise suspicion of an autoimmune rheumatic disease are listed in the 2025 myocarditis guideline (see Chapter 15)[2]. Disease-specific workups are provided in Chapters 5 to 14.

Inflammatory cardiomyopathy is the chronic form of myocarditis. It should be suspected in nonischemic ventricular dysfunction with low ECG voltage and persistent modest elevation of high-sensitivity troponin[2]. Myocarditis resolves in more than half of cases, but approximately 25% of patients have persistent dysfunction[2]. Confirmation relies on imaging and endomyocardial biopsy, with histology, immunohistology and viral polymerase chain reaction (PCR); genetic testing is considered in rare familial forms[2].

Biopsy guides treatment. Biopsy-guided immunosuppressive treatment should be considered in inflammatory cardiomyopathy without a viral genome (Class IIa, Level B)[2]. Specific treatment of the underlying systemic disease is recommended (Class I, Level C), in addition to heart failure treatment[2]. Anti-heart autoantibodies, tested according to local availability, require specialist assessment (see Chapter 15)[2].

In primary care, the search for an infiltrative cause starts with red flags. For cardiac amyloidosis, these include left ventricular hypertrophy with sinoatrial or atrioventricular block, atrial fibrillation or flutter, heart

failure with preserved ejection fraction, low-flow, low-gradient aortic stenosis and, sometimes before cardiac involvement, carpal tunnel syndrome or lumbar spinal stenosis, peripheral neuropathy, autonomic dysfunction or nephrotic syndrome[4]. Suspicion requires urgent assessment, particularly for immunoglobulin light chain (AL) amyloidosis: the treating physician or cardiologist refers the patient to a French reference or competence center, and the initial workup looks for a gammopathy through serum protein electrophoresis and immunofixation, serum free light chains and Bence Jones proteinuria[4]. Once the diagnosis is established, the treating physician monitors the course and alerts the coordinating cardiologist[4].

17.3 Pulmonary hypertension: the etiologic workup

In the Treatise: § 11.1 and § 20.9

Laboratory testing does not diagnose pulmonary hypertension: confirmation is hemodynamic. At diagnosis, it serves to identify comorbidities, possible causes and complications[5]. The 2022 European guideline lists the tests: complete blood count including hemoglobin, sodium and potassium, creatinine with estimated filtration rate and urea, uric acid, liver tests, iron status (iron, transferrin saturation and ferritin) and BNP or NT-proBNP[5].

Viral hepatitis and HIV serology are part of the same workup, as is a basic immunologic assessment including antinuclear, anticentromere and anti-Ro antibodies[5]. Pulmonary arterial hypertension and other severe forms may be associated with thyroid disease: at a minimum, thyroid-stimulating hormone (TSH) is therefore measured[5]. The recommendation table summarizes these tests: biochemistry, hematology, immunology, HIV serology and thyroid function are recommended in every patient with pulmonary arterial hypertension (Class I, Level C)[5].

The main pitfall is confusing two questions: the etiologic workup seeks an associated disease; it does not establish pulmonary hypertension. Genetic counseling and annual screening are recommended for carriers of a causative mutation and first-degree relatives of patients with a heritable form (Class I, Level B)[5]; this evaluation belongs in the referral center. Abdominal ultrasonography, recommended to screen for portal hypertension, completes the etiologic workup[5].

In primary care, pulmonary hypertension often first presents to the primary care physician with nonspecific symptoms[5]. The first stage includes the history, including family history, examination with pulse oximetry, BNP or NT-proBNP measurement and a resting electrocardiogram; echocardiography then establishes a probability of pulmonary hypertension[5]. The patient is referred to a pulmonary hypertension center if that probability is intermediate or high, or if there are risk factors for pulmonary arterial hypertension or a history of pulmonary embolism; the full workup and invasive investigation are performed at the center[5]. Warning signs require immediate intervention: rapidly progressive or severe symptoms, severely reduced exercise capacity, presyncope or syncope on mild exertion and signs of right heart failure[5].

17.4 Connective tissue diseases: screening for pulmonary arterial hypertension

In the Treatise: § 11.2 and § 11.2.2

In systemic sclerosis, annual assessment of the risk of pulmonary arterial hypertension is recommended (Class I, Level B)[5]. In adults with disease duration over 3 years, forced vital capacity (FVC) of at least 40% and diffusing capacity for carbon monoxide (DLCO) below 60%, the DETECT algorithm is recommended to identify asymptomatic disease (Class I, Level B)[5]. Its first step, which determines whether to perform echocardiography, combines six assessments: three laboratory measures, anticentromere antibodies, NT-proBNP and serum uric acid, and three others, the FVC/DLCO ratio, current or past telangiectasias and right-axis deviation on the electrocardiogram[6]. In the validation study, the complete algorithm had 96% sensitivity and a 98% negative predictive value, at the cost of 48% specificity and a 35% positive predictive value: it referred 62% of patients for catheterization and missed only 4% of pulmonary arterial hypertension cases[6]. The systemic sclerosis workup is provided in Chapter 6.

Risk assessment based on dyspnea, echocardiography or pulmonary function tests and BNP or NT-proBNP should be considered in systemic sclerosis (Class IIa, Level B)[5]. If dyspnea remains unexplained after the noninvasive workup, right heart catheterization is recommended (Class I, Level C)[5]. In connective tissue diseases with systemic sclerosis features, annual assessment may be considered[5]. Outside systemic sclerosis, the rule is symptom-based. In patients with connective tissue disease, portal hypertension or HIV infection, further tests, including echocardiography and BNP or NT-proBNP, should be considered when symptoms are present (Class IIa, Level B)[5].

In primary care, pulmonary arterial hypertension is sought in systemic sclerosis even without symptoms, because early management is a determining factor in survival[7]. The French National Diagnostic and Care Protocol (PNDS), in its opening summary for the treating physician, sets the schedule: annual electrocardiography and echocardiography, NT-proBNP at least once a year and annual DLCO[7]. The PNDS cites serum uric acid as a predictive marker in the DETECT score[7]. New dyspnea, episodes of faintness or presyncope are among the warning signs that should prompt a rapid consultation[7]. Dyspnea that remains unexplained after the noninvasive workup prompts referral for right heart catheterization (Class I, Level C)[5]. Follow-up at an expert center is at least annual[7].

17.5 Chronic thromboembolic pulmonary hypertension and antiphospholipid antibodies

In the Treatise: § 11.4 and § 11.4.2

Testing for antiphospholipid syndrome is recommended in every patient with chronic thromboembolic pulmonary hypertension (Class I, Level C)[5]. The guideline does not make this conditional on age or known autoimmune disease. Testing is not a formality: in a meta-analysis of eight studies, approximately 12% of patients with chronic thromboembolic pulmonary hypertension had antiphospholipid antibodies[8]. Lifelong therapeutic anticoagulation is recommended for all these patients (Class I, Level C)[5]; testing for the syndrome then determines the drug: in the presence of antiphospholipid syndrome, vitamin K antagonists are recommended (Class I, Level C)[5].

Other thrombophilias are not routinely investigated unless a therapeutic consequence is expected[5]. The reasoning thus starts at the other end: it is

not known autoimmune disease that prompts the search for thrombosis, but organized thrombosis that prompts the search for the syndrome. Sampling conditions for antiphospholipid tests, anticoagulant interference and confirmation at 12 weeks are covered in Chapter 5.

In primary care, chronic thromboembolic disease should be considered after pulmonary embolism: diagnostic evaluation is recommended for persistent or new dyspnea or exercise limitation (Class I, Level C)[5]. In symptomatic patients with persistent perfusion defects beyond 3 months of anticoagulation, referral to a chronic thromboembolic pulmonary hypertension center is recommended, taking account of echocardiography, BNP or NT-proBNP and, when appropriate, cardiopulmonary exercise testing (Class I, Level C)[5]. Testing for antiphospholipid syndrome is performed at diagnosis[5]. Every affected patient is reviewed by a team specializing in this condition (Class I, Level C)[5].

Table 17.1. The immune workup of heart failure and pulmonary hypertension, tier by tier

Situation	Essential	Depending on the context	Specialist assessment
Suspected heart failure	NT-proBNP or BNP; complete blood count, renal function with urine albumin-to-creatinine ratio, electrolytes, liver tests, thyroid function, HbA1c, lipids, ferritin and transferrin saturation	Amyloidosis: serum and urine immunofixation, free light chains; ANA, ANCA; ACE; HIV, Lyme and Chagas serology; α-galactosidase A	Biopsy with viral PCR; anti-heart autoantibodies
Diagnosed pulmonary hypertension	Complete blood count, electrolytes, creatinine, urea, uric acid, liver tests, iron status, natriuretic peptide, HIV, hepatitis testing, ANA, anticentromere, anti-Ro, TSH	—	Genetics of heritable forms
Systemic sclerosis	Annual risk assessment; NT-proBNP at least once a year	DETECT according to disease duration, FVC and DLCO: anticentromere, NT-proBNP, serum uric acid	Right heart catheterization
Chronic thromboembolic disease	Antiphospholipid antibodies	Other thrombophilias if there is a therapeutic consequence	—

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18

Rhythm and conduction: immune and acquired causes

Chapter contents

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An arrhythmia or conduction disorder is first identified on the electrocardiogram; laboratory testing follows, to rule out a reversible cause and then, in a few defined situations, to seek an immune or infectious cause. Three questions define the field: is a long QT acquired, does an adult's heart block conceal inflammatory disease or borreliosis, and does a child's heart block arise from maternal antibodies?

18.1 Acquired long QT: electrolytes and medications first

In the Treatise: § 6.5.1

Acquired long QT is common, far more so than the congenital form, and is most often associated with an electrolyte disorder, a medication or structural heart disease[1]. The 2022 international consensus on cardiac genetics defines it as a prolonged QT, usually exceeding 500 ms or rising 60 to 70 ms above baseline during drug treatment, sometimes complicated by torsades de pointes[2]. It is induced by QT-prolonging drugs and, less often, by hypokalemia or bradycardia[2].

The same document establishes the rule that makes laboratory testing a prerequisite: before diagnosing congenital long QT, secondary causes, including QT-prolonging drugs and electrolyte disorders, must be excluded[2]. Medication review and electrolyte measurement are therefore essential in evaluating any prolonged QT. The choice of electrolytes depends on the presentation; in a large cohort, potassium and calcium levels were among the few factors explaining marked prolongation of the corrected QT interval (QTc)[1].

Several factors usually have to combine to produce significant prolongation or torsades: female sex, advanced age, bradycardia, electrolyte abnormalities and medications[1]. This is why an isolated factor, even a modest one, should not be disregarded in a patient who already has others. Inflammation is one such factor: the 2025 European guideline notes that QT prolongation may occur in acute myocarditis[3].

Specialist referral concerns patients whose long QT persists after acquired causes have been corrected or who have experienced drug-induced torsades. The 2022 consensus proposes targeted genetic testing for patients younger than 40 who have had drug-induced torsades and whose QTc remains above 440 ms in men or 450 ms in women off the implicated drug[2]; in older people, the yield is too low for routine use[2].

In primary care, when a prolonged QTc is found on an outpatient tracing, the first step is medication review: each drug's risk can be checked in the CredibleMeds database, to which the 2022 consensus refers[2]. The second is an electrolyte panel including potassium, supplemented by calcium: together with age, diuretics and anti-Ro/SSA antibodies (Sjögren syndrome antigen A), these were the only variables retained in stepwise analysis for a QTc above 490 or 500 ms in the veterans cohort[1]. Patients who have had drug-induced torsades, or whose QT remains prolonged after acquired causes have been corrected, require specialist assessment[2].

18.2 Long QT associated with anti-Ro/SSA antibodies

In the Treatise: § 6.5.3

Anti-Ro/SSA antibodies are considered responsible for an acquired form of long QT through autoimmune inhibition of cardiac hERG potassium channels[1]. These antibodies occur in 0.5 to 2.7% of apparently healthy people[1]. In a series of 25 consecutive patients with torsades de pointes recruited from the general

population, anti-Ro/SSA 52-kDa positivity was found in 60%, in every case without associated connective tissue disease[1].

A large retrospective cohort published in 2021 included 7,339 US veterans, 8.3% of whom had anti-Ro/SSA antibodies[1]. Positivity was associated with marked QTc prolongation independently of a history of connective tissue disease; after stepwise adjustment, the odds ratio was 2.27 for a QTc above 500 ms[1]. Adjustment for QT-prolonging drugs substantially attenuated the association without eliminating it at the highest thresholds[1].

The authors propose considering anti-Ro/SSA testing in an "idiopathic" arrhythmia and informing people who test positive about medications and risk factors to avoid[1]. This is an authors' proposal, not a guideline recommendation. Testing therefore depends on the context: long QT without a sufficient acquired cause, or QT prolongation in a patient with connective tissue disease. It is not population screening.

The source's limitations constrain the conclusion. The cohort was predominantly male and older, selection was retrospective, and antibodies were reported only qualitatively in the vast majority of cases, with thresholds varying across centers; Ro52 and Ro60 subtypes were not distinguished[1]. No benefit of immunomodulatory treatment has been demonstrated for this indication. Anti-Ro/SSA testing and interpretation of subspecificities are covered in Chapter 4.

In primary care, management centers on medications and the electrocardiogram. The 2022 European algorithm contraindicates a QT-prolonging drug in long QT syndrome or with a baseline QTc above 500 ms; in the presence of hypokalemia, hypomagnesemia, renal or hepatic impairment, left ventricular hypertrophy, heart failure or another QT-prolonging drug, it should be prescribed only for a strong indication, with close follow-up. Whenever such a drug is started, an electrocardiogram is recorded at baseline, on day 1 and 1 to 2 weeks after initiation or any dose increase[4]. For anti-Ro/SSA-positive patients, with or without connective tissue disease, the veterans cohort authors propose education about these drugs and other risk factors[1]. The effect on hERG channels is attributed to the 52-kDa subtype[1]; yet in France most immunology laboratories report anti-SSA positivity only for anti-Ro60, which should be checked with the laboratory[5]. In long QT, anti-Ro52 should therefore be requested explicitly alongside anti-Ro60: a negative anti-SSA result based solely on Ro60 does not exclude anti-Ro52.

18.3 Acquired atrioventricular block in adults

In the Treatise: § 13.7.8, § 6.5.2 and § 14.4.1

High-grade block in a young adult should prompt a search for an inflammatory cause. In a Finnish study cited by the 2025 European guideline, 25% of people younger than 55 with clinically idiopathic block had giant cell myocarditis or cardiac sarcoidosis on biopsy[3]. The 2022 consensus calls for cardiac sarcoidosis to be systematically excluded before diagnosing a genetic form of sporadic isolated block and considers imaging screening useful before age 60 in unexplained Mobitz type II second-degree or third-degree block[2].

First-line laboratory testing looks for the acquired causes listed in the same consensus. For conduction disorders, these are degenerative fibrosis, ischemia, infiltration, valvular calcification, tumors and thyroid dysfunction[2]. For sinus node dysfunction, extrinsic causes include hypothyroidism, hyperkalemia, hypokalemia, hypocalcemia, hypoxia and medications[2]. Testing for thyroid

dysfunction with thyroid-stimulating hormone (TSH) and for electrolyte abnormalities follows from this list in unexplained conduction disease or sinus node dysfunction. The 2021 European pacing guideline makes this a rule: when the clinical presentation suggests a reversible cause of bradycardia, specific tests are recommended, such as thyroid function, Lyme serology, digoxin level, potassium, calcium and pH (Class I, Level C)[6].

Immune and infectious testing depends on the context. Anti-Ro/SSA antibodies may be found in unexplained block in Sjögren syndrome[3]. Lyme serology is recommended in high-grade block when Lyme carditis is suspected (see 18.4)[3]. In patients exposed in an endemic area, Chagas disease, which may present with bradyarrhythmias or tachyarrhythmias, is investigated using two serologic tests with different antigens[3].

Endomyocardial biopsy, sarcoidosis imaging and the myocarditis workup require specialist assessment; high-grade block is a high-risk criterion for myocarditis[3]. Conduction disorders in immune checkpoint inhibitor myocarditis are covered in Chapter 19, and those in sarcoidosis in Chapter 12. The epidemiologic context, tick exposure or a stay in a Chagas-endemic area, determines these two serologic investigations[3,7].

In primary care, unexplained conduction disease or sinus node dysfunction prompts laboratory testing for the extrinsic causes listed in the 2022 consensus: thyroid dysfunction, hyperkalemia or hypokalemia, hypocalcemia and medications[2]. When a reversible cause of bradycardia is clinically suspected, the 2021 European guideline adds digoxin measurement and pH (Class I, Level C)[6]. Lyme serology is requested after tick exposure, and the two Chagas serologic tests in people who have stayed in an endemic area[3]. Before age 60, unexplained Mobitz type II second-degree or third-degree block prompts investigation for cardiac sarcoidosis using magnetic resonance imaging or positron emission tomography[2]. In suspected myocarditis, high-grade block is a high-risk criterion, and hospitalization is recommended (Class I, Level C)[3].

18.4 Lyme carditis

In the Treatise: § 18.5 and § 13.8.14

Lyme carditis is an early manifestation of disseminated borreliosis. It presents mainly with varying degrees of atrioventricular block, complete in approximately 25% of cases, sometimes with myocarditis or pericarditis[3]. A PR interval above 300 ms is a marker of risk of progression to complete block and requires continuous electrocardiographic monitoring, as does syncope[3].

Serology is essential for the defined indication. The 2025 European guideline recommends it in high-grade block with suspected Lyme carditis[3]. The 2020 North American guideline recommends Lyme disease testing in acute myocarditis or pericarditis of unknown cause in an appropriate epidemiologic setting (strong recommendation, low-quality evidence)[7]. Serum antibodies are tested with validated assays following the conventional two-tier protocol: an enzyme immunoassay or immunofluorescence assay followed by immunoblots[7].

The limitations concern the indication. The same guideline suggests against routine Lyme disease testing in chronic cardiomyopathy of unknown cause (weak recommendation, low-quality evidence)[7]. In patients with Lyme borreliosis, it suggests performing an electrocardiogram only when there are signs or symptoms of carditis (weak recommendation, low-quality evidence)[7]. The 2019 French recommendations adopt the same two-tier strategy: a screening

enzyme-linked immunosorbent assay (ELISA), followed, if positive, by a confirmatory Western blot; they do not recommend serologic follow-up, since treatment success is judged on clinical grounds alone[8]. The 2025 French update is discussed in 20.2. Diagnosis has therapeutic consequences: the block is often transient and usually resolves within 1 to 2 weeks of antibiotic treatment; the European guideline concludes that a permanent pacemaker is not justified before treatment has begun[3].

In primary care, two-tier serology is ordered for unexplained acute myocarditis or pericarditis in a person exposed to ticks, and an electrocardiogram for any sign of carditis in a patient with borreliosis[7]. The urgent issue is electrical: marked PR prolongation beyond 300 ms or another severe cardiac complication requires hospitalization with continuous electrocardiographic monitoring (strong recommendation)[7]; the European guideline adds syncope[3]. In outpatients with carditis, the North American guideline suggests oral rather than intravenous antibiotics, for a total of 14 to 21 days[7]. The 2025 European guideline, however, makes intravenous ceftriaxone the first-line treatment for carditis with atrioventricular conduction disease, followed by oral treatment[3]. Recovery is judged clinically, not by repeat serology[8].

18.5 Congenital heart block and maternal anti-Ro/SSA antibodies

In the Treatise: § 8.9.1 and § 6.5.3

Neonatal lupus presents with skin, hematologic, hepatic or cardiac involvement; its cardiac manifestation is congenital atrioventricular block in a structurally normal heart, and more rarely endocardial fibroelastosis[5]. It is associated with maternal anti-SSA antibodies, Ro60 and/or Ro52, with or without anti-La/SSB (Sjögren syndrome antigen B)[5]. Unlike the other manifestations, the block is permanent, with mortality around 20%[5]. In the French registry, most mothers had no known disease[5].

Maternal anti-SSA status is established before pregnancy. The French National Diagnostic and Care Protocol (PNDS) for lupus places the risk of congenital block at 1% of pregnancies, generally between 16 and 26 weeks of gestation, and the recurrence risk after an affected child at 10 to 17%[9]. The Sjögren syndrome PNDS gives a frequency of 0.7 to 2% and a recurrence rate of 17 to 19%[5].

Surveillance uses echocardiography and is managed by the specialist team. In patients with Sjögren syndrome and anti-Ro/SSA antibodies, fetal heart rhythm surveillance is often proposed every 2 weeks between 16 and 26 weeks of gestation, or weekly after a prior affected pregnancy; some teams have reduced this schedule[5]. A review of 10 prospective studies covering 1,248 pregnancies in mothers with anti-SSA or anti-SSB antibodies identified 24 complete blocks (1.9%), including 3 after 24 weeks; its authors suggest continuing surveillance beyond that point, on the basis of published surveillance data they consider incomplete and inconsistent[10].

Laboratory findings also have a therapeutic consequence: hydroxychloroquine, started no later than 10 weeks of gestation, reduces recurrence risk in women who have already had an affected child; the Sjögren PNDS considers it reasonable to offer it to all these women[5]. Without a history of an affected child, it does not recommend starting it for this reason alone[5]. Pregnancy planning and monitoring of pregnancies in anti-SSA-positive women are covered in 5.2 and 20.8.

In primary care, anti-SSA antibodies in a woman with Sjögren syndrome confer a very low risk of fetal block, below 2%, warranting preconception consultation and follow-up in an obstetric unit experienced in autoimmune diseases[5]. In women with lupus, anti-SSA status is one of the four areas addressed in the preconception visit, alongside lupus itself, antiphospholipid antibodies and treatments[9]. At birth, the child of a mother with anti-SSA or anti-SSB antibodies has an electrocardiogram within the first three days of life and receives sun protection[5].

Table 18.1. The etiologic workup of an arrhythmia or conduction disorder, tier by tier

Situation	Essential	Depending on the context	Specialist assessment
Prolonged QT	Electrolytes; medication review; electrocardiogram before and during QT-prolonging drug treatment	Anti-Ro52, explicitly requested alongside anti-Ro60, for long QT without a sufficient acquired cause or with connective tissue disease	Evaluation of persistent long QT
Acquired block in adults	TSH, electrolytes	Digoxin level, calcium and pH if a reversible cause is suspected; Lyme serology; anti-Ro/SSA; two Chagas serologic tests based on exposure	Biopsy; sarcoidosis imaging
Suspected Lyme carditis	Two-tier serology	—	—
Pregnancy in an anti-SSA-positive mother	Anti-Ro60, anti-Ro52 and anti-SSB status before pregnancy	—	Fetal rhythm surveillance; hydroxychloroquine after a prior pregnancy affected by heart block

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PART V

Clinical Settings and Monitoring

19

Cancer, checkpoint inhibitors, CAR-T cells and hematologic disorders

Chapter contents

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Modern cancer treatments cause immune-mediated cardiac injury, while some inflammatory diseases can, conversely, progress to a hematologic disorder. In both directions, laboratory testing has a precise role: it screens before and during treatment, supports confirmation alongside imaging and recognizes when to refer to a hematologist.

19.1 Immune checkpoint inhibitor myocarditis

In the Treatise: § 17.1

Immune checkpoint inhibitor (ICI) myocarditis occurs early: in Mahmood's multicenter registry of 35 cases, the median interval was 34 days after the first administration, 81% of cases occurred within the first 3 months and 54% of patients had no other immune-related adverse event[1]. Combined anti-PD-1 (programmed cell death protein 1) and anti-CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) treatment was more frequent (34% of cases versus 2% of controls), as was diabetes (34% versus 13%)[1]. The 2022 European cardio-oncology guideline considers myocarditis suspected in any patient treated with an ICI within the preceding 12 weeks who develops new cardiac symptoms, an arrhythmia, heart block or a new troponin elevation[2].

Before the first dose, an electrocardiogram (ECG), natriuretic peptide measurement and troponin are recommended for all patients (Class I, Level B)[2]. During treatment, ECG and troponin should be considered before the second, third and fourth doses and then, if normal, every three doses until treatment ends (Class IIa, Level B)[2]. High-risk patients, receiving dual ICIs or a cardiotoxic combination, or with an extracardiac immune-related adverse event, cancer therapy-related cardiac dysfunction or cardiovascular disease, also undergo baseline echocardiography (Class I, Level B)[2]. If treatment continues beyond 12 months, these patients are assessed every 6 to 12 months (Class I, Level C): clinical examination, blood pressure, natriuretic peptides, lipid panel, glycated hemoglobin (HbA1c) and ECG[2].

Troponin, ECG and imaging, including echocardiography and cardiac magnetic resonance imaging (MRI), are recommended to establish the diagnosis (Class I, Level B)[2]. The international definition from the International Cardio-Oncology Society (IC-OS), adopted by the 2022 guideline, is histologic or clinical[2]. A clinical diagnosis requires troponin elevation that is new or significantly changed from baseline[2]. This is accompanied by one major criterion, diagnostic MRI according to the modified Lake Louise criteria, or two minor criteria: a suggestive clinical syndrome, ventricular arrhythmia or new conduction disease, a decline in left ventricular systolic function, another immune-related manifestation, particularly myositis, myopathy or myasthenia, or suggestive but nondiagnostic MRI[2]. Acute coronary syndrome and infectious myocarditis are excluded according to clinical suspicion[2]. Confirmation by MRI or biopsy is sought when possible, without delaying immunosuppression in symptomatic patients[2].

Troponin guides corticosteroid therapy: a decrease of more than 50% from the peak within 24 to 72 hours, together with resolution of ventricular dysfunction, heart block and arrhythmias, permits a switch to oral prednisolone at 1 mg/kg, up to a maximum of 80 mg daily[2]. Tapering, usually by 10 mg per week, is conducted with clinical, electrocardiographic and troponin monitoring, with reassessment of ventricular function and troponin at 20 mg daily[2]. A troponin rise during tapering prompts a return to a higher dose and a slower taper[3].

If troponin does not decrease by more than half, or if heart block, ventricular arrhythmias or dysfunction persist after 3 days of intravenous methylprednisolone and cardiac treatment, corticosteroid resistance is established and second-line immunosuppression should be considered[2]. The 2025 European myocarditis guideline assigns this Class IIa, Level C; up to half of patients are corticosteroid resistant[4].

In a single-center prospective cohort of 40 definite cases of ICI myocarditis, respiratory muscle involvement affected 27 of the 38 patients assessed, and 15 required ventilation[5]. Among the first 10 patients, treated according to guidelines, 6 died from myotoxicity[5]. The next 30 underwent repeated arterial blood gas testing for hypercapnia, early ventilation and, in severe cases, high-dose abatacept adjusted to monocyte CD86 receptor occupancy, most often combined with ruxolitinib; there was only one myotoxicity-related death (1/30), although 3-month all-cause mortality remained 23% (7/30), compared with 60% (6/10) in the first 10 patients[5]. The study was not randomized, and its authors consider these findings hypotheses requiring confirmation[5]; the 2025 European guideline cites it and lists abatacept among second-line treatments[4]. ICI rechallenge is decided by a multidisciplinary team according to myocarditis severity, cancer prognosis, oncologic options and patient preference[4]; if undertaken, monitoring includes repeated biomarkers and echocardiography[3].

Troponin T may be falsely elevated with associated myositis without myocarditis; either troponin can still be used, but a review recommends troponin I when ICI myocarditis is suspected[2,3]. In Mahmood's registry, troponin was elevated in 94% of patients at presentation, natriuretic peptides in 66%, and ejection fraction remained normal in 51%[1]. A discharge troponin T of at least 1.5 ng/mL, or 1,500 ng/L, measured with a fourth-generation assay in 86% of cases, was associated with a fourfold risk of major cardiovascular events, and 38% of those events occurred with a normal ejection fraction[1]: preserved ventricular function is not reassuring. In older patients, finding concomitant coronary disease does not end the search for myocarditis[4].

In primary care, the published testing schedule is followed: baseline assessment before the first dose, then ECG and troponin before doses 2, 3 and 4 and every three doses thereafter[2]. At any time, a new ECG abnormality, troponin elevation or new cardiac symptom requires prompt cardio-oncology evaluation, with echocardiography and, if myocarditis is suspected, MRI[2]. Diagnostic triage takes place within 24 hours (Class I, Level C)[4]. ICI treatment is withheld until the diagnosis is confirmed or excluded (Class I, Level C), and confirmed myocarditis requires hospitalization with continuous electrocardiographic monitoring[2]. Patients are taught to recognize warning symptoms[3]. After discharge, corticosteroids are tapered with ECG and troponin monitoring[2].

19.2 CAR-T cells and cytokine release syndrome

In the Treatise: § 17.2

Most cardiovascular toxicities described after chimeric antigen receptor T-cell (CAR-T) therapy are associated with cytokine release syndrome (CRS)[2]. It is suspected when fever occurs, with or without tachypnea, tachycardia, hypotension, hypoxia or other organ failure, within hours to days after infusion[2]. In Alvi's registry of 137 patients, CRS occurred in 59%, at a median of 5 days after infusion, and was grade 2 or higher in 39% of cases[6].

Before infusion, an ECG, natriuretic peptides and troponin are recommended for all patients (Class I, Level C)[2]. Baseline echocardiography is

recommended in preexisting cardiovascular disease (Class I, Level C)[2]. Once CRS reaches American Society for Transplantation and Cellular Therapy (ASTCT) grade 2, meaning fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal oxygen, natriuretic peptides, troponin and echocardiography are recommended (Class I, Level C)[2].

In Alvi's registry, troponin was elevated in 29 of the 53 patients tested and only in grade 2 or higher CRS[6]. All 17 cardiovascular events (12%) occurred after grade 2 or higher CRS, at a median of day 21, and 95% occurred after troponin elevation[6]. Each 12-hour delay in tocilizumab was associated with a 1.7-fold risk; this is an association observed in a registry, not proof of an effect of delay[6]. A 2024 meta-analysis combining 13 observational studies and 1,528 patients treated for advanced hematologic malignancy, lymphoma in 80%, found left ventricular dysfunction in 8.7%, supraventricular arrhythmia in 7.8% and cardiovascular death in 0.6% over a median follow-up of 487 days; most included studies were retrospective and single-center, without systematic baseline assessment or regular monitoring using echocardiography, biomarkers and ECG[7].

CRS grading is clinical: the ASTCT consensus deliberately excludes laboratory parameters, including C-reactive protein, from its definition and grading[8]. The same consensus notes that most moderate to severe CRS cases meet the laboratory criteria for hemophagocytic lymphohistiocytosis or macrophage activation syndrome[8]. The diagnostic evaluation must also exclude infection, heart failure, a drug reaction and pulmonary embolism[2].

In primary care, a cardiologist consulted before infusion provides baseline ECG, natriuretic peptides and troponin, plus echocardiography if cardiovascular disease is known[2]. In the days after infusion, fever accompanied by tachycardia, hypotension or hypoxia raises suspicion of CRS and calls for heightened vigilance, while infection, heart failure, a drug reaction and pulmonary embolism still need to be excluded[2]. Troponin elevation is common during CRS and signals an increased risk of cardiovascular events: it calls for early cardiac evaluation with natriuretic peptides, ECG and echocardiography[2].

19.3 Cancer survivors exposed to radiation or cardiotoxic treatment

In the Treatise: § 17.4

The cardiovascular toxicity of radiotherapy progresses slowly and typically becomes apparent 5 to 10 years after treatment; coronary disease and heart failure are up to six times more frequent than in the general population[2]. Among high-risk survivors, the guideline distinguishes early risk, within 5 years after treatment completion, from late risk[2]. Laboratory testing here supports overall cardiovascular risk assessment and screening for dysfunction.

For survivors treated with a potentially cardiotoxic drug or radiation to a volume exposing the heart, annual cardiovascular risk assessment with correction of risk factors is recommended (Class I, Level B)[2]. It includes clinical examination, blood pressure, a lipid panel, HbA1c, ECG and natriuretic peptides[2]. Risk is restratified 5 years after treatment completion to organize long-term follow-up (Class I, Level C)[2].

For survivors at high late risk, such as young adults treated for Hodgkin lymphoma or sarcoma with a high cumulative anthracycline dose, or patients receiving high-dose radiation to a field including the heart, clinical examination, ECG and natriuretic peptides are recommended annually from the

fifth year if the end-of-treatment assessment at 12 months was normal[2]. For moderate-risk survivors with a normal end-of-treatment assessment, clinical examination, ECG, echocardiography and natriuretic peptides should be considered every 5 years[2].

The schedule does not extend to all treatments: the effects of trastuzumab and other targeted therapies beyond 10 years are unknown, and lifelong surveillance is not recommended for these survivors without another indication[2]. Radiation risk is preferably classified by mean heart dose, since the prescribed dose may poorly reflect cardiac exposure[2].

In primary care, annual follow-up may be performed by the primary care physician or a cardiologist with expertise in risk factors[2]. The laboratory tests can be ordered in primary care: lipid panel, HbA1c and natriuretic peptides, alongside ECG[2]. Any new cardiovascular symptom prompts referral to cardio-oncology or, if unavailable, to a cardiologist experienced in patients with cancer[2]. Echocardiography follows the risk level: at years 1, 3 and 5, then every 5 years in survivors at very high or high early risk, and every 5 years from the fifth year after radiation in those at high late risk (Class IIa, Level C)[2]. In women treated during childhood or adolescence, cardiovascular assessment including fasting glucose, HbA1c, a lipid panel, ECG and echocardiography is recommended before pregnancy or in the first trimester (Class I, Level C)[2].

19.4 Monoclonal IgM gammopathy and Waldenström macroglobulinemia

In the Treatise: § 10.4

Schnitzler syndrome carries a risk of AA amyloidosis (amyloid A protein) and progression to a lymphoid hematologic malignancy, particularly Waldenström macroglobulinemia (Treatise, § 10.4). The same question arises with any monoclonal immunoglobulin M (IgM).

The diagnosis of Waldenström macroglobulinemia requires, according to the second International Workshop on Waldenström's Macroglobulinemia (IWWM-2) consensus recalled by the European consortium, bone marrow infiltration by clonal lymphoplasmacytic cells demonstrated on a core bone marrow biopsy and a serum monoclonal IgM, regardless of its level[9]. The 2016 World Health Organization (WHO) classification defines IgM monoclonal gammopathy of undetermined significance by IgM below 30 g/L, marrow infiltration below 10% and no organ involvement[9]. The eleventh workshop consensus panel (IWWM-11) reaffirmed in 2023 that no arbitrary IgM level or infiltration threshold should distinguish the two entities[10]. For this panel, morphologic marrow infiltration by lymphoplasmacytic lymphoma is sufficient for diagnosis even when it represents less than 10% of cellularity[10]. B-cell clonality detected only by flow cytometry or molecular testing is not sufficient, and monoclonal IgM must be visible on serum protein electrophoresis; positive immunofixation alone is insufficient[10]. Bone marrow biopsy therefore remains necessary to distinguish Waldenström macroglobulinemia, IgM monoclonal gammopathy of undetermined significance and other B-cell lymphoproliferative disorders[9].

In asymptomatic people with monoclonal IgM below 15 g/L and a normal free light chain ratio, the risk of progression is very low and bone marrow biopsy is generally not recommended outside a trial and in the absence of IgM-related symptoms[9]. The MYD88 L265P mutation, present in more than 90% of Waldenström macroglobulinemia cases, helps distinguish it from other IgM-associated hematologic disorders[9].

Monoclonal IgM does not establish Waldenström macroglobulinemia, and a low level does not exclude it: marrow infiltration, IgM level and symptoms do not correlate, and disease with limited plasma cell differentiation may secrete little IgM[9]. In the presence of cardiac, renal or neurologic signs, amyloid deposits should be specifically sought on biopsy[9].

In primary care, the monoclonal component level and serum free light chain ratio provide initial triage for monoclonal IgM: in asymptomatic people, IgM below 15 g/L with a normal ratio indicates very low risk, generally without bone marrow biopsy[9]. In contrast, systemic symptoms (fever, night sweats and weight loss), anemia, bleeding or thrombocytopenia, signs of hyperviscosity (epistaxis, headache, blurred vision, dizziness and tinnitus) and any IgM-attributable manifestation without overt lymphoma warrant marrow assessment and therefore hematology referral[9]. Cardiac, renal or neurologic signs prompt a search for amyloidosis on biopsy[9]. The 15 g/L threshold is not reassuring on its own, since the IgM level does not reflect infiltration[9].

19.5 Cytopenias, myelodysplasia, leukemia and lymphoma

In the Treatise: § 12.9 and § 12.5

In relapsing polychondritis, associated myelodysplastic syndrome is, together with cardiac involvement and male sex, among the factors independently associated with death (Treatise, § 12.9). The 2021 French National Diagnostic and Care Protocol (PNDS) describes this association particularly in men whose disease begins after age 50 and includes it among manifestations that worsen prognosis[11]. Unexplained cytopenia in such a patient therefore calls for hematology consultation, without making marrow assessment routine in every case of polychondritis. Polychondritis in an older man with cytopenias also raises the possibility of VEXAS syndrome, an acronym for vacuoles, E1 enzyme, X-linked, autoinflammatory and somatic (Treatise, § 12.9; see 11.5).

The diagnosis of myelodysplastic syndrome rests on a complete blood count with differential, blood smear, marrow aspirate and core bone marrow biopsy, with cytogenetic analysis[12]. In acute myeloid leukemia, flow cytometry establishes the lineage, and conventional karyotyping remains mandatory[13]. Since the fifth edition of the WHO classification in 2022, the 20% blast threshold in blood or marrow no longer applies to acute myeloid leukemias with a defining genetic abnormality, except for BCR::ABL1 fusion or CEBPA mutation; it remains required for other forms, and removal of the threshold requires correlation of the genetic abnormality with morphology[14]. These investigations are performed by the hematologist.

In suspected non-Hodgkin lymphoma, excisional biopsy is the first procedure to consider; core needle biopsy is used only when surgical risk outweighs the benefit[15]. In high-grade B-cell lymphoma, testing for a MYC rearrangement by fluorescence in situ hybridization should be considered[15]. Previously treated lymphoma or leukemia should not be confused with a hematologic disorder awaiting diagnosis: prior treatments, radiation and cellular therapies have their own cardiac consequences (see 19.2 and 19.3).

In primary care, the complete blood count is part of the initial workup and laboratory monitoring of patients with polychondritis and is examined for evidence of myelodysplasia[11]. A persistent abnormality in a blood cell lineage, including isolated macrocytosis, prompts consideration of marrow aspiration with cytogenetic analysis[11]. In men over 50, atypical or treatment-resistant polychondritis with fever, neutrophilic dermatosis, pulmonary infiltrates, macrocytic anemia, myelodysplasia, chronic myelomonocytic leukemia

or monoclonal gammopathy prompts investigation for VEXAS syndrome[11]. UBA1 mutation testing is performed on whole blood or marrow; vacuoles in marrow precursors are suggestive, but their absence or scarcity does not exclude the diagnosis when suspicion is high, and only sequencing confirms it (see 11.5)[16]. Polychondritis associated with myelodysplastic syndrome, like VEXAS syndrome, requires specialist management with a team experienced in myelodysplasia; the treating physician provides local follow-up[11].

Table 19.1. The workup during cancer treatment and for a hematologic disorder, situation by situation

Situation	Essential	Frequency or timing
Checkpoint inhibitor	ECG, natriuretic peptides, troponin; echocardiography if high risk[2]	Before the first dose, then ECG and troponin before doses 2, 3 and 4 and every three doses thereafter[2]
ICI beyond 12 months, high risk	Examination, blood pressure, natriuretic peptides, lipid panel, HbA1c, ECG[2]	Every 6 to 12 months[2]
ICI myocarditis during corticosteroid therapy	Troponin, ECG[2]	Consider an oral switch after clinical improvement, with a troponin decrease of more than 50% from the peak within 24 to 72 hours and resolution of ventricular dysfunction, heart block and arrhythmias; during tapering; reassessment at 20 mg daily[2]
CAR-T cells	ECG, natriuretic peptides, troponin; echocardiography if cardiovascular disease[2]	Before infusion; repeated once CRS reaches grade 2, with echocardiography[2]
Exposed survivor (cardiotoxic drug or cardiac irradiation)	Lipid panel, HbA1c, ECG, natriuretic peptides[2]	Annually; restratification at 5 years[2]
Monoclonal IgM	IgM level, free light chain ratio; core bone marrow biopsy if symptomatic or Waldenström macroglobulinemia is suspected[9]	Hematology consultation
Polychondritis	Complete blood count; marrow aspirate with cytogenetics if a persistent blood cell lineage abnormality is present[11]	At each follow-up assessment[11]

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20

Infections, pregnancy and transplantation

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Three contexts change the interpretation of an immunologic workup: infection, which may mimic or trigger autoimmune disease; pregnancy, which has its own pitfalls; and transplantation, where immunity is measured before it is treated. In each, laboratory testing has specified thresholds and schedules, as well as limitations that must be understood.

20.1 Acute rheumatic fever

In the Treatise: § 18.2 and § 12.4

Acute rheumatic fever is considered when arthritis, carditis, chorea, erythema marginatum or subcutaneous nodules follow pharyngitis in a child or young adult, particularly from an at-risk population. The Jones criteria revised in 2015 adjust thresholds according to that risk[1]. Evidence of recent group A streptococcal infection is required whenever obtainable; without it, the diagnosis remains uncertain[1]. It rests on one of three findings: an elevated or rising antistreptolysin O titer, or another antistreptococcal antibody such as anti-deoxyribonuclease B (anti-DNase B); a positive throat culture; or a positive rapid antigen test in a child whose presentation makes streptococcal pharyngitis highly likely (Class I, Level B for each)[1]. A rising titer provides stronger evidence than a single measurement[1].

Erythrocyte sedimentation rate (ESR) is a minor criterion from 60 mm in the first hour in a low-risk population and 30 mm in the first hour in a moderate- or high-risk population; the highest observed value is used because ESR changes during the illness[1]. The C-reactive protein (CRP) threshold does not vary: 3.0 mg/dL, or 30 mg/L, and the value must exceed the laboratory's upper limit of normal[1]. Normal ESR and CRP should prompt serious reconsideration of the diagnosis because they are almost never normal in acute rheumatic fever, except in isolated chorea[1]. Where streptococcal skin or pharyngeal infections are endemic, negative serology helps exclude recent infection, but positive serology does not date the infection[1]. Chorea, which may be the sole manifestation, and insidiously developing chronic carditis do not require this evidence, which their long latency often makes impossible to obtain[1].

In primary care, suspected disease prompts testing for antistreptolysin O and anti-DNase B, ESR and CRP; a rising titer on repeat testing provides stronger evidence than a single value[1]. Doppler echocardiography is recommended in all confirmed or suspected cases (Class I, Level B), including in the absence of a murmur, to detect subclinical carditis (Class I, Level B); a murmur without a compatible echocardiographic abnormality excludes carditis (Class I, Level B)[1]. Repeating echocardiography is reasonable even if carditis is absent at diagnosis (Class IIa, Level C)[1]. When uncertainty persists, 12 months of secondary prophylaxis followed by clinical and echocardiographic reassessment is reasonable (Class IIa, Level C)[1]. In patients with prior rheumatic fever, a recurrence based solely on minor criteria is accepted only after other causes have been excluded (Class I, Level C)[1].

20.2 Lyme carditis

In the Treatise: § 18.5

Lyme carditis is considered in atrioventricular block (AV block), often fluctuating, in a young person exposed to ticks, particularly in summer and fall; carditis occurs on average 21 days after infection, and only about 40% of patients recall erythema migrans[2]. The French guideline updated in 2025 calls for Lyme serology and cardiology consultation in first- to third-degree AV block without

predisposing heart disease in a person exposed to ticks within the preceding 6 months (expert agreement)[3]. Serology is performed in two tiers: an enzyme-linked immunosorbent assay (ELISA), followed, if positive or equivocal, by confirmatory immunoblotting, or Western blot (Grade A)[3]. The 2020 North American guideline recommends Lyme disease testing in acute myocarditis or pericarditis of unknown cause in a compatible epidemiologic setting (strong recommendation, low-quality evidence)[2].

In the North American guideline, an electrocardiogram (ECG) is indicated only in the presence of signs or symptoms suggestive of carditis (weak recommendation)[2]; the French guideline requests it for every patient with cardiac symptoms, supplemented by Holter monitoring if necessary (expert agreement)[3]. Elevated biomarkers such as troponin are among the manifestations that influence hospitalization decisions, alongside a PR interval above 300 ms[2]. Isolated immunoglobulin M (IgM) should be interpreted cautiously: cross-reactions are common, particularly with rheumatoid factors and antinuclear antibodies, and isolated IgM beyond 6 weeks of symptoms is considered a false positive (Grade B)[3]. Rare cases of seronegative active disease have been reported during anti-CD20 treatment[3]. Routine Lyme disease testing is discouraged in chronic cardiomyopathy of unknown cause (weak recommendation)[2]. Acute carditis usually resolves with antibiotics[2]; heart block in a young person has other causes, including sarcoidosis (Treatise, § 18.5.1).

In primary care, conduction disease in an exposed person prompts two-tier serology and an ECG; if immunoglobulin G (IgG) is negative while symptoms have been present for less than 6 weeks, serology is repeated 3 weeks later (Grade B)[3]. Only first-degree AV block with a PR interval below 300 ms is managed on an outpatient basis, with doxycycline for 21 days (expert agreement)[3]. Syncope or second- or third-degree AV block requires hospitalization with telemetry, as does a PR interval above 300 ms (Grade A), in a hospital able to provide temporary cardiac pacing (expert agreement)[3]. Cardiology consultation is essential for any cardiac involvement (expert agreement), and joint cardiology and infectious disease follow-up continues until recovery is confirmed over time (expert agreement)[3].

20.3 Chagas disease

In the Treatise: § 18.4

Chagas disease is considered in conduction disease, ventricular arrhythmia, an apical aneurysm or heart failure in someone born in or who has lived in Latin America; cardiac involvement develops decades after infection (Treatise, § 18.4). In the chronic phase, diagnosis is serologic[4]. No single test is sufficiently sensitive and specific: at least two tests detecting antibodies against different antigens are needed; common methods are enzyme immunoassay and indirect immunofluorescence[4]. The 2023 Brazilian guideline likewise requires two serologic tests based on different principles to confirm chronic infection[5].

In the acute phase, diagnosis rests on microscopic identification of the parasite in blood[4]. In the chronic phase, parasitemia becomes undetectable by most methods[4]. Reactivation during immunosuppression is demonstrated by the parasite in blood, through direct examination or quantitative polymerase chain reaction (PCR), or in a biopsy; serology is not useful here, and seroreversion has been reported in transplant recipients[5]. Blood donation screening assays are not diagnostic tests[4]. Chagas cardiomyopathy may mimic isolated cardiac sarcoidosis; the exposure history provides the clue (Treatise, § 18.4.1).

In primary care, infected people without cardiac or gastrointestinal symptoms and with a normal examination and ECG need no further testing; the history, examination and ECG are repeated annually or every 2 years (strong recommendation, Level B)[5]. In autoimmune diseases, experience is limited and consists mainly of lupus case reports: before immunosuppressive-dose corticosteroids, the Brazilian guideline does not endorse preventive benznidazole treatment and favors monitoring for reactivation, which is treated if it occurs[5]. In an infected transplant recipient, unexplained fever, skin involvement, myocarditis or encephalitis prompts a search for reactivation[5].

20.4 HIV infection

In the Treatise: § 18.6

Human immunodeficiency virus (HIV) infection is accompanied by excess myocardial infarction, heart failure and pulmonary hypertension, even during effective treatment (Treatise, § 18.6). It also enters the differential diagnosis of autoimmune diseases: the French National Diagnostic and Care Protocol (PNDS) for lupus calls for HIV, hepatitis C virus and parvovirus B19 testing to exclude viral infection mimicking lupus[6].

In pulmonary arterial hypertension, the 2022 European guideline requests biochemistry, hematology, an immunologic assessment, HIV serology and thyroid tests for all patients to identify associated conditions[7]. HIV serology is part of the workup before an immunosuppressant or biologic therapy (see 21.1)[6]. In symptomatic patients with HIV, echocardiography, B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), pulmonary function tests or exercise testing should be considered to screen for pulmonary arterial hypertension (Class IIa, Level B)[7]. Because of its low prevalence, asymptomatic patients should not be screened[7].

Atherosclerotic risk is assessed through a lipid panel, recommended for every person living with HIV: at entry into care or initiation of antiretroviral therapy, 3 to 6 months later once viral load is controlled, then annually after age 40 or during statin therapy, and every 1 to 3 years before age 40 without a statin[8]. Between ages 40 and 75, 10-year risk is calculated at least annually using the US Pooled Cohort Equations, which underestimate risk in people living with HIV, particularly women[8]. In the SMART trial (Strategies for Management of Antiretroviral Therapy), interleukin-6 and D-dimer were strongly associated with mortality, and interrupting antiretroviral therapy increased them[9]. In a REPRIEVE trial substudy involving people living with HIV on antiretroviral therapy and at low or moderate cardiovascular risk, 24 months of pitavastatin reduced noncalcified coronary plaque volume and progression (relative risk 0.67), as well as two markers of lipid oxidation and arterial inflammation: oxidized low-density lipoproteins (29% reduction versus 13% with placebo) and lipoprotein-associated phospholipase A2 (7% reduction versus a 14% increase); high-sensitivity CRP did not decline significantly, nor did immune activation markers, including interleukin-6[10]. The 2025 US guideline nevertheless considers the evidence insufficient to stratify risk using inflammatory biomarkers[8].

In primary care, HIV serology is ordered for a lupus-like presentation to exclude a viral mimic, and before any immunosuppressive-dose corticosteroid, immunosuppressant or biologic therapy, alongside hepatitis B and C serology and a chest radiograph[6]. It forms part of every pulmonary arterial hypertension workup[7]. In people living with HIV, echocardiography and BNP or NT-proBNP are requested for symptoms, not as routine screening[7].

Diagnosing HIV-associated pulmonary arterial hypertension requires right heart catheterization, which also excludes left heart disease[7].

20.5 Tuberculosis

In the Treatise: § 7.2.6 and § 5.4.2

Tuberculosis is investigated before any immunosuppressant or biologic therapy and whenever mycobacterial infection enters the differential diagnosis. A positive interferon-gamma release assay (IGRA) or tuberculin skin test most often indicates tuberculosis infection; further investigations, including a chest radiograph, are necessary to rule out active tuberculosis[11]. Latent infection is diagnosed after a positive test when medical evaluation shows no active tuberculosis; the chest radiograph helps distinguish latent infection from pulmonary tuberculosis[11].

Before biologic or targeted therapy, the 2022 European recommendation calls for screening; it also considers screening an option before conventional disease-modifying drugs, glucocorticoids and immunosuppressants, and prefers IGRA to the tuberculin skin test when available[12]. In cardiac sarcoidosis, the 2024 US statement calls for latent tuberculosis to be excluded before oral corticosteroids, methotrexate and biologic therapies (Treatise, § 7.2.6). A negative test does not exclude active tuberculosis[11]. A positive *Mycobacterium tuberculosis* culture confirms the disease, but a negative culture or direct examination does not exclude it[11].

In primary care, pretreatment screening combines an IGRA, preferred in people vaccinated with bacillus Calmette-Guérin (BCG)[11], and a chest radiograph[6]. The tuberculin skin test remains an alternative when IGRA is unavailable, too costly or too burdensome[11]. A positive test requires active tuberculosis to be excluded by clinical assessment and radiography before concluding that infection is latent[11]. If signs of active tuberculosis are present, other diagnostic investigations are initiated without waiting for the IGRA result[11]. Screening takes place before treatment begins: it belongs to the core workup for any immunosuppressant (see 21.1)[6].

20.6 *Tropheryma whipplei* endocarditis and syphilis

In the Treatise: § 18.5 and § 9.5.2

Whipple disease is investigated in blood culture-negative endocarditis, which accounts for approximately 10% of endocarditis cases in industrialized countries[13]. Syphilis is excluded in a presentation suggestive of Cogan syndrome, which remains a diagnosis of exclusion (Treatise, § 9.5.2); it is also among the uncommon causes of aortic aneurysm (Treatise, § 9.2.8). In blood culture-negative endocarditis, the 2023 European guideline proposes serology according to local epidemiology, including *Coxiella burnetii* and *Bartonella*, followed by specific *Tropheryma whipplei* PCR on blood and tissue[14]. Since 2023, a positive blood PCR for *T. whipplei* is a major microbiologic criterion for endocarditis, as it is for *C. burnetii* and *Bartonella*[13]. Identifying the organism on a vegetation or cardiac tissue in the setting of active endocarditis is a pathologic criterion for definite endocarditis[13]. When all microbiologic tests remain negative, nonbacterial endocarditis is systematically considered: antinuclear antibodies, IgG anticardiolipin antibodies and IgG and IgM anti-β2-glycoprotein I antibodies are tested, although these antibodies may also occur in proven infective endocarditis[14].

For syphilis, presumptive diagnosis rests on two serologic tests: a nontreponemal and a treponemal test; one test type alone is insufficient[15]. A nontreponemal test may be falsely positive in other infections, including HIV, in autoimmune diseases, after vaccination, in people who inject drugs, during pregnancy and with aging[15]. Most treponemal tests remain positive for life, even after treatment[15]. In lupus, false-positive syphilis serology is included among antiphospholipid markers in classification criteria[6]; an isolated positive nontreponemal test is therefore insufficient to diagnose syphilis.

In primary care, the order of procedures matters. At least three blood culture sets, 10 mL each, are collected at 30-minute intervals from a peripheral vein before any antibiotic[14]. Prior antibiotic therapy is the most common cause of negative blood cultures[14]. If cultures remain negative at 48 hours while endocarditis is still suspected, microbiology consultation is necessary[14]. In patients with lupus or antiphospholipid antibodies, a positive syphilis serology result is interpreted using both treponemal and nontreponemal tests; a diagnosis is never based on a single type of test[6, 15].

20.7 Preeclampsia

In the Treatise: § 8.9

Preeclampsia is considered with any hypertension discovered during pregnancy, particularly in women with lupus or antiphospholipid syndrome, which the 2025 European guideline lists as high-risk factors for preeclampsia[16]. In systemic sclerosis, new-onset hypertension raises the question of preeclampsia or scleroderma renal crisis (see 20.8). The 2025 European guideline includes urinalysis, complete blood count, hematocrit, liver enzymes, creatinine and uric acid for monitoring hypertensive disorders of pregnancy[16]. The 2019 UK guideline, updated in 2023, calls for a complete blood count (CBC), liver function and renal function at diagnosis of gestational hypertension, then weekly, whether or not hypertension is severe[17]. In preeclampsia, these tests are performed twice weekly, or three times weekly with severe hypertension[17]. Proteinuria is screened with a dipstick, read by an automated device in hospital; a positive dipstick (1+ or more) is quantified[17].

The urine protein-to-creatinine ratio is significant from 30 mg/mmol; the albumin-to-creatinine ratio is an alternative, with a threshold of 8 mg/mmol[17]. A placental growth factor (PlGF)-based test is performed once per episode of suspected preterm preeclampsia, between 20 weeks and 36 weeks and 6 days of gestation[17, 18]. A ratio of soluble fms-like tyrosine kinase 1 (sFlt-1), the soluble form of vascular endothelial growth factor receptor 1, to PlGF below 38 reliably rules out preeclampsia within 7 days in women with suspected disease[16]. After preeclampsia with mild or moderate hypertension, platelets, transaminases and creatinine are checked 48 to 72 hours after birth and repeated only if abnormal, until normalization[17]. A urine dipstick is performed 6 to 8 weeks after birth[17]. Proteinuria is always interpreted as part of a comprehensive clinical assessment[17].

In primary care, a systolic blood pressure of at least 160 mmHg or a diastolic blood pressure of at least 110 mmHg in a pregnant woman is an emergency requiring hospital treatment (Class I, Level C)[16]. Gestational hypertension is assessed from the outset in a specialist setting by a professional trained in hypertensive disorders of pregnancy[17]. In preeclampsia, new and persistent laboratory abnormalities, including creatinine of at least 90 µmol/L, alanine aminotransferase (ALT) above 70 IU/L or twice the upper limit of normal, or platelets below 150,000/µL, prompt consideration of hospitalization[17].

After birth, the woman is reviewed by her physician or a specialist 6 to 8 weeks later; proteinuria still at 1+ or more then warrants renal function testing at 3 months, and an abnormality at 3 months prompts consideration of nephrology consultation[17].

20.8 Pregnancy in lupus, antiphospholipid syndrome and systemic sclerosis

In the Treatise: § 8.9 and § 8.5

Every pregnancy in a woman with lupus is planned through a preconception consultation[6]. Antiphospholipid antibodies, isolated or as part of antiphospholipid syndrome, substantially increase obstetric risk, and anti-SSA or anti-SSB antibodies (Sjögren syndrome antigens A and B) confer a risk of neonatal lupus[6]. Antiphospholipid antibodies should be sought in every patient with lupus[6]. Anti-SSA and anti-SSB status is established before pregnancy: congenital atrioventricular block occurs in 1% of children of antibody-positive mothers, generally between 16 and 26 weeks of gestation, and recurs in 10 to 17% after a first affected child[6]. During pregnancy, monitoring is monthly: creatinine, proteinuria, complement, anti-double-stranded DNA, transaminases, platelets, hemoglobin (and, if needed, lactate dehydrogenase and haptoglobin), glucose, and toxoplasmosis and rubella serology if previously negative[6].

The sFlt-1/PlGF ratio may be assessed in patients with a high-risk pregnancy profile[6]. In systemic sclerosis, the preconception workup includes anti-topoisomerase I, anti-RNA polymerase III, anti-SSA, anti-SSB and antiphospholipid antibodies if not already tested; during pregnancy, creatinine, proteinuria, transaminases, gamma-glutamyl transferase, platelets, hemoglobin and glucose are monitored periodically, with a monthly urine dipstick[19]. Complement rises physiologically during pregnancy, complicating interpretation[6]. Obstetric risk is strongly correlated with lupus anticoagulant positivity[6]. Routine platelet monitoring during low-molecular-weight heparin treatment is no longer recommended[6]. In systemic sclerosis, renal crisis and preeclampsia can be difficult to distinguish; the absence of liver enzyme elevation and rapidly worsening renal failure point toward renal crisis, in which plasma renin is very high[19].

In primary care, pregnancy in lupus is planned: effective contraception is discussed from the first visit and is essential during teratogenic treatment with mycophenolate, cyclophosphamide, methotrexate or thalidomide[6]. Mycophenolate is stopped at least 6 weeks before conception, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are replaced from the preconception consultation[6]. A recent flare, corticosteroid dependence above 10 mg daily, a glomerular filtration rate below 40 mL/min/1.73 m^2, severe hypertension, poorly controlled pulmonary hypertension or poorly tolerated valvular disease prompts postponement of pregnancy[6]. Any monitoring abnormality should lead promptly to multidisciplinary discussion, most often at a specialist center[6]. In women with systemic sclerosis, renal crisis is treated urgently with an angiotensin-converting enzyme inhibitor, regardless of gestational age[19].

20.9 Heart transplantation

In the Treatise: § 21.2, § 21.3, § 21.4, § 21.5 and § 21.6

Before listing, every candidate undergoes immunologic evaluation because transfusions, pregnancies, homografts, prior transplantation and ventricular assist devices may have caused sensitization (Treatise, § 21.2). Before transplantation, screening for antibodies against human leukocyte antigens (HLA), expressed as a panel percentage (PRA, panel reactive antibodies), is performed in every candidate, and further evaluation is recommended from 10% (Class I, Level C)[20]. Calculated PRA, based on the recipient's antibody specificities and the frequency of antigens in the population, is determined and reported to assist matching (Class I, Level C); above 10%, a prospective or virtual crossmatch is performed (Class I, Level C)[20]. Specificities are determined using solid-phase assays; in the absence of an international standard, each center sets its threshold, with a mean fluorescence intensity below 5,000 generally considered acceptable (Class I, Level C)[20]. This intensity measures antibody binding to the bead, not its titer; useful values are therefore laboratory-specific[20]. Endogenous molecules can mask anti-HLA antibodies: this is the prozone effect, overcome by dilution, heat inactivation or addition of dithiothreitol or ethylenediaminetetraacetic acid (EDTA)[20]. Anti-HLA screening may be repeated every 6 months in nonsensitized outpatients (Class IIb, Level C); according to the consensus cited in the guideline, it is performed every 3 months in sensitized candidates or those receiving circulatory support[20]. After transfusion, it is repeated 1 to 2 weeks later (Class IIb, Level C)[20].

After transplantation, routine surveillance for antibody-mediated rejection is recommended, with particular attention to de novo donor-specific antibodies, which are associated with reduced survival[20]. Measuring them is reasonable when antibody-mediated rejection is suspected or biopsy-proven (Class IIa, Level C)[20]. The 2011 working group aligned staining of surveillance biopsies with each center's donor-specific antibody testing schedule, for example at 1, 3, 6 and 12 months, and advised against C4d staining in the first 2 weeks except in highly sensitized patients[21]. In pediatric ABO-incompatible transplantation, isohemagglutinins must be measured and negative before aortic cross-clamp removal (Class I, Level C)[20].

Donor-derived cell-free DNA rises during rejection. At a threshold of 0.2%, sensitivity was 44% and negative predictive value 97%[22]; at 0.25%, another cohort found a negative predictive value of 99%[23]. These values depend on the population studied and do not replace biopsy when suspicion is high (Treatise, § 21.6.1). The 2024 European Society for Organ Transplantation (ESOT) consensus accepts its use beyond 4 weeks after transplantation to rule out clinical or subclinical rejection, as a weak recommendation based on low-level evidence; the assay does not distinguish antibody-mediated from cellular rejection, and the data come from centralized laboratories[24]. The same document considers the evidence insufficient to diagnose rejection using troponin or natriuretic peptides[24].

After heart transplantation, pregnancy is deferred for at least one year, according to individual risk factors (Class I, Level C)[16]. Blood immunosuppressant levels are measured every 4 weeks until 32 weeks, every 2 weeks until 36 weeks, then weekly until delivery and for 6 to 12 months afterward (Class I, Level C)[16]. Donor-specific antibodies are measured weekly for at least 6 to 12 months after delivery (Class I, Level C), and paternal HLA typing should be considered before conception (Class IIa, Level C)[16].

In primary care, a calcineurin inhibitor trough level is sampled just before the dose: 12 hours after the last dose for cyclosporine and twice-daily tacrolimus, and 24 hours for once-daily tacrolimus (Class IIa, Level C)[20]. Adding or withdrawing a drug that interacts with cytochrome P450 or P-glycoprotein requires close level monitoring and dose adjustment to avoid toxicity or rejection[20]. Everolimus and sirolimus are measured at least 5 days after any dose change (Class IIa, Level B)[20]. In transplant recipients planning pregnancy, mycophenolate is not recommended during pregnancy and must be stopped 6 weeks before conception (Class III, Level C); the woman is counseled beforehand about the risks of rejection, infection, graft dysfunction and teratogenicity[16].

20.10 Graft-versus-host disease

In the Treatise: § 21.8

Cardiac involvement in graft-versus-host disease is considered in heart failure, bradycardia or recurrent serosal effusions after allogeneic hematopoietic stem cell transplantation. Cardiac involvement is rare, and post-transplant cardiotoxicity is usually nonimmune (Treatise, § 21.8). Diagnosing chronic graft-versus-host disease requires at least one diagnostic manifestation or a distinctive manifestation supported by biopsy, laboratory examination or another test[25]. Serositis, cardiac involvement, myasthenia and nephrotic syndrome have been attributed to it, but they are rare and attribution is often a diagnosis of exclusion[25].

Hematologic and immune abnormalities are common but cannot establish the diagnosis[25]. Lymphopenia (≤ 500/μL), eosinophilia (≥ 500/μL) and hypogammaglobulinemia or hypergammaglobulinemia may be present; autoantibodies may appear with autoimmune hemolytic anemia or thrombocytopenia[25]. The 2014 consensus emphasizes the lack of diagnostic and activity biomarkers[25]. Drugs, infection, relapse or a new malignancy must always be excluded[25]. Cardiac attribution is difficult: it must be distinguished from nonimmune transplant cardiotoxicity, and cytomegalovirus complicates interpretation (Treatise, § 21.8). Thrombocytopenia below 100,000/μL at diagnosis is among the factors associated with higher transplant-related mortality[25].

In primary care, the 2014 consensus organ score was designed for use by physicians and nurses outside transplant services; the only laboratory testing it requires is liver tests[25]. A rapid rise in transaminases, almost always after immunosuppression tapering or donor lymphocyte infusion, calls for prompt diagnosis and treatment, with liver biopsy if needed[25]. Myositis is investigated with creatine kinase or aldolase measurement[25]. Screening pulmonary function tests are performed at 100 days after transplantation, at diagnosis of chronic graft-versus-host disease, at 1 year after transplantation, then every 6 months for the 2 years after that diagnosis[25].

Table 20.1. The workup of infections, pregnancy and transplantation, situation by situation

Situation	Key test	Threshold or frequency
Acute rheumatic fever	Antistreptolysin O or anti-DNase B, culture or rapid test; ESR, CRP; echocardiography[1]	CRP ≥ 3.0 mg/dL; ESR ≥ 60 or ≥ 30 mm according to risk[1]
Lyme carditis	ELISA then Western blot serology; ECG[3]	Hospitalization for syncope, second- or third-degree AV block or PR interval > 300 ms[3]
Chronic Chagas disease	Two serologic tests using different antigens[4]	Without organ involvement: ECG every 1 to 2 years[5]
Person living with HIV	Lipid panel; 10-year risk using Pooled Cohort Equations between ages 40 and 75[8]	At entry into care, 3 to 6 months after antiretroviral initiation, then annually after age 40 or during statin therapy, every 1 to 3 years otherwise[8]
Before an immunosuppressant	IGRA[11]; chest radiograph; HIV and hepatitis B and C serology[6]	Before initiation[6]
Blood culture-negative endocarditis	Serology, then *T. whipplei* PCR; if all negative, antinuclear and antiphospholipid antibodies[14]	Three blood culture sets before any antibiotic[14]
Syphilis	Treponemal and nontreponemal tests[15]	At diagnosis
Gestational hypertension	CBC, liver tests, renal function[17]	At diagnosis, then weekly[17]
Preeclampsia	CBC, liver tests, renal function[17]	Twice weekly; three times with severe hypertension[17]
Pregnancy in lupus	Creatinine, proteinuria, complement, anti-double-stranded DNA, transaminases, platelets, hemoglobin, glucose[6]	Monthly[6]
Heart transplant candidate	Anti-HLA antibodies, calculated PRA; crossmatch if PRA > 10%[20]	Every 6 months; every 3 months if sensitized or receiving support; 1 to 2 weeks after transfusion[20]
Pregnancy after transplantation	Immunosuppressant levels; donor-specific antibodies[16]	Every 4 weeks, then every 2 weeks, then weekly; antibodies weekly for 6 to 12 months after delivery[16]

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21

Before and during treatment: pretreatment workup, monitoring and schedules

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An immunosuppressant is prescribed on the basis of a workup and monitored according to a schedule. National protocols, European recommendations and each drug's Summary of Product Characteristics (SmPC) provide both, with schedules that do not always agree and limitations that must be read alongside them.

21.1 The common pretreatment assessment

In the Treatise: § 15.13

Before immunosuppressive-dose corticosteroids, an immunosuppressant or biologic therapy, the French National Diagnostic and Care Protocol (PNDS) for lupus requests serology for human immunodeficiency virus (HIV), hepatitis C and hepatitis B (HBs antigen, or surface antigen; anti-HBs and anti-HBc antibodies, the latter directed against the nucleocapsid, or core, antigen), and a chest radiograph[1]. The PNDS for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis includes the same serologic tests, plus hepatitis C virus RNA if serology is positive or equivocal[2].

The rituximab SmPC requires hepatitis B virus (HBV) screening in all patients before treatment, including at least HBs antigen and anti-HBc antibody; active hepatitis B contraindicates the drug, and any positive serology prompts hepatology referral before initiation[3]. The azathioprine SmPC recommends the same screening in all patients[4]. During baricitinib treatment, anti-HBc-positive patients without HBs antigen are monitored by measuring HBV DNA[5]. The 2022 European recommendation states that antiviral treatment should be guided by the status established before treatment and that all patients with hepatitis C virus RNA should be referred for treatment[6].

Before biologic or targeted synthetic therapy, the 2022 European recommendation calls for latent tuberculosis screening; this may also be considered before a conventional disease-modifying drug, corticosteroids or an immunosuppressant[6]. An interferon-gamma release assay (IGRA) is preferred to the tuberculin skin test when available[6]. The SmPCs for baricitinib and upadacitinib, Janus kinase (JAK) inhibitors, request screening before treatment; the tofacitinib SmPC recommends it before and during treatment[5,7,8]. In lupus, the PNDS notes that no disease-specific recommendation exists and that no reliable data establish the value of IGRA[1].

Before corticosteroid therapy, the prednisone SmPC calls for any visceral focus of infection, particularly tuberculosis, to be excluded[9]. Above all, in anyone from an endemic area (tropical and subtropical regions, and southern Europe), it requires a stool examination for parasites and routine eradication treatment before corticosteroids because of the risk of *Strongyloides* hyperinfection (malignant strongyloidiasis)[9].

Depending on the options considered, the lupus PNDS adds electrolytes, glucose, serum albumin, protein electrophoresis, a lipid panel, serum immunoglobulin A (IgA) measurement and a pregnancy test; contraception is required before methotrexate, mycophenolate or cyclophosphamide[1]. Vaccinations are updated as early as possible before immunosuppression, particularly live vaccines: these are contraindicated during immunosuppressant or biologic therapy or corticosteroid treatment above 10 mg daily prednisone equivalent for more than two weeks, and for at least 3 months after discontinuation, or 6 months after rituximab[1]. Patients without immunity to varicella are informed that postexposure prophylaxis is available[6].

HIV serology serves both the diagnosis of a secondary form and the pretreatment workup; these are separate questions[2]. *Pneumocystis* prophylaxis

appears beneficial above 15 to 30 mg daily of prednisolone for more than 2 to 4 weeks[6]; the lupus PNDS does not make it routine in that disease[1], whereas the vasculitis PNDS considers it useful throughout rituximab treatment and until immune reconstitution[2].

In primary care, the pretreatment workup is ordered through the laboratory: complete blood count, creatinine, liver tests, serum albumin, HIV and hepatitis C serology, hepatitis B serology with HBs antigen, anti-HBs and anti-HBc antibodies, a pregnancy test when relevant, and a chest radiograph[1]. A positive HBs antigen or anti-HBc antibody prompts hepatology consultation before rituximab or azathioprine[3,4]; detectable hepatitis C virus RNA prompts referral for treatment[6]. Patients born in or who have lived in a strongyloidiasis-endemic area undergo a stool examination for parasites before corticosteroids[9]. Vaccinations are updated before treatment begins and completed at least 4 weeks before the first rituximab infusion[1,3].

21.2 Corticosteroids

In the Treatise: § 15.13

Before prolonged corticosteroid therapy, the lupus PNDS calls for blood pressure and weight measurement, an electrocardiogram, fasting glucose, a lipid panel and electrolytes, as well as bone densitometry[1]. During treatment, fasting and two-hour postmeal glucose and a lipid panel are checked annually, as is an ophthalmologic examination[1]. In the absence of corticosteroids, tacrolimus or a specific risk factor, glucose and lipid testing follows general population recommendations[1].

Prednisone reduces the effectiveness of insulin, metformin and sulfonylureas: patients with diabetes intensify glucose self-monitoring, particularly at the start of treatment[9]. Combined with another potassium-lowering drug, it requires potassium monitoring[9]. In systemic sclerosis, a daily prednisolone dose of 15 mg or more is associated with an increased incidence of renal crisis: blood pressure and creatinine are then checked regularly[9].

In a UK cohort of 87,794 patients with immune-mediated inflammatory diseases, cardiovascular risk was already increased below 5 mg daily prednisolone equivalent (hazard ratio 1.74), regardless of disease activity level[10]. The authors conclude that early, regular cardiovascular risk monitoring and primary prevention are needed at all doses[10]. In this observational cohort, no dose was therefore free of excess cardiovascular risk[10]; a normal baseline metabolic workup does not remove the need for annual testing. Live vaccines remain contraindicated for 3 months after corticosteroid discontinuation[9].

In primary care, blood pressure and weight are monitored during long-term corticosteroid treatment; fasting and two-hour postmeal glucose and a lipid panel are checked annually, with annual ophthalmologic examination[1]. Potassium is checked during diuretic or other potassium-lowering treatment[9]. In patients with systemic sclerosis receiving 15 mg or more of prednisolone, blood pressure and creatinine are checked regularly[9]; any new-onset hypertension or acute kidney injury should raise concern for scleroderma renal crisis, which the PNDS lists as an emergency[11].

21.3 Conventional immunosuppressants and hydroxychloroquine

In the Treatise: § 15.13

Azathioprine. The initial workup includes a complete blood count, creatinine, liver tests, albumin and testing for thiopurine methyltransferase (TPMT) deficiency[1]. The SmPC recommends testing before treatment begins[4], whereas elsewhere the PNDS describes it as "not routine"[1]. NUDT15 genotyping may be added, and neither test removes the need for blood count monitoring[4]. Results are interpreted according to the Clinical Pharmacogenetics Implementation Consortium (CPIC), whose 2025 update appeared in January 2026. For a standard starting dose of at least 2 mg/kg/day, normal metabolizers for both genes receive the standard dose; intermediate metabolizers for either gene receive a reduced starting dose of 30 to 80%; intermediate metabolizers for both receive 20 to 50%[12]. For partial TPMT deficiency, the Imurel SmPC gives a starting dose of 30 to 70% of the standard dose, or 1 to 1.5 mg/kg/day, and favors a nonthiopurine treatment in complete deficiency[4]. In poor metabolizers for either gene, myelosuppression can be fatal, and a nonthiopurine immunosuppressant should be considered[12]. The consortium explains how to use the result, not whether to order the test[12]. According to the SmPC, the complete blood count is checked weekly for the first 8 weeks, then monthly or at intervals no longer than 3 months; liver tests are checked monthly for 3 months, then every 3 months[4]. The lupus PNDS calls for a complete blood count and transaminases weekly for 8 weeks, monthly for 3 months, then every 3 months, and 1 to 2 weeks after any dose change; combination with allopurinol or febuxostat is contraindicated, and 6-thioguanine nucleotide measurement can assess adherence[1].

Methotrexate. Before treatment, the SmPC requests a complete blood count with platelets, liver enzymes, bilirubin, serum albumin, a chest radiograph and renal function; tuberculosis or hepatitis is investigated if clinically indicated[13]. Creatinine clearance below 30 mL/min contraindicates methotrexate; between 30 and 59 mL/min, the dose is halved[13]. The complete blood count, liver tests and renal function are then checked weekly for the first two weeks, every two weeks over the following month, at least monthly for the next six months and at least every three months thereafter, more often after dose increases and in older people[13].

The lupus PNDS adopts a simpler schedule: weekly during the first month, monthly for 3 months, then every 3 months; it reduces the dose or stops treatment if transaminases exceed 3 times normal, hemoglobin falls below 10 g/dL, platelets below 100,000/mm³ or leukocytes below 3,000/mm³ [1]. Cirrhosis can occur with normal transaminases: the SmPC calls for consideration of noninvasive methods to assess liver fibrosis[13].

Mycophenolate. The SmPC calls for a complete blood count weekly during the first month, twice monthly in the second and third months, then monthly through the end of the first year; a neutrophil count below $1.3 \times 10^3/\mu L$ may prompt withholding treatment[14]. The lupus PNDS adopts a complete blood count weekly for 1 month, monthly for 3 months, then every 3 months, with protein electrophoresis to look for hypogammaglobulinemia[1]. In women of childbearing potential, two negative blood or urine pregnancy tests with sensitivity of at least 25 mIU/mL, performed 8 to 10 days apart, precede the first dose[14].

Cyclophosphamide and cyclosporine. Before cyclophosphamide: C-reactive protein, complete blood count and creatinine; the blood count is checked

7 to 10 days after each infusion[1]. The SmPC also requests a platelet count and hemoglobin before each administration and testing for microscopic hematuria[15]. During cyclosporine treatment, creatinine is measured every two weeks for 3 months, then every 4 to 8 weeks; the dose is reduced by 25 to 50% if estimated glomerular filtration rate (eGFR) falls by more than 25% on more than one occasion[1]. Liver tests, potassium, magnesium, a lipid panel and trough levels are added[1] (see 21.6).

Hydroxychloroquine. Blood hydroxychloroquine measurement is requested mainly when nonadherence is suspected, particularly during a flare[1]. An electrocardiogram to look for long QT and creatine kinase measurement may be performed during treatment[1]. For long-term treatment, the SmPC calls for regular blood count monitoring, glucose testing when there are signs of hypoglycemia and investigation for chronic toxicity in conduction disease or biventricular hypertrophy; cardiomyopathy requires discontinuation[16]. This rare, late cardiomyopathy is due to lysosomal storage demonstrated by biopsy (Treatise, § 15.13).

In primary care, these drugs are monitored through laboratory testing. The complete blood count and liver tests follow the SmPC or PNDS schedule, with closer monitoring in the early months[1, 4, 13, 14]. A severe fall in leukocytes or platelets during methotrexate treatment requires immediate drug withdrawal[13]. With methotrexate, hemoglobin below 10 g/dL, platelets below 100,000/mm³, leukocytes below 3,000/mm³ or transaminases above 3 times normal prompt dose reduction or withholding[1]; jaundice during azathioprine treatment prompts immediate contact with the physician[4]. With hydroxychloroquine, a baseline ophthalmologic assessment is performed in the first weeks or months[1, 16]; the PNDS then calls for annual surveillance from year five, or from the first year when a toxicity risk factor is present[1].

21.4 Biologic therapies: rituximab, belimumab and anifrolumab

In the Treatise: § 15.13 and § 9.4

Rituximab. The SmPC recommends immunoglobulin measurement before treatment and a neutrophil count before each course, then regularly until 6 months after discontinuation because of late-onset neutropenia[3]. In ANCA-associated vasculitis, the 2026 PNDS schedules protein electrophoresis and quantitative immunoglobulin G, A and M (IgG, IgA and IgM) measurement every 6 months, with CD19+ B-cell measurement every 6 months in rituximab-treated patients[2]. During induction, the complete blood count, creatinine, glucose, C-reactive protein and urine dipstick are checked before each infusion[2].

Yet the same PNDS specifies that regular CD19+ cell phenotyping should not be routine outside clinical trials: its follow-up schedule and recommendation therefore disagree on this point[2]. Measurement is most useful in poorly controlled vasculitis: incomplete depletion (CD19 > 0/mm³) less than 6 months after the last infusion may prompt testing for anti-rituximab antibodies[2]. Relapses also occur without circulating CD19+ cells, which do not precisely reflect the tissue B-cell population[2].

During maintenance treatment, ANCA are checked using an antigen-specific assay every 3 to 6 months according to the context[2]. Their course alone should not guide treatment but may prompt closer monitoring[2].

Belimumab and anifrolumab. During belimumab treatment, the lupus PNDS calls for mood assessment and contraception; during anifrolumab

treatment, it calls for checking for prior herpes zoster, contraception and vaccination against herpes zoster, pneumococcus, influenza and SARS-CoV-2 according to current recommendations[1]. The belimumab SmPC calls for assessment of depression and suicide risk before treatment and monitoring during treatment; no live vaccine is administered within the preceding 30 days or concurrently[17]. The anifrolumab SmPC excludes active tuberculosis and calls for consideration of treatment for untreated latent tuberculosis before the first infusion[18].

In primary care, between infusions, the physician checks a complete blood count with neutrophils regularly until 6 months after the last rituximab infusion, and whenever there are signs of infection[3]. Protein electrophoresis and IgG, IgA and IgM are measured every 6 months[2]. Fever or a sign of infection during rituximab treatment requires immediate examination and appropriate treatment[3]. An isolated ANCA rise does not establish relapse but requires closer monitoring, particularly after renal involvement; recurrence of the clinical signs or laboratory abnormalities present at diagnosis raises the possibility of relapse[2].

21.5 JAK inhibitors

In the Treatise: § 15.13 and § 12.7

JAK inhibitors are targeted synthetic therapies: tuberculosis and viral hepatitis screening applies before initiation[5,6,7]. Treatment is not started or is interrupted if neutrophils are below 1×10^9/L, lymphocytes below 0.5×10^9/L or hemoglobin below 8 g/dL[5,7]. For tofacitinib, initiation thresholds are 1,000 neutrophils and 750 lymphocytes per mm³, and 9 g/dL hemoglobin[8].

During baricitinib treatment, neutrophils, lymphocytes, hemoglobin and transaminases are measured before treatment, then according to routine follow-up; with upadacitinib, the complete blood count is repeated no later than 12 weeks after initiation[5,7]. Lipids are checked approximately 12 weeks after initiation, then according to dyslipidemia recommendations[5,7]. With tofacitinib, lymphocytes are counted at baseline and every 3 months; neutrophils and hemoglobin at baseline, after 4 to 8 weeks and every 3 months; lipids 8 weeks after initiation[8].

The increases in lipids and cancers observed with tofacitinib led to the ORAL Surveillance trial, conducted in patients with rheumatoid arthritis aged at least 50 with a cardiovascular risk factor[19]. Noninferiority to tumor necrosis factor inhibitors (anti-TNF agents) was not demonstrated for major cardiovascular events or cancers, and opportunistic infections, including herpes zoster and tuberculosis, were more frequent[19]. The baricitinib SmPC now restricts its use: after age 65, in current or long-term former smokers and in patients with atherosclerotic cardiovascular disease or other risk factors, it is used only when no suitable alternative is available[5].

In interferonopathies treated with a JAK inhibitor, BK polyomavirus load in blood and urine and renal function are measured before initiation and at every visit[20]. Before treatment, renal involvement is assessed with ultrasonography and a urine protein-to-creatinine or albumin-to-creatinine ratio[20]. In patients with Aicardi-Goutières syndrome treated with baricitinib, thrombocytosis, leukopenia and infections require close monitoring[20]. In children, dosing based on weight and eGFR has been proposed: renal function also determines the dose[20].

In primary care, the baseline workup, including a complete blood count with neutrophils and lymphocytes, transaminases, hepatitis serology and tu-

berculosis screening, precedes the first dose[5,7]. The lipid panel is checked at 12 weeks, or 8 weeks with tofacitinib, and cardiovascular risk is managed according to dyslipidemia recommendations[5,8]. Neutrophils below 1×10^9/L, lymphocytes below 0.5×10^9/L or hemoglobin below 8 g/dL prompt treatment interruption[5]. Herpes zoster prompts withholding baricitinib until resolution, and detectable HBV DNA prompts hepatology consultation[5].

21.6 Calcineurin and mTOR inhibitors

In the Treatise: § 21.5 and § 15.13

During calcineurin inhibitor treatment, monitoring targets blood pressure and renal function; with an mTOR inhibitor (mechanistic target of rapamycin), it targets the lipid profile (Treatise, § 15.13). Outside transplantation, the cyclosporine SmPC calls for renal function to be established by at least two measurements before treatment, then assessed frequently; an eGFR fall of more than 25% on more than one occasion prompts a 25 to 50% dose reduction, and a fall above 35% prompts a further reduction[21]. Blood pressure is monitored regularly; bilirubin and liver tests, lipids, potassium, magnesium and uric acid are measured before treatment and regularly thereafter[21].

In nontransplant patients, the SmPC requests only occasional cyclosporine concentration measurements in the presence of a drug interaction or an unusual clinical response[21]. The level is only one element of dose adjustment and must be interpreted alongside other tests[21]. The lupus PNDS, in contrast, calls for trough measurement (see 21.3)[1].

In transplant recipients during the post-transplant period, the prolonged-release tacrolimus SmPC calls for routine monitoring of blood pressure, electrocardiogram, fasting glucose, electrolytes including potassium, liver and renal function, complete blood count, hemostasis and plasma proteins[22]. During pregnancy after heart transplantation, immunosuppressant levels are measured every 4 weeks until 32 weeks, then every 2 weeks until 36 weeks, then weekly until delivery and for 6 to 12 months afterward (Class I, Level C; see 20.9)[23]; during pregnancy, a stable trough level does not by itself prove that the dose is appropriate (Treatise, § 21.5.3). Tacrolimus is among the treatments warranting annual glucose and lipid checks in lupus[1].

In primary care, during cyclosporine treatment outside transplantation, creatinine and eGFR are checked every two weeks for 3 months, then every 4 to 8 weeks, and blood pressure is monitored regularly[1,21]. The lipid panel is repeated after the first treatment month[21]. A repeated eGFR fall of more than 25% calls for a dose reduction, decided with the prescriber; uncontrolled hypertension may require discontinuation[21]. Every new medication is checked for interactions because cytochrome P450 3A4 (CYP3A4) inhibitors and inducers alter concentrations; creatinine is checked more often after a nonsteroidal anti-inflammatory drug is introduced[21].

21.7 Schedules by disease

In the Treatise: § 8.1, § 9.4, § 8.3 and § 7.3

Systemic lupus erythematosus. Proteinuria is checked every 3 to 6 months and quantified if positive[1]. Repeating anti-double-stranded DNA antibody testing more often than every 6 to 12 months is generally of no value; complement C_3, and sometimes C_4, is measured, recognizing that active disease may coexist with normal C_3 and vice versa[1]. Glucose and lipids are checked annually

during corticosteroid or tacrolimus treatment; pregnancy requires monthly monitoring (see 20.8)[1].

ANCA-associated vasculitis. During induction, the workup is performed before each cyclophosphamide or rituximab infusion, or monthly with another treatment[2]. During maintenance treatment, the complete blood count, electrolytes, creatinine, glucose, C-reactive protein, urine dipstick and liver tests are checked every 3 months; ANCA every 3 to 6 months; immunoglobulins every 6 months[2]. Every 6 months, the PNDS schedule adds CD_4+ T cells during cytotoxic immunosuppressant treatment and CD19+ B cells during rituximab treatment, although regular CD19+ phenotyping is not routine and is mainly useful in poorly controlled vasculitis (see 21.4)[2].

Systemic sclerosis. At least annually, fasting glucose, calcium, creatine kinase, protein electrophoresis, N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP), thyroid-stimulating hormone (TSH), ferritin, folate and vitamin B12 are checked according to the context[11]. Pulmonary hypertension is screened annually with echocardiography and pulmonary function tests including diffusing capacity for carbon monoxide[11].

Amyloidosis. In immunoglobulin light chain (AL) cardiac amyloidosis, free light chains and cardiac biomarkers, NT-proBNP and troponin, are measured monthly during treatment[24]. In transthyretin (ATTR) cardiac amyloidosis, patients are seen at least every 6 months with review of cardiac biomarker trends; echocardiography and Holter monitoring are annual[24]. With acoramidis, a transient creatinine rise averaging 0.2 mg/dL occurs during the first month and resolves after discontinuation; transthyretin silencers, including vutrisiran, lower serum retinol, and a 2025 review recommends daily supplementation with 3,000 IU vitamin A in all patients treated with a silencer[25].

Colchicine. In familial Mediterranean fever, renal and liver function are assessed once or twice yearly, and the dose is adjusted for declining function and age[26]. Colchicine must not be combined with macrolides, such as erythromycin, clarithromycin and josamycin, or pristinamycin; cyclosporine, tacrolimus, azole antifungals, certain antiretrovirals such as ritonavir, verapamil, diltiazem, amiodarone, statins, digoxin, ranolazine and grapefruit juice, which interact with it through P-glycoprotein (P-gp) or CYP3A4, carry a risk of colchicine overdose. The familial Mediterranean fever PNDS states that these combinations are strictly contraindicated in renal or hepatic impairment; otherwise, if one of them is unavoidable, the dose and duration are reduced and signs of overdose are monitored (see 11.1 and 16.2)[26]. The French SmPC classifies these interactions drug by drug: pristinamycin and macrolides other than spiramycin are contraindicated; cyclosporine, verapamil, ritonavir-boosted protease inhibitors, telaprevir, the azole antifungals itraconazole, ketoconazole, voriconazole and posaconazole, and strong CYP3A4 inhibitors are not recommended; statins require precautions for use; and colchicine itself is contraindicated in severe renal impairment (creatinine clearance below 30 mL/min) or severe hepatic impairment[27].

Cancer and transplantation. Schedules for checkpoint inhibitors, chimeric antigen receptor T cells (CAR-T cells) and irradiated survivors are provided in Chapter 19; those for heart transplantation and pregnancy are in Chapter 20.

In primary care, a urine dipstick is performed at least at every visit in lupus and every 3 months over the long term; any change or worsening of symptoms prompts a consultation[1]. In vasculitis, the primary care physician manages intercurrent illness in close liaison with the French reference or competence center[2]. In cardiac amyloidosis, the treating physician identifies breathlessness,

weight gain, edema, fatigue and arrhythmias and contacts the reference center for any acute problem[24].

Table 21.1. Laboratory monitoring during treatment, drug by drug

Treatment or disease	Tests	Frequency
Azathioprine	TPMT before treatment, NUDT15 if tested, results interpreted according to CPIC[4, 12]; complete blood count; liver tests[4]	Weekly for 8 weeks, then monthly to every 3 months; liver tests monthly for 3 months, then every 3 months[4]
Methotrexate	Complete blood count, liver tests, renal function; contraindicated if creatinine clearance < 30 mL/min[13]	Weekly for 2 weeks, every two weeks the following month, at least monthly for 6 months, then at least every 3 months[13]
Mycophenolate	Complete blood count[14]	Weekly in month 1, twice monthly in months 2 and 3, then monthly during year 1[14]
Cyclosporine (outside transplantation)	Creatinine and eGFR, blood pressure; lipids, potassium, magnesium[1, 21]	Every two weeks for 3 months, then every 4 to 8 weeks; lipids after 1 month[1, 21]
Corticosteroids	Glucose, lipid panel[1]	Annually[1]
Hydroxychloroquine	Complete blood count[16]; blood drug level if nonadherence is suspected[1]	Regularly during long-term treatment[16]
Colchicine	Renal function, liver tests; interactions (see 11.1)[26]	Once or twice yearly[26]
Rituximab	Neutrophils; immunoglobulins[2, 3]	Before each course and until 6 months after discontinuation; immunoglobulins every 6 months[2, 3]
Baricitinib, upadacitinib	Complete blood count, transaminases; lipids[5, 7]	At baseline, then according to follow-up (upadacitinib: blood count no later than 12 weeks); lipids at 12 weeks[5, 7]
Tofacitinib	Lymphocytes; neutrophils and hemoglobin; lipids[8]	Every 3 months; at 4 to 8 weeks, then every 3 months; at 8 weeks[8]
JAK inhibitor (interferonopathy)	BK virus in blood and urine, renal function[20]	Before treatment and at every visit[20]
Stable lupus	Proteinuria; anti-double-stranded DNA[1]	3 to 6 months; no more often than every 6 to 12 months[1]
ANCA-associated vasculitis, maintenance	Standard workup; ANCA[2]	3 months; 3 to 6 months[2]
Systemic sclerosis	Laboratory testing including NT-proBNP[11]	At least annually[11]
Cardiac AL amyloidosis	Free light chains, NT-proBNP, troponin[24]	Monthly during treatment[24]
Cardiac ATTR amyloidosis	Cardiac biomarkers[24]	At least every 6 months[24]

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THE LABS

A test is ordered for a reason,
a sample is collected at the right time
and a result is read alongside its source.

When an autoimmune, autoinflammatory or rare disease affects the heart, we set out to make laboratory testing readable. Each test here is assigned a tier: essential for a defined indication, useful depending on the clinical context, or a matter for specialist assessment. The tier states why the test is ordered.

We begin with how to read a laboratory workup, from specimen collection to the meaning of a result, then work through the diseases, cardiac involvement and monitoring during treatment.

Each threshold and monitoring interval is linked to its source,
and each chapter cross-references the Treatise.

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