**Supplemental table 1**: List of alternative diagnoses to be considered at the time of Still's disease diagnosis

| ***Differential diagnoses to be explored*** | |
|---|---|
| ***Adults*** | ***Children*** |
| ***Infections*** | |
| - Bacterial septicemia<br>- Bacterial endocarditis<br>- Occult or deep sepsis: biliary, colonic or urinary<br>- Tuberculosis, brucellosis, yersiniosis<br>- Viral hepatitis, HIV infection, abscessed parasitosis<br>- Whipple's disease | - Bacterial septicemia<br>- Bacterial endocarditis<br>- Occult or deep sepsis: biliary, colonic or urinary<br>- Tuberculosis, brucellosis, yersiniosis<br>- Viral hepatitis, HIV infection, abscessed parasitosis<br>- Whipple's disease |
| ***Neoplasia*** | |
| - Hodgkin or non-Hodgkin lymphoma<br>- Acute lymphoblastic leukemia<br>- Angioimmunoblastic T-cell lymphoma<br>- Solid cancers: kidney, colon, lung<br>- Myelodysplastic syndrome<br>- Clonal hematopoiesis of Indeterminate Significance (CHIP)<br>- Paraneoplastic syndromes | - Hodgkin or non-Hodgkin lymphoma<br>- Acute lymphoblastic leukemia<br>- Angioimmunoblastic T-cell lymphoma<br>- Myeloproliferative syndromes<br>- Paraneoplastic syndromes<br>- Neuroblastoma |
| ***Systemic diseases*** | |
| - ANCA vasculitis or other vasculitis<br>- Reactive or post-streptococcal arthritis<br>- Inflammatory myopathies<br>- Systemic lupus erythematosus<br>- Seronegative rheumatoid arthritis<br>- Sarcoidosis<br>- Sweet's syndrome<br>- Drug hypersensitivity reaction, drug pseudo-lymphoma<br>- Hereditary auto-inflammatory syndromes (familial Mediterranean fever, partial mevalonate kinase deficiency, TRAPS)<br>- Late-onset acquired systemic autoinflammatory disorders (CAPS/NLRC4 mutations, VEXAS syndrome)<br>- Schnitzler syndrome | - Kawasaki or other vasculitis<br>- Reactive or post-streptococcal arthritis<br>- Inflammatory myopathies<br>- Systemic lupus erythematosus<br>- Seronegative rheumatoid arthritis<br>- Sarcoidosis or other pediatric granulomatosis<br>- Sweet's syndrome<br>- Drug hypersensitivity reaction, drug pseudo-lymphoma<br>- Hereditary auto-inflammatory syndromes (familial Mediterranean fever, partial mevalonate kinase deficiency, TRAPS) |

**Supplemental table 2**: List of workups to be considered at the time of Still's disease onset

| | Onset | Depending on the context |
|---|---|---|
| ***Biology*** | | |
| Hemogram, blood smears | x | |
| Hemostasis (Prothrombin rate, Activated partial thromboplastin time) | x | |
| Fibrinogen, D-dimers, fibrin degradation products (PDF) | | x if DIC is suspected |
| Blood electrolytes, urea, creatinine | x | |
| Transaminases (AST, ALT) and other LFT | x | |
| C-reactive protein (CRP) | x | |
| Serum protein electrophoresis | x | |
| Ferritinemia, (glycosylated ferritin if available) | x | |
| Creatine kinase (CK) | x | |
| Lactate dehydrogenase (LDH) | x | x if MAS suspected |
| Triglyceridemia | | x if MAS suspected |
| ***Microbiological examinations*** | | |
| Blood cultures, cyto-bacteriological examination of urine | x | |
| Bacterial serology: brucellosis, syphilis, yersiniosis, other | | x |
| Tuberculosis testing (BK sputum, tubing, IFNγ releasing assays) | | x |
| PCR for Whipple's disease (blood, saliva, stool, digestive biopsies) | | x |
| Viral serologies: HIV, HBV, HCV, EBV, CMV | x | |
| Viral serologies: HSV, parvo-B19, coxsackie, rubella, measles | | x |
| PCR EBV, CMV, HSV | | x |
| Parasitic serology: toxoplasmosis | | x |
| ***Immunological examinations*** | | |
| Anti-nuclear, anti-DNA and anti-ENA Ab, complement fractions | x | |
| Rheumatoid factors, Anti-citrullinated peptide Ab (ACPA) | x | |
| Anti-neutrophil cytoplasmic antibodies (ANCA) | x | |
| Interleukin-18 blood levels | x if available | |
| Blood immunofixation and free light chains, b2 microglobulinemia | | x |
| HLA DRB1*15 | | x if available |
| ***Cytology - Biopsy*** | | |
| Joint aspiration if arthritis | | |
| Bone marrow aspirate / biopsy to exclude acute leukemia, lymphoma and myelodysplasia (depending on age) | | x |
| Lymph node biopsy | | x if asymmetrical adenopathy |
| Temporal artery biopsy | | x if headache |
| Minor salivary gland biopsy | | x only if context suggestive of Sjögren, Sarcoidosis or amyloidosis |
| ***Imaging*** | | |
| Thoracic-abdominal-pelvic scan | x in adults | x in children |
| Trans-thoracic cardiac ultrasound | | x |
| Trans-esophageal cardiac ultrasound | | x if suspected endocarditis |
| TEP scanner | | x |
| X-ray of affected joints if arthritis | x | |
| Joint ultrasound of affected joints if arthritis | x | |

| | | |
|---|---|---|
| Sinus X-ray or CT-scan, dental panoramic | | x if prolonged fever |
| Pulmonary function test | | x if suspected Still's LD |
| ***Genetics*** | | |
| In patients with signs or symptoms suggestive of a monogenic autoinflammatory disease (e.g. family history, peritonitis, neutrophilic dermatitis…), consider genetic analyses (Sanger or NGS) | | X |
| If age > 50: consider search for UBA1 somatic mutations | | x |

LFT: liver function tests – HIV: Human Immunodeficiency virus – HBV: B hepatitis virus – HCV: C hepatitis virus – EBV: Epstein-Barr virus – CMV: cytomegalovirus – HSV: Herpes simplex virus – PCR : Polymerase chain reaction – DNA : desoxyribonucleic acid – ENA : extractible nuclear antigen – Ab : antibodyes – PET : position emission tomography.

**Supplemental table 3**: List of treatments of interest for patients with Still's disease in both children (sJIA) and adults (AOSD)

| Therapeutics | Dose for children | Dose for adults | Effect latency | Side effects |
|---|---|---|---|---|
| ***Glucocorticoids*** | | | | |
| Prednisone (oral) | Up to 2 mg/kg/d | Up to 1 mg/kg/d | A few hours to a few days | Weight gain, cushing's disease, diabetes, infections, hypertension, osteoporosis, aseptic osteonecrosis, cardiovascular events, cataract, glaucoma<br>growth retardation, pubertal delay in children |
| Methyl-prednisolone (IV) | 30 mg/kg/d (max 1 g per infusion) | 15 mg/kg/d (max 1 g per infusion) | | |
| ***IL-1 inhibitor*** | | | | |
| Anakinra (SC) | 2 to 4 mg/kg/d (max 100 mg) | 100 mg/d (sometimes twice per day) | A few days | Infections, Neutropenia<br>Hepatic cytolysis<br>Hypersensitivity, injection site reaction (anakinra) |
| Canakinumab (SC) | 4 mg/kg/month (max 300 mg) | 4 mg/kg/month (or 2 mg/kg eow) | | |
| Rilonacept (SC) | Loading dose of 2.2-4mg (max 360 mg) then 2.2 mg/kg/week (max 160 mg) | NA | | |
| ***IL 6R inhibitors*** | | | | |
| Tocilizumab (IV or SC) | BW ≥ 30 kg: 8 mg/kg eow IV or 162 mg/week SC<br>BW < 30 kg: 12 mg/kg eow IV or 162 mg/eow SC | 8 mg/kg/month or 162 mg/week | A few days | Leucopenia, elevated LFT, infections, dyslipidemia, low GI perforation |
| ***CsDMARD*** | | | | |
| Methotrexate (oral or SC) | 15 mg/m²/wk (maximum 25 mg/wk) | 0.2 to 0.3 mg/kg/wk | 4 weeks | Hypersensitivity, elevated LFT, Aplasia if overdosed.<br>Infections |
| Ciclosporin A (oral) | 2 to 5 mg/kg/d<br>(target through concentration 200 µg/L) | 2 to 5 mg/kg/day per os<br>(target through concentration 200 µg/L) | 1 to 2 months | Hypertension, renal insufficiency<br>Hypertrichosis, gum hypertrophy, neuropathy |

SC: subcutaneously – IV: intravenously – mg: milligrams – d: day – wk: week – eow : every other week – BW: body weight – NA: non available – LFT: liver function tests

**Supplemental table 4**: Possible schedules ofIL-1 or IL-6 inhibitor tapering with the final aim to achieve their withdrawal (i.e. remission off medication) in Still's disease patients who achieved and maintain CID on medication (for 3 to 6 months).

| | Full dosing | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 | Step 5 | Step 6 |
|---|---|---|---|---|---|---|---|---|
| Anakinra (schedule 1) | SC daily | SC every 2 days for 3 months | SC every 3 days for 3 months | withdrawal | | | | |
| Anakinra (schedule 2) | SC daily | SC 6 days/week for 1 month | SC 5 days/week for 1 month | SC 4 days/week for 1 month | SC 3 days/week for 1 month | SC 2 days/week for 1 month | SC 1 day/week for 1 month | withdrawal |
| Canakinumab (schedule 1) | 4 mg/Kg SC every 4 weeks | 2 mg/Kg SC every 4 weeks for 6 months | 1 mg/Kg SC every 4 weeks for 6 months | withdrawal | | | | |
| Canakinumab (schedule 2) | 4 mg/Kg SC every 4 weeks | 4 mg/Kg SC every 8 weeks for 6 months | 4 mg/Kg SC every 12cweeks for 6 months | withdrawal | | | | |
| Tocilizumab | IV every 2 weeks | IV every 3 weeks for 3 months | IV every 4 weeks for 3 months | withdrawal | | | | |

For each scheme, moving to the subsequent step requires maintenance of CID for at least 1 to 4 months depending on the drug. For anakinra, 2 schedules are shown as both are being used in several centers. For canakinumab, the proposed schedules have been designed during the extension phase of the phase 3 studies and the results published (Quartier 2021 doi:10.1002/art.41488.). As the frequency of flares was not different between the two schedules (dose decrease and dose interval prolongation), both are proposed. For TCZ, the proposed schedule was designed during the extension phase of the phase 3 trial in sJIA (de benedetti NEJM 2012), is available in the trial protocol in the Supplementary materials of the original publication and results have been reported in an abstract Form.

**Supplemental Table 5**: Scores and classification criteria facilitating MAS diagnosis in Still's disease

| **Tools** | **H-score** | **M-score** | **EULAR/ACR/PReS classification criteria** |
|---|---|---|---|
| Author | Fardet et al. 2014 | Minoia et al. 2019 | Ravelli et al. 2016 |
| Items (coefficient) | - Immunodeficiency* (18)<br>- Fever ≥ 38°4 (33)<br>> 39°4 (49)<br>- Hepatomegaly or splenomegaly (23)<br>Hepatomegaly and splenomegaly (38)<br>- Cytopenia**2 lines (24)<br>3 lines (34)<br>- Ferritin ≥ 2000 µg/L (35)<br>> 6000 µg/L (50)<br>- Fibrinogen ≤ 2.5 g/L (30)<br>- ASAT ≥ 30 IU/L (19)<br>- Bone marrow hemophagocytosis (35) | - Central neurological impairment§ ( 2.44)<br>- Hemorrhagic events§ ( 1,54)<br>- Active arthritis§ (-1.30)<br>- Platelets (G/L)§§ (-0.003)<br>- LDH (U/L)§§ (0.001)<br>- Fibrinogen (g/L)§§ (-0.004)<br>- Ferritin (µg/L)§§ (0.0001) | Mandatory criterion<br>- Ferritin > 684 µg/L<br>Additional criteria<br>- Platelets ≤ 181 G/L<br>- ASA > 48 UI/L<br>- Triglycerides > 1.56 g/L<br>- Fibrinogen ≤ 3.6 g/L |
| Diagnostic threshold | > 169 | ≥ -2,1 | Presence of the mandatory criterion + 2 of the 4 secondary criteria |
| Performance | Sensitivity 93%,<br>Specificity 86<br>AUC ROC 0.95 | Sensitivity 85%.<br>Specificity 95%.<br>AUC ROC 0.95 | Sensitivity 73<br>Specificity 99%.<br>AUC ROC 0.86 |

* Acquired immunodeficiency or related to long-term immunosuppressive treatment (glucocorticoid, ciclosporin, azathioprine, etc.).
** Hemoglobin ≤ 9.2 g/dL, white blood cells ≤ 5000/mm$^3$ or platelets ≤110000/mm$^3$.
§Value of 0 if absent, 1 if present (to be multiplied by the coefficient).
§§Value to be multiplied by the coefficient

**Supplementary table 6:** List of treatments of interest for patients with MAS occurring in the context of Still's disease

| Therapeutics | Dose for children | Dose for adults | Effect latency | Adverse events |
|---|---|---|---|---|
| ***Methyl-prednisolone*** | 10 to 30 mg/kg/d IV (max 1 gr) x 1-3 d, then 2-3 mg/kg/day in multiple daily doses | 15 mg/kg/d IV (max 1 g/infusion) x 1-3 d then 1 mg/kg/d orally | A few hours to a few days | Weight gain, cushing's disease, diabetes, Infections, hypertension Osteoporosis, osteonecrosis Vascular risk |
| ***Dexamethasone*** | 10 to 20 mg/m2 (in 2 daily injections) *Only in children ≥ 1 month* | 100 to 200 mg per day (in 2 daily injections) | A few hours to a few days | |
| ***Anakinra*** | 5-15 mg/kg/day SC or IV divided in multiple daily doses (2 to 4 per day) *Only in children ≥ 8 months or 10 kg* | 2 to 10 mg/kg/day (in 2 doses per day) | A few days | Infections, neutropenia, elevated LFT, hypersensitivity |
| ***Ciclosporin A*** | 3 to 6 mg/kg/day orally or IV (target through concentration 200 µg/L) | 3 to 5 mg/kg/day orally or IV (target through concentration 200 µg/L) | A few days | Hypertension, renal failure, hypertrichosis, PRES |
| ***Emapalumab*** | Initial dose at 6 mg/kg/day IV, then 3 mg/kg every 3 days | Initial dose at 6 mg/kg/day IV, then 3 mg/kg every 3 days | 2 weeks | Infections, including tuberculosis Hypersensitivity |
| ***JAK inhibitors*** | Ruxolitinib 5 to 20 mg bid | Ruxolitinib 5 to 20 mg bid | 1 week | Viral infection, anemia, neutropenia, thrombopenia, elevated LFT, increase serum lipoprotein |
| ***Etoposide (VP-16)*** | 50 to 100 mg/m² once weekly IV | 50 to 100 mg/m² once weekly IV | 1 week | Hypersensitivity, cytopenia, infections, arrythmia, elevated LFT, alopecia, fatigue |