APPENDIX

The 2021 EULAR and ACR points to consider for diagnosis, management and monitoring of the IL 1 mediated autoinflammatory diseases: CAPS, TRAPS, MKD and DIRA

CONTENTS

I. SUPPLEMENTARY METHODS

I.1. Task force meetings proceedings:

Per EULAR[1] and ACR Standard Operating Procedures (SOPs) the following steps were followed.

- A EULAR task force was established and consisted of: 22 pediatric rheumatologists, 1 health care professional, 3 fellows, 2 patient representatives (one for each disease) from the autoinflammatory alliance, 1 methodologist and 1 senior methodologist.
- August 2019 (NIH Bethesda): A face-to-face meeting was convened to define the focus of the task force and identify the target population.
- Two rounds of pre-consensus meeting Delphi questionnaires were sent using RedCap, a secure Web-based system with the technical help of the University of Toronto. For one-week, daily reminders were sent to all task force members who had not yet replied to the questionnaire, and the response rate for each questionnaire was 100%. The same procedure was followed for the second Delphi survey. The questionnaire data and the results from the SLR were used to generate draft statements that were discussed in two consensus meetings.
- Due to the COVID-19 pandemic restrictions that prohibited face-to-face meetings, three consensus meetings were held virtually online. One consensus meeting included voting members with expertise in CAPS on October 27, 2020 one in TRAPS on November 24, 2020 and one in MKD and DIRA on November 4, 2020.
    - The SLR results were presented by the fellows for each disease and discussed during the consensus meetings.
    - The draft statements that were distributed to the task force members were discussed, refined and voted on.
    - Overarching statements and statements pertaining to all groups were voted on in all consensus meetings while statements pertaining to only CAPS, TRAPS or MKD and DIRA were voted on in the respective meetings only.
    - Statements with 20-80% agreement were chosen for ongoing discussion and possible major revision during the second part of the consensus meeting, while the rest (<20% agreement) were dropped and were not included as points to consider statements. Two conveners, 1 health care professional and 3 experts attended both meetings, and the rest of the expert panel attended one meeting based on their disease specific experience/expertise.
- Reaching consensus: All statements included reached the minimum 80% consensus to be retained in the final formulation of the recommendations. If one of the sub-statements did not reach that threshold in the pre-consensus Delphi or at the consensus meetings, it was discussed and reworded or modified with the aim of achieving a secondary 80% consensus. If the 80% level was not achieved in any way, the statement was eliminated. Eliminated statements were listed in the Supplementary II.5 below.
- A post-consensus meeting Delphi questionnaire with the finalized statements was distributed among all voting members of both consensus meetings and a level of agreement was obtained based on marking on a Likert scale from 0 to 10, with 0 indicating no agreement and 10 indicating full agreement. Using those data, the mean and standard deviation (SD) of level of agreement for each statement was calculated.

The manuscript was reviewed and approved by all task force members and the EULAR executive committee before submission.

I.2. Search Terms

a) *Search Terms for* ***CAPS***

"cryopyrin associated periodic syndromes"[MeSH] OR "Cryopyrin Associated Periodic Syndromes"[tiab] OR "Cryopyrin Associated Periodic Syndrome"[tiab] OR "Cryopyrin Associated Periodic Fever Syndromes"[tiab] OR "Cryopyrin Associated Periodic Fever Syndrome"[tiab] OR cryopyrinopath*[tiab] OR FCAS[tiab] OR "Familial Cold Autoinflammatory Syndrome"[tiab] OR "Familial Cold Urticaria"[tiab] OR MWS[tiab] OR "Muckle Wells Syndrome"[tiab] OR CINCA[tiab] OR (Chronic[tiab] AND Infantile[tiab] AND Neurological[tiab] AND Cutaneous[tiab] AND Articular[tiab]) OR NOMID[tiab] OR "Neonatal Onset Multisystem Inflammatory Disease"[tiab] OR "Infantile Onset Multisystem Inflammatory Disease"[tiab]

b) ***Search Terms for TRAPS***

"Periodic fever, familial, autosomal dominant"[Supplementary Concept] OR "familial Hibernian fever"[tiab] OR ((((("tumor necrosis factor"[tiab] OR "tumour necrosis factor"[tiab] OR TNF[tiab]) AND receptor[tiab]) OR TNFR[tiab] OR TNFR1[tiab]) AND associated[tiab] AND periodic[tiab] AND syndrome[tiab])

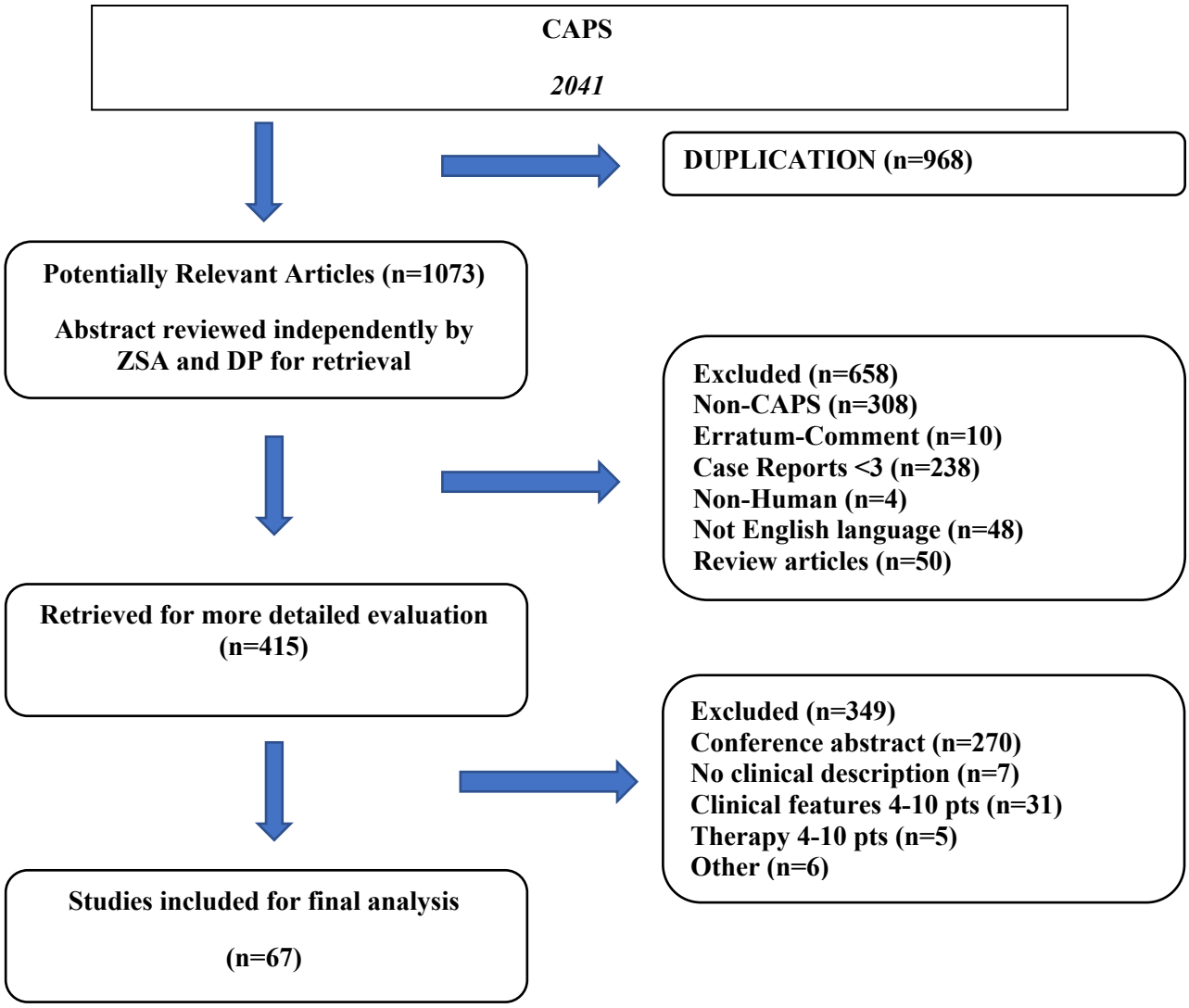
c) ***Search Terms for MKD***
"mevalonate kinase deficiency"[MeSH] OR MKD[tiab] OR "mevalonate kinase deficiency""[tiab] OR "mevalonicaciduria"[tiab] OR HIDS[tiab] OR HyperIgD[tiab] OR "hyperimmunoglobulin D"[tiab] OR "hyperimmunoglobulinemia D"[tiab] OR "hyperimmunoglobulinaemia D"[tiab] OR (Hyper[tiab] AND (IgD[tiab] OR "Ig D"[tiab] OR "immunoglobulin D"[tiab]))

d) ***Search Terms for DIRA***

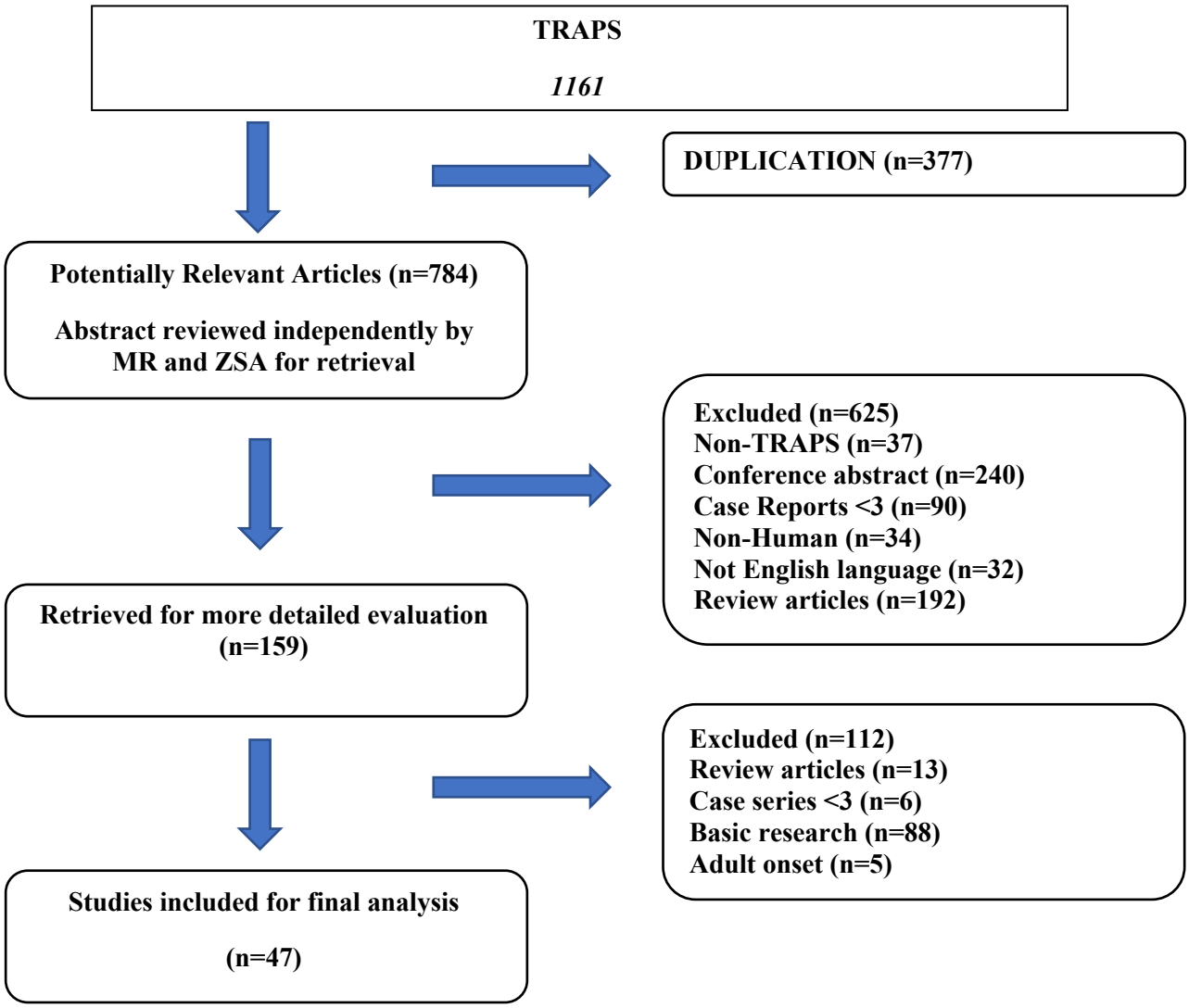
((((((((((((("Interleukin 1 Receptor Antagonist Protein/deficiency"[Mesh]) OR IL-1 receptor antagonist deficiency[TIAB]) OR DIRA[TIAB]) OR Deficiency of interleukin-1 receptor antagonist[Supplementary Concept])))) OR Deficiency of interleukin-1 receptor antagonist[TIAB])) OR ((((Hereditary Autoinflammatory Diseases[MH]) AND Interleukin 1 Receptor Antagonist Protein[MH])) AND ((interleukin-1 receptor antagonist[TIAB] OR IL1RN[TIAB] OR DIRA[TIAB])))))) OR ((IL1RN[TIAB]) AND deficien*[TIAB]))) OR ((((Interleukin 1 Receptor Antagonist Protein[MAJR]) AND Hereditary Autoinflammatory Diseases[MAJR])) AND deficien*[TIAB]))) OR (("IL-1 receptor antagonist"[Text Word]) AND ((Interleukin 1 Receptor Antagonist Protein[MAJR]) AND Hereditary Autoinflammatory Diseases[MAJR]))

I.3. Flowcharts

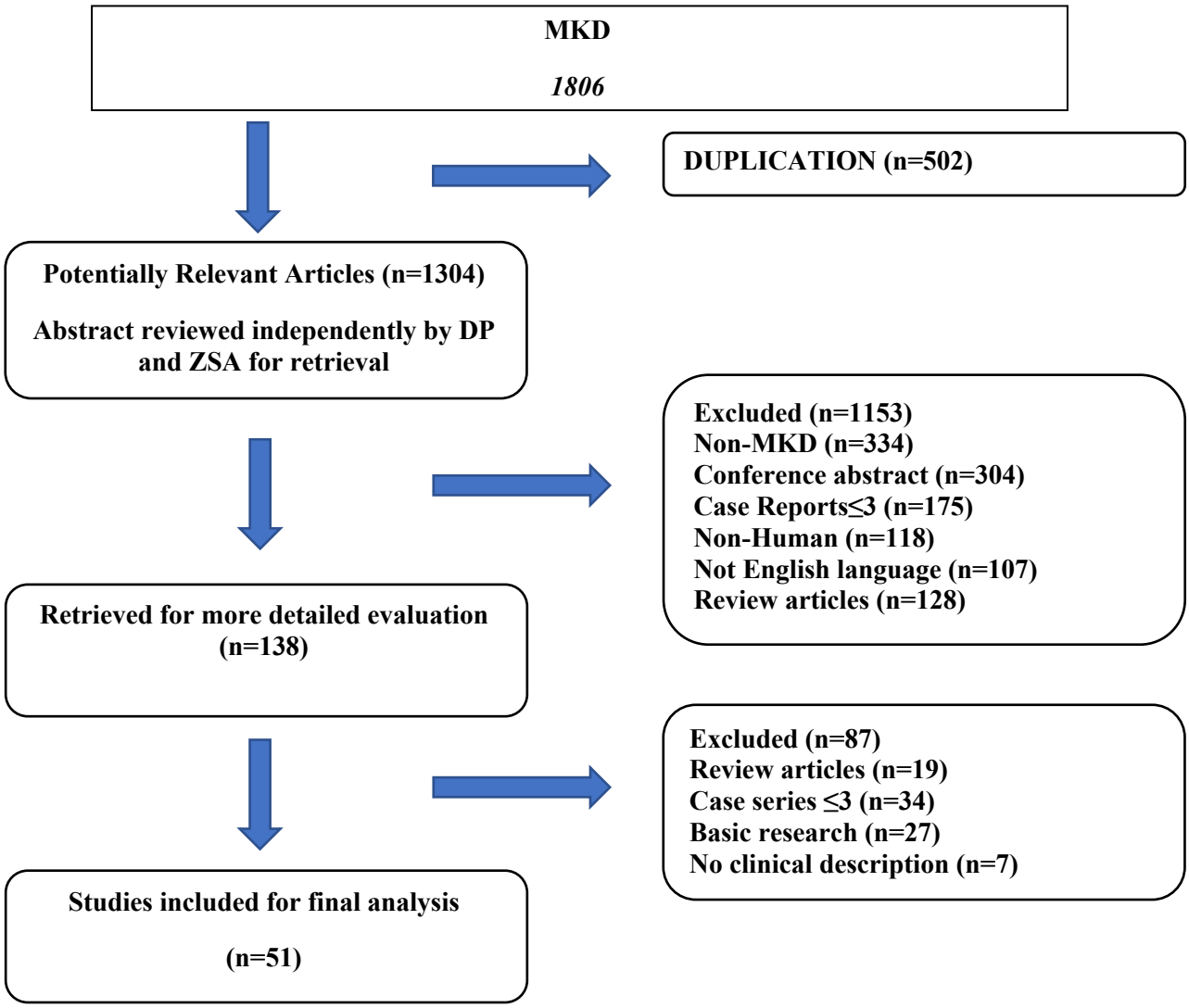
a. *Flowchart for **CAPS***



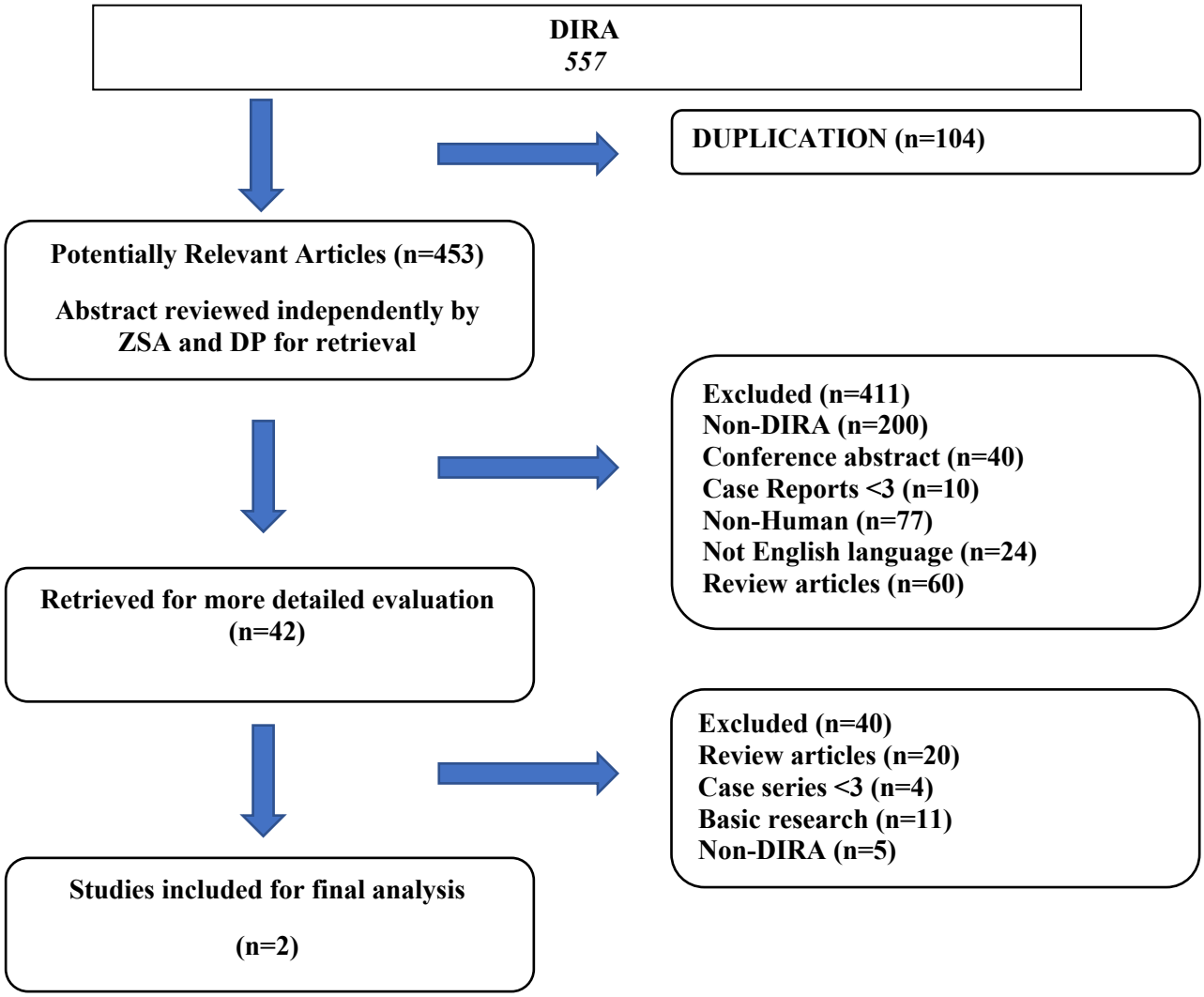
b) *Flowchart for* ***TRAPS***



c) *Flowchart for* ***MKD***



d) *Flowchart for* ***DIRA***



II. SUPPLEMENTARY MATERIALS

II.1. Included Articles for **CAPS**

1.Ahmadi N, Brewer CC, Zalewski C, King KA, Butman JA, Plass N, et al. Cryopyrin-associated periodic syndromes: otolaryngologic and audiologic manifestations. Otolaryngol Head Neck Surg. 2011;145(2):295-302.
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23.Imagawa T, Nishikomori R, Takada H, Takeshita S, Patel N, Kim D, et al. Safety and efficacy of canakinumab in Japanese patients with phenotypes of cryopyrin-associated periodic syndrome as established in the first open-label, phase-3 pivotal study (24-week results). Clin Exp Rheumatol. 2013;31(2):302-9.
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II.2. Included Articles for **TRAPS**

1.Bulua AC, Mogul DB, Aksentijevich I, Singh H, He DY, Muenz LR, et al. Efficacy of etanercept in the tumor necrosis factor receptor-associated periodic syndrome: A prospective, open-label, dose-escalation study. Arthritis Rheum 2012;64:908-13.
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II.4. Included Articles for **DIRA**

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II.5. Statements that cannot reached consensus

1. CAPS

1. In patients with clinical features of autoinflammatory disease and blood parameters of systemic inflammation in the absence of infection are the following clinical features listed below highly likely to suggest CAPS, compared with patients lacking these characteristics?

- visual loss (57%)

2. In patients with clinical features of autoinflammatory disease suggestive of CAPS are there features listed below that can differentiate patients within the CAPS spectrum compared with patients lacking these characteristics in order to define such patients as having mild, moderate or severe disease?

- visual loss (64%)

3. In patients with presumed CAPS can we use similar diagnostic tests listed below compared to non-CAPS patients to more definitively make a diagnosis on the CAPS spectrum?

- Measurement of markers of inflammasome activation such as IL-1 release in whole blood assays, ASC speck may be helpful (64%)
- MRI (77%)
- Spinal tap (54%)
- Bone film or MRI for suspected bone damage (46%)

6. For patients with CAPS symptoms, are certain lab markers listed below, compared to healthy donors, helpful in the diagnosis of CAPS

- Cytokine panels (46%)

7. For patients with CAPS is additional diagnostic workup including studies listed below, compared to serologic labs only, useful in the diagnosis of CAPS

- In vitro secretion of IL-1 by monocytes (or ASC) in patients with variants of unknown origin (61.1%)

19. What are the recommendations for pneumococcal vaccination in CAPS patients?

- Pneumococcal polysaccharide (No:86%)

22. Should disease activity and damage be monitored in CAPS patients using the following methods, and does this differ along the clinical CAPS spectrum?

- Tissue biopsy for amyloidosis (31%)
- Muckle Wells activity score (54%)
- CNS MRI (including inner ear) (69%)

23. Which of the following tests listed below should be included in yearly monitoring of CAPS patients along the CAPS spectrum

- Head MRI (75%)

2. TRAPS

7. In patients with a suspected TRAPS, which additional examination in respect to acute phase reactants, would be useful to complete the diagnostic work-up?

- Abdominal fat pad aspirates evaluated by polarizing microscopy of Congo Red stained sections in patients with suspected SAA amyloidosis (78.3%)

9. When checking a patient with recurrent fever, which other conditions should be taken into account as differential diagnosis with TRAPS?

- PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis) syndrome (70%)

12. Apart from IL-1 blockade, does the following drugs have a beneficial efficacy/safety ratio (trade-off) for improving symptoms for TRAPS compared to no treatment?

- Anti-TNF monoclonal antibody (33.3%)
- Anti-IL6 (63.2%)

3. MKD

5. Are the following drugs effective for the treatment of MKD, compared to no treatment?

- Anti IL-6 (55%)

4. DIRA

1. In patients with presumed DIRA can a similar diagnostic approach compared to patients who do not have a suspicion of an IL-1 mediated disease be used to make the diagnosis of DIRA?

- Blood and functional measures of organ damage (42.9%)

2. For patients with DIRA symptoms, is additional diagnostic workup such as bone scan and MRI/CT to assess odontoid compared to serologic labs only useful in the diagnosis DIRA?

- Bone scan for all patients regardless of the severity of disease (33%)

3. Is a firm genetic diagnosis always required before treatment can be started?

- Genetic diagnosis is required (22.2%)

II.6. Dropped statements

1. CAPS

2. In patients with clinical features of autoinflammatory disease suggestive of CAPS are there features listed below that can differentiate patients within the CAPS spectrum compared with patients lacking these characteristics in order to define such patients as having mild, moderate or severe disease?

- Urticaria-like rash (No: 86%)

3. In patients with presumed CAPS can we use similar diagnostic tests listed below compared to non-CAPS patients to more definitively make a diagnosis on the CAPS spectrum?

- Blood and functional measures of organ damage (No:100%)

12. In patients with CAPS, which of the therapies from the list below compared to no therapy have been shown to reduce flares and long-term complications

- Corticosteroids (No: 100%)

22. Should disease activity and damage be monitored in CAPS patients using the following methods, and does this differ along the clinical CAPS spectrum?

- Nuclear medicine scanning for amyloidosis (No:92%)

2. TRAPS

1. Skin biopsy is useful for the diagnosis of TRAPS (No:90%)

10. In patients with a suspected TRAPS, the presence of a positive genetic test, in respect to other autoinflammatory diseases, is always mandatory before treatment can be started? (No: 87.5%)

12. Apart from IL-1 blockade, does the following drugs have a beneficial efficacy/safety ratio (trade-off) for improving symptoms for TRAPS compared to no treatment?

- Colchicine (83.3%)

3. MKD

5. Are the following drugs effective for the treatment of MVKD, compared to no treatment?

- DMARDs (No: 94.7%)
- Colchicine (No: 82 %)

4. DIRA

5. In patients with DIRA, which of the therapies from the list below compared to no therapy have been shown to reduce flares and long-term complications

- Corticosteroids (No:92.9%)

- NSAIDs (No:97.5 %)

14. In patients with DIRA, is every other day therapy with anakinra compared to daily therapy sufficient to reduce flares and long-term complications in DIRA? (46.2%)

21. How should disease activity and damage be monitored? Does this differ along the clinical spectrum?

- PASI (100%)
- Other Psoriasis QoL measures (100%)
- CHAQ 100% (decided during the discussion)

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