MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN ASSOCIATED WITH COVID-19 (MIS-C)
DIAGNOSI DIFFERENZIALE E TERAPIA

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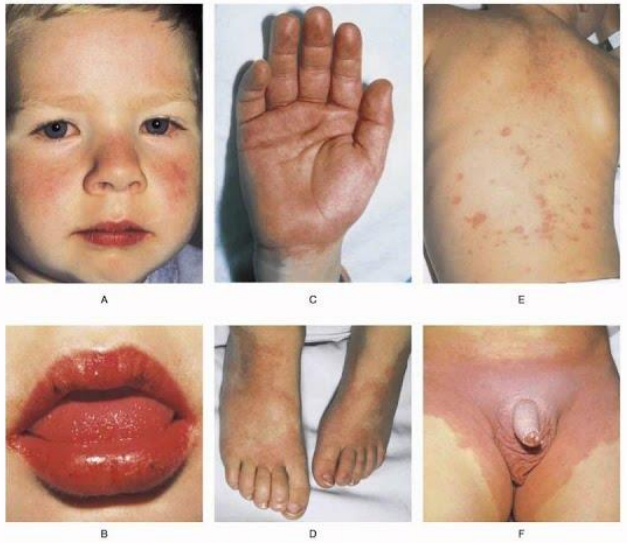
Diagnosi differenziale:

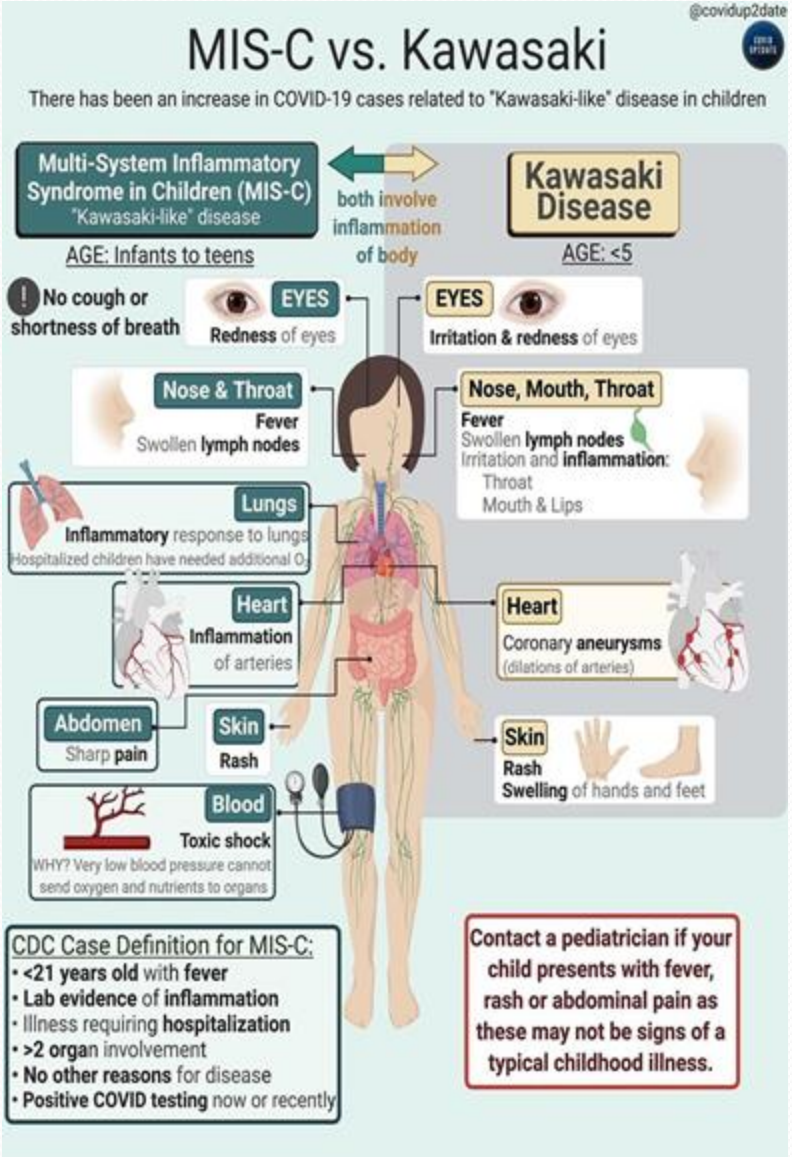
- ✓ **Malattia di Kawasaki (KD)** – Alcuni bambini (40-50%) lungo lo spettro MIS-C soddisfano i criteri per KD completo o incompleto:

Diagnostic criteria

- Presence of fever for at least 5 days + four of five criteria:
  - Bilateral bulbar conjunctival injection
  - Oral mucous membrane changes
  - Extremity changes
  - Polymorphous rash
  - Cervical lymphadenopathy



MIS-C VS. KAWASAKI



Recommendation Statement	Consensus Level
Patients with KD that is unrelated to SARS-CoV-2 will continue to require evaluation, diagnosis, and treatment during the SARS-CoV-2 pandemic.	High
MIS-C and KD unrelated to SARS-CoV-2 infections may share overlapping clinical features, including conjunctival infection, oropharyngeal findings (red and/or cracked lips, strawberry tongue), rash, swollen and/or erythematous hands and feet, and cervical lymphadenopathy.	Moderate to High
Several epidemiologic, clinical, and laboratory features of MIS-C may differ from KD unrelated to SARS-CoV-2. 1) There is an increased incidence of MIS-C in patients of African, Afro-Caribbean, and Hispanic descent, but a lower incidence in those of East Asian descent. 2) Patients with MIS-C encompass a broader age range, have more prominent GI and neurologic symptoms, present more frequently in shock, and are more likely to display cardiac dysfunction (arrhythmias and ventricular dysfunction) than children with KD. 3) At presentation, patients with MIS-C tend to have lower platelet counts, lower absolute lymphocyte counts, and higher CRP levels than patients with KD.	Moderate to High
Epidemiologic studies of MIS-C suggest that younger children are more likely to present with KD-like features while older children are more likely to develop myocarditis and shock.	Moderate
It is unknown if the incidence of CAA is different in MIS-C compared to KD; however, MIS-C patients without KD features can develop CAA.	Moderate to High

MIS-C

- Bambini più grandi e adolescenti
- Incidenza maggiore bambini neri e ispanici
- I sintomi gastrointestinali (in particolare il dolore addominale) sono molto evidenti
- La disfunzione miocardica e lo shock si verificano più comunemente
- I marcatori infiammatori (soprattutto CRP, ferritina e D-dimero) sono più elevati
- la conta assoluta dei linfociti e delle piastrine tende ad essere più bassa

KD classica

- Tipicamente neonati e bambini piccoli
- Incidenza maggiore nell'Asia orientale e nei bambini di origine asiatica
- Sintomi gastrontestinali meno evidenti
- La disfunzione miocardica e lo shock si verificano meno comunemente
- I marcatori infiammatori (soprattutto CRP, ferritina e D-dimero) sono meno elevati
- la conta assoluta dei linfociti e delle piastrine tende ad essere più alta

I pazienti con test SARS-CoV-2 positivo (o con esposizione a un individuo con COVID-19) che soddisfano anche i criteri per KD completo o incompleto sono considerati affetti da MIS-C e sono trattati con un trattamento standard per KD.

Diagnosi differenziale:

- **Lupus eritematoso sistemico (LES)** - Il LES è una malattia multisistemica, che può presentarsi all'esordio con una sintomatologia simile a quella della MIS-C. Tuttavia i pazienti con LES hanno un più frequente coinvolgimento renale e del SNC; inoltre l'esordio della malattia tende ad essere più subdolo e graduale rispetto alla MIS-C, sebbene possano esistere delle forme acute, anche se molto più rare.

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis or tenderness in at least 2 joints	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria > 0.5 g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG > 40 GPL *or* anti-β2GP1 IgG > 40 units *or* lupus anticoagulant	2
Complement proteins domain	
Low C3 *or* low C4	3
Low C3 *and* low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Sm antibody	6

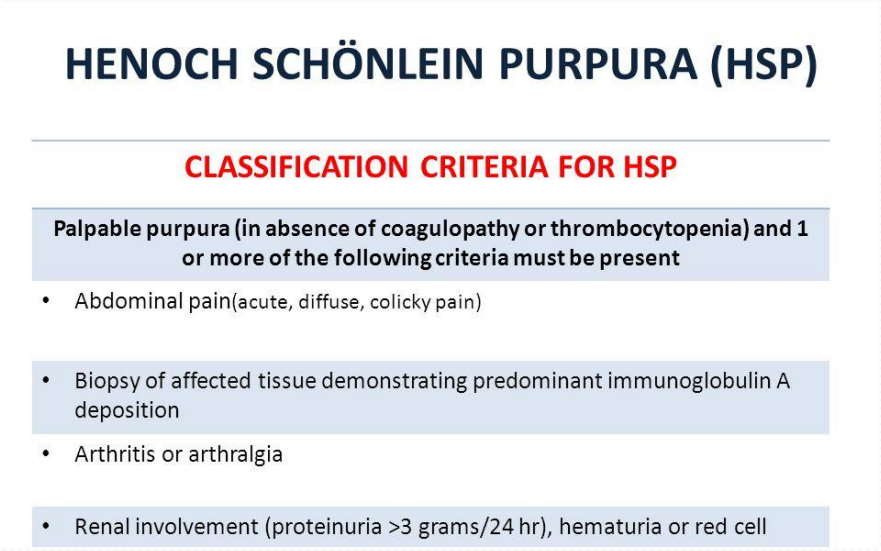
REFERENCE: Aringer et al. Abstract #2928. 2018 ACR/ARHP Annual Meeting

- ✓ **Classification criteria are not diagnosis criteria**
- ✓ All patients classified as having SLE must have ANA ≥ 1:80 (entry criterion)
- ✓ Patients must have ≥ 10 points to be classified as SLE
- ✓ Items can only be counted for classification if there is no more likely cause
- ✓ Only the highest criterion in a given domain counts
- ✓ SLE classification requires points from at least one clinical domain

@Lupusreference

Diagnosi differenziale:

- **Vasculite** – Le vasculiti diverse dalla KD possono presentarsi con febbre, eruzioni cutanee e marcatori infiammatori elevati. Una delle più frequenti vasculiti in età pediatrica è la porpora di Schonlein-Henoch. Le eruzioni cutanee osservate nella malattia associata a COVID-19 possono avere un aspetto che può simulare la vasculite (p. es., lesioni simili all'eritema pernio delle superfici acrali, a volte denominate "dita dei piedi COVID-19"), ma non sono vasculitiche.



HENOCH SCHÖNLEIN PURPURA (HSP)

CLASSIFICATION CRITERIA FOR HSP

Palpable purpura (in absence of coagulopathy or thrombocytopenia) and 1 or more of the following criteria must be present

- Abdominal pain(acute, diffuse, colicky pain)
- Biopsy of affected tissue demonstrating predominant immunoglobulin A deposition
- Arthritis or arthralgia
- Renal involvement (proteinuria >3 grams/24 hr), hematuria or red cell

Diagnosi differenziale:

- **Linfoistiocitosi emofagocitica (HLH)/sindrome da attivazione dei macrofagi (MAS)** – HLH e MAS hanno alcune caratteristiche in comune con MIS-C. HLH/MAS sono sindromi da eccessiva attivazione immunitaria che possono verificarsi in bambini precedentemente sani (spesso innescate da un'infezione) e in bambini con condizioni reumatologiche sottostanti (malattia di Still- artrite idiopatica giovanile). La maggior parte dei bambini con HLH/MAS presentano un coinvolgimento multiorgano, citopenie, anomalie della funzionalità epatica e sintomi neurologici. Il coinvolgimento cardiaco e gastrointestinale è meno comune e i sintomi neurologici sono più evidenti.

A febrile patient with known or suspected systemic JIA is classified as having MAS if patient has ferritin >700 ng/L *and* at least two of the following laboratory abnormalities:

- Platelets <180 x 10^9/mL
- Aspartate aminotransferase (AST) >50 U/L
- Triglycerides >160 mg/dL
- Fibrinogen <360 mg/mL

Review > Lancet Child Adolesc Health. 2020 Sep 18;S2352-4642(20)30304-7. doi: 10.1016/S2352-4642(20)30304-7. Online ahead of print.

A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process

Rachel Harwood [1], Benjamin Allin [2], Christine E Jones [3], Elizabeth Whittaker [4], Padmanabhan Ramnarayan [5], Athimalaipet V Ramanan [6], Musa Kaleem [7], Robert Tulloh [8], Mark J Peters [9], Sarah Almond [10], Peter J Davis [11], Michael Levin [4], Andrew Tometzki [12], Saul N Faust [3], Marian Knight [13], Simon Kenny [14], PIMS-TS National Consensus Management Study Group

Collaborators, Affiliations + expand

PMID: 32956615 PMCID: PMC7500943 DOI: 10.1016/S2352-4642(20)30304-7

Free PMC article

Practice Guideline > Arthritis Rheumatol. 2021 Apr;73(4):e13-e29. doi: 10.1002/art.41616. Epub 2021 Feb 15.

American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 2

Lauren A Henderson [1], Scott W Canna [2], Kevin G Friedman [1], Mark Gorelik [3], Sivia K Lapidus [4], Hamid Bassiri [5], Edward M Behrens [5], Anne Ferris [6], Kate F Kernan [7], Grant S Schulert [8], Philip Seo [9], Mary Beth F Son [1], Adriana H Tremoulet [10], Rae S M Yeung [11], Amy S Mudano [12], Amy S Turner [13], David R Karp [14], Jay J Mehta [5]

Affiliations + expand

PMID: 33277976 DOI: 10.1002/art.41616

Table 5. Immunomodulatory Treatment in MIS-C.

Recommendation Statement	Consensus Level
Patients under investigation for MIS-C without life-threatening manifestations should undergo diagnostic evaluation for MIS-C as well as other possible infectious and non-infectious etiologies before immunomodulatory treatment is initiated.	Moderate
Patients under investigation for MIS-C with life-threatening manifestations may require immunomodulatory treatment for MIS-C before the full diagnostic evaluation can be completed.	High
After evaluation by specialists with expertise in MIS-C, some patients with mild symptoms may require only close monitoring without immunomodulatory treatment. The panel noted uncertainty around the empiric use of IVIG in this setting to prevent CAAs.	Moderate

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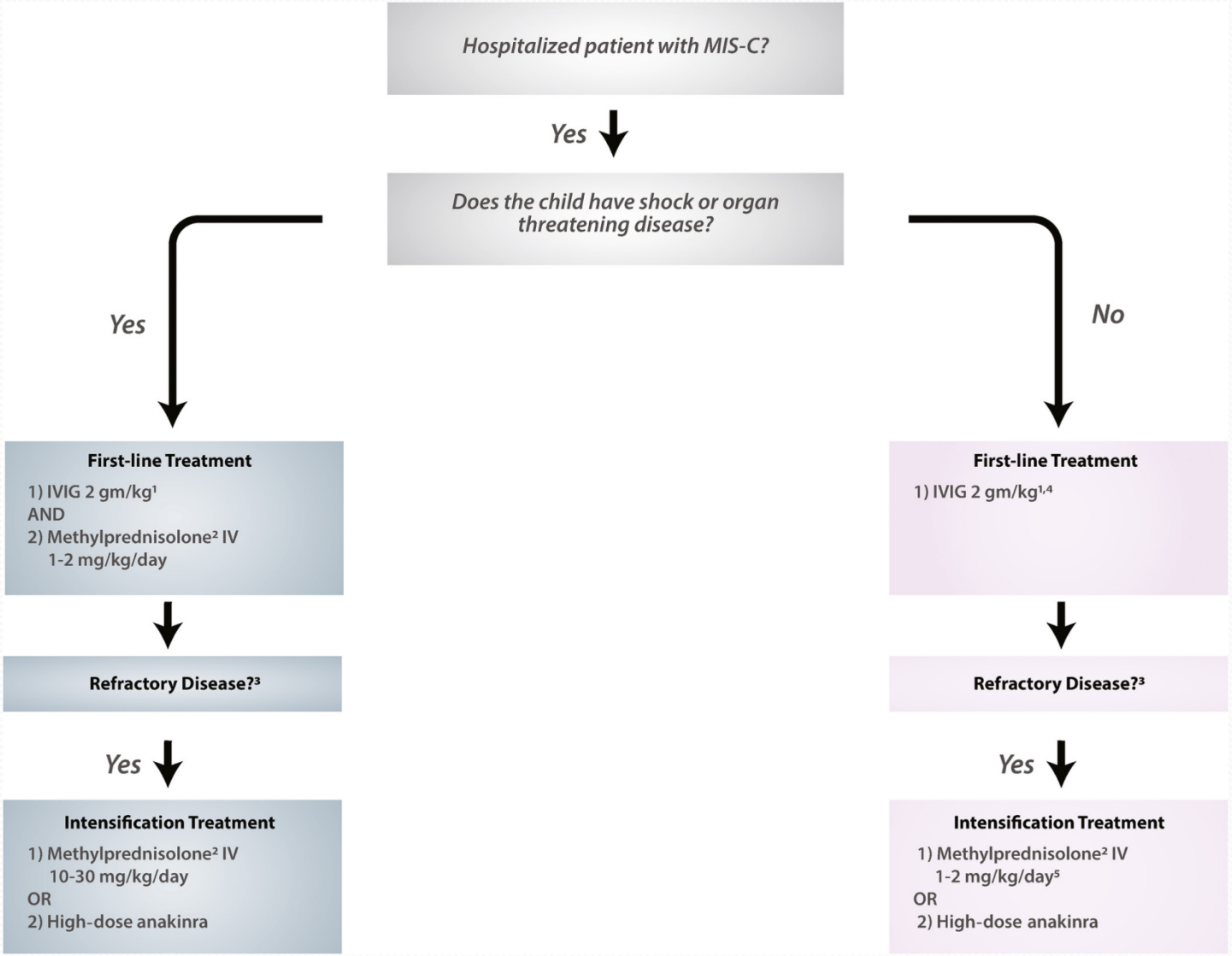

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Childhood multisystem inflammatory syndrome associated with COVID-19 (MIS-C): a diagnostic and treatment guidance from the Rheumatology Study Group of the Italian Society of Pediatrics

Marco Cattalini[1,2*†], Andrea Taddio[3,4†], Claudia Bracaglia[5], Rolando Cimaz[6], Sara Della Paolera[4], Giovanni Filocamo[7], Francesco La Torre[8], Bianca Lattanzi[9], Alessandra Marchesi[10], Gabriele Simonini[11], Gianvincenzo Zuccotti[12], Fiammetta Zunica[2], Alberto Villani[10†], Angelo Ravelli[13†] and on behalf of the Rheumatology Study Group of the Italian Society of Pediatrics

FIRST LINE THERAPY → HIGH DOSE IVIG

IVIG should be given to MIS-C patients who are hospitalized and/or fulfill KD criteria.	High

Cardiac function and fluid status should be assessed in MIS-C patients before IVIG treatment is provided. Patients with depressed cardiac function may require close monitoring and diuretics with IVIG administration.	High

Intravenous immunoglobulin	**2g/kg IV** (up to 70-80g) to be administered over at least 12 hours. In patients with heart failure immunoglobulins should be administered ***over at least 16 hours*** or, alternatively, the total dose should be splitted in two infusions 12 hours apart. A second dose of immunoglobulins should be considered in case of inadequate response

In patients with refractory MIS-C despite a single dose of IVIG, a second dose of IVIG is not recommended given the risk of volume overload and hemolytic anemia associated with large doses of IVIG.	High

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ADJUNCTIVE THERAPY → LOW-MODERATE OR HIGH DOSE GLUCOCORTICOIDS

Glucocorticoids
To be administered with IVIg upfront in case of heart involvement, severe disease, impending sHLH or toxic shock syndrome.

Low-moderate dose glucocorticoids (1-2 mg/kg/day) should be given with IVIG as adjunctive therapy for treatment of MIS-C patients with shock and/or organ threatening disease.	Moderate
In patients who do not respond to IVIG and low-moderate dose glucocorticoids, high dose, IV pulse glucocorticoids (10-30 mg/kg/day) may be considered, especially if a patient requires high dose or multiple inotropes and/or vasopressors.	Moderate

→ Methylprednisolone 1 mg/kg BID IV

→ Metylprednisolone 30 mg/kg (max 1 g) IV pulse q1d for 1-3 days, followed by Metylprednisolone i.v./Prednisone orally, based on the severity of clinical/laboratory features

→ Consider Dexamethasone 10mg/m2 q1d in case of sHLH or CNS involvement

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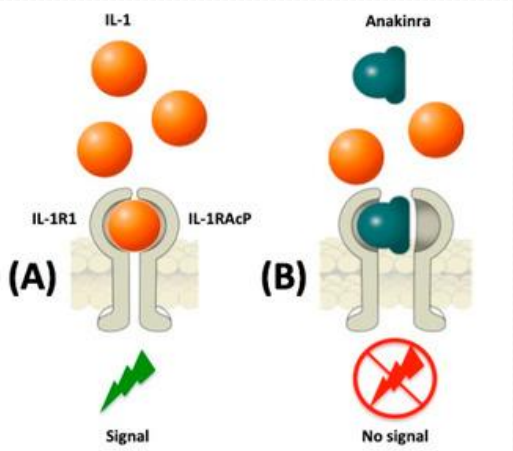
SECOND LINE THERAPY → ANAKINRA (ANTI-IL-1R)

Anakinra (>4 mg/kg/day IV or SQ) may be considered for treatment of MIS-C refractory to IVIG and glucocorticoids, in patients with MIS-C and features of macrophage activation syndrome (MAS), or in patients with contraindications to long-term use of glucocorticoids.	Moderate



→ **Anakinra**: 4-6mg/kg q1d SQ ***in case of persistent disease activity 48 hours after first-line treatment*** or in case of sHLH

→ **Anakinra**: 2mg/kg IV (max 100mg/dose) x 4/day

→ **Anakinra**: 2mg/kg (max 100mg) IV pulse followed by continuous infusion at a total daily dose of no more than 12 mg/kg or 400mg **in adjunction** to corticosteroids and IVIg in case of severe sHLH or **shock with cardiac failure**

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→ Large-spectrum antibiotics: while waiting for microbiology tests

→ Acetylsalicilic acid: 5mg/kg for at least 6-8 wks

→ Thromboprophylaxis with LMWH

RISK STRATIFICATION

↙ D-Dimer **> 5X** normal values

↘ Other known pro-thrombotic factors (current or prior VTE, severe LV dysfunction, large or giant CA aneurysms)

Administer LMWH at treatment dose → Enoxaparin 100 UI/kg BID

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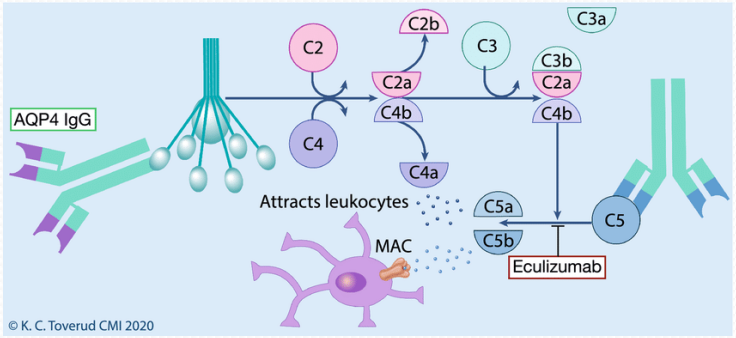
Eculizumab → in case of acute kidney failure and evidence of microangiopathy, consider treatment with eculizumab iv

Peso corporeo paziente	Fase iniziale	Fase di mantenimento
da 5 a < 10 kg	300 mg alla settimana x 1	300 mg alla settimana 2; poi 300 mg ogni 3 settimane
da 10 a < 20 kg	600 mg alla settimana x 1	300 mg alla settimana 2; poi 300 mg ogni 2 settimane
da 20 a < 30 kg	600 mg alla settimana x 2	600 mg alla settimana 3; poi 600 mg ogni 2 settimane
da 30 a < 40 kg	600 mg alla settimana x 2	900 mg alla settimana 3; poi 900 mg ogni 2 settimane
superiore a 40 kg	900 mg alla settimana x 4	1200 mg alla settimana 5; poi 1200 mg ogni 2 settimane



GRAZIE PER L'ATTENZIONE!