Flowchart detecting causes AA-amyloidosis

Blood cultures, tissue cultures

TPHA, IgG4, C3/C4

START: New patient with AA amyloidosis Positive family history or suggestive presentation: Tissue positively stained with Congo red and green birefringence or typical fibrils genetic testing (electron microscope) Immunohistochemistry with anti-AA is positive or proteomics showing AA amyloid to Periodic fever: FMF, TRAPS, CAPS, HIDS/MKD (and serum IgD), PAPA No histologic and serologic (FLC) evidence for another amyloid type (i.e. AL, ATTR) Infection: CVID, congenital neutropenia, XLA Still no obvious underlying inflammatory process Other: GSD, PAP, CF, PCD Travel history / country of origin **CORE:** Basic diagnostic approach Infections depending on region, see: www.cdc.gov Mediterranean ancestry: testing for FMF Complete and detailed history; including family history, country of origin, travel history, risky sexual behavior, drug abuse, animal contacts Complete and thorough physical examination; including mouth and dental Drug history / risky sexual behavior inspection, meticulous skin inspection, joint examination, and BMI Routine blood tests: CRP, SAA, ESR, Hb, MCV, thrombocytes, leukocytes with Serological testing HBV, HCV, HIV differential count, creatinine, eGFR, ASAT, ALAT, AF, GGT, LDH, ferritin, calcium, uric Consider skin popping / infection acid, albumin, NT-proBNP, Troponin, FLC, IgM, IgG, IgA, and M-protein Urinalysis, microscopic urine sediment, and 24h proteinuria Recurrent infections Chest X-ray, abdominal ultrasound TBC skin test or interferon gamma assay. Genetic testing on PCD, PAP, CF, CVID, CGD Immunoglobulins, C3/C4, HIV Rheumatic symptoms **Pulmonary symptoms Abdominal symptoms** Arthritis: X-rays hand/feet Anti-CCP, RF, ANA, ENA, ANCA Pain: pyelogram, CT abdomen anti-CCP, RF, ANA, ENA, ANCA Inflammatory bowel symptoms: gastroscopy and Genetic testing on PCD, PAP, Inflammatory back pain, SPA: X-ray or colonoscopy Abnormal liver function: HCV, HBV MRI of SI-ioints CF. CGD on indication Joint fluid analysis Duodenum biopsy for Whipple's disease Elderly headache/vision loss: arteritis Lung function tests AMA, pANCA, AECA, tTG-IgA temporalis biopsy Jejunum biopsy for celiac disease **EXTENSION:** Inflammation without localizing symptoms or diagnostic clues, consider: MRI neck, thorax, and abdomen Whole body PET CT Biopsy of bone marrow, liver, lymph node

Flow chart of the diagnostic approach to detect the underlying disease process in a patient with newly diagnosed AA amyloidosis, but still without an obvious cause (yellow box). First step is obtaining a complete history and performing a thorough physical examination, together with a core set of basic laboratory measurements and imaging (orange box). Second step shows the possible investigations in six directions guided by specific clues obtained from history or from symptoms (green boxes). If localizing symptoms or diagnostic clues remain absent, a full search for the underlying inflammatory process is justified (blue box).

Abbreviations: AA, amyloid A; AECA, anti-endothelial cell antibody; AF, alkaline phosphatase; AL, amyloid light chain-related; ALAT, alanine amino transferase; AMA, anti-mitochondrial antibody; ANA, antinuclear antibody; ANCA, antinuclear antibody; anti-CCP, anti-cyclic citrullinated protein; ASAT, aspartate amino transferase; ATTR, amyloid transthyretin-related; BAL, bronchoalveolar lavage; BMI, body mass index; C3/C4, complement factor 3 and 4; CAPS, cryopyrin-associated periodic syndrome; CF, cystic fibrosis; CGD, chronic granulomatous disease; CRP, C-reactive protein; CT, computed tomography; CVID, common variable immunodeficiency disorder; eGFR, estimated glomerular filtration rate; ENA, antibodies against extractable nuclear antigen; ESR, erythrocyte sedimentation rate; FLC, immunoglobulin free light chain; FMF, familial Mediterranean fever; GGT, gamma glutamyl transferase; GSD, glycogen

storage disease; Hb, hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; HIDS, hyperimmunoglobulinemia D syndrome; HIV, human immunodeficiency virus; HRCT, high-resolution computed tomography; IgA, immunoglobulin A; IgD, immunoglobulin D; IgG, immunoglobulin G; IgG4, Immunoglobulin G subtype 4; IgM, immunoglobulin M; LDH, lactate dehydrogenase; M-protein, monoclonal protein; MCV, mean corpuscular volume; MKD, mevalonate kinase deficiency; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic protein; pANCA, perinuclear ANCA; PAP, pulmonary alveolar proteinosis; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, and acne; PCD, primary ciliary dyskinesia; PET, positron emission tomography; RF, rheumatoid factor; SAA, serum amyloid A protein; TPHA, treponema pallidum haemagglutinase; TRAPS, Tumor necrosis factor receptor-associated periodic syndrome; tTG-IgA, anti-tissue transglutaminase IgA antibodies; XLA, X-linked agammaglobulinemia.