

Pharmacologic Management of Multisystem Inflammatory Syndrome in Children (MIS-C)

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Fall Advanced Practice Provider Conference



Akron Children's Hospital

Objectives

- Recognize symptoms of Multisystem Inflammatory Syndrome in Children (MIS-C)
 - Review pathophysiology of MIS-C
 - Describe pharmacologic options for MIS-C
-
- No relevant disclosures



Case: Jordan, 11-year-old black male

12/30/2020: Tactile fever, headache, body aches, fatigue, and cough.

1/1/2021: SARS-CoV-2 RT-PCR +

1/31/2021: Fevers, dizziness, fatigue, poor appetite, emesis, and myalgias

2/4/2021: Presented to ACH ED

- Temp 38.3 C; Tachycardic (133 bpm).
- Procalcitonin, troponin, Brain Natriuretic Peptide (BNP), lactic acid, and ESR normal
- CMP showed Na 131 mEq/L, Cl 93 mEq/L, mildly elevated liver enzymes (AST 65 U/L & ALT 52 U/L)
- C-Reactive Protein 13.3 mg/dL
- Hemoglobin 11.1 g/dL, Platelets $124 \times 10^9/L$



Evaluation of Children with Suspected MIS-C

MIS-C: Diagnostic and Management Guidelines:

Initial Evaluation / Management for MIS-C

Does the patient meet ALL of the following?

- Age ≤ 21 years
- Fever ≥ 24 hours (objective or subjective)
- At least 2 suggestive clinical features:
 - Gastrointestinal
 - Cardiovascular
 - Mucocutaneous
 - Edema/erythema of the hands or feet
 - Non-vesicular rash
 - Cervical Lymphadenopathy
 - Neurologic

Epidemiologic link to COVID-19 preferred but not required

- History, exam, Vital signs with BP
- O₂ to keep sats > 90%
- PIV, fluid resuscitation – limit boluses to 5-10 ml/kg. Check for rales, hepatomegaly & gallop after each bolus.
- Measure liver using measuring tape & mark liver edge with a pen
- Exclude alternative diagnoses

Alternative diagnoses:

- Viral myocarditis
- Lyme myocarditis with or without heart block
- Bartonella myocarditis (much less common than endocarditis)
- Septic shock
- Toxic shock (Staph or Streptococcal)
- Appendicitis with/without shock
- Kawasaki disease: If patient presents with symptoms consistent with incomplete or complete KD without known COVID-19 exposure or personal history of COVID-19 illness within the previous 4 weeks → Manage as per Kawasaki Disease algorithm.

- Ill-appearing
- Hypotension, poor perfusion
- Signs of sepsis or shock

- Well-appearing
- Vital signs normal for age

Yes

- MIS-C workup **Priority 1**¹

¹Screening labs may be appropriate at the discretion of the ED provider

No

- Obtain MIS-C workup **Priority 1 & 2**²
- Give Ceftriaxone & Vancomycin after cultures obtained. **Vancomycin should be reserved for children with critical illness (admitted to PICU)**

Are both Criteria met?

- CRP ≥ 5 mg/dl
- At least 1 additional laboratory feature
 - ALC < 1000/μL if older than 8 months (< 4500 if age < 8 mo)
 - Platelet count < 150,000/μL
 - Na < 135 mmol/L
 - Neutrophilia
 - Albumin < 3 g/dl

Lab results should not delay transfer to PICU if clinically indicated

No

- MIS-C less likely
- Re-evaluate in 1-2 days if symptoms do not improve or if new symptoms develop
- Follow up with PCP within 24 hours with repeat labs if symptoms persist

Are any of the following present?

- Shock/hypotension
- Cardiac dysrhythmias
- ↑ Troponin T (should be discussed with PICU attending)
- Need for invasive or non-invasive respiratory support
- Concern for rapid progression

Yes

- Admit to PICU for management
- Obtain STAT Echocardiogram
- Rheumatology, Infectious Disease & Cardiology consults
- Go to Severe MIS-C Algorithm**

No

- Admit to Hospital Medicine
- Obtain routine Echocardiogram
- Infectious Disease & Cardiology consults
- Go to Mild MIS-C Algorithm**

MIS-C Workup

Screening Labs

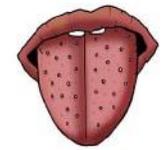
Additional testing as indicated to evaluate for other etiologies (See MIS-C Order set & Smart phrase)

- Screening Labs:** Appropriate workup if well-appearing & high probability of discharge to home would include CBC with differential, CMP & CRP.
- Priority 1:** CBC with differential, CMP, CRP, Lactate, Blood culture, UA (bag), Urine culture, BNP, Troponin T, Procalcitonin, D-dimer, Respiratory Film Array (NP swab) and SARS-CoV-2 IgG; CXR and EKG.
 - If patient has a + SARS-CoV-2 PCR + on admission or within 6 weeks of admission, do not order SARS-CoV-2 nucleocapsid antibody
 - BNP and Troponin T to be ordered STAT
- Priority 2:** Fibrinogen, Ferritin, LDH, PT/PTT/INR
 - Lyme antibodies, Bartonella antibodies (treatable causes of myocarditis)
 - Triglycerides & sIL2-R if HLH or MAS is on the differential

Symptoms of Multisystem Inflammatory Syndrome in Children (MIS-C)



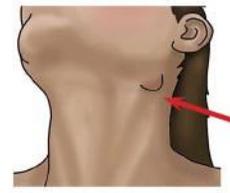
Red or Pink Eyes (Conjunctivitis)



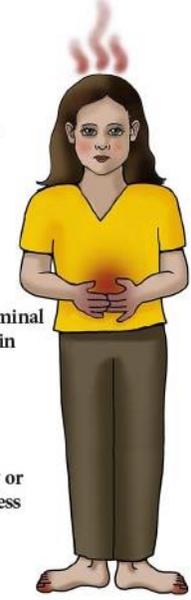
Loss of Appetite

Red, Cracked Lips or Red Tongue (looks like a strawberry)

Enlarged Gland (lymph node on one side of neck)



Fever Lasting Several Days (100.4F or more)



Diarrhea and/or Vomiting



Swollen Hands and Feet (may also be red)

Hive-like Skin Rash



Abdominal Pain

Irritability or Sluggishness



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MIS-C interim guidance algorithm v. 3.2 – 6/21/2021



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Case: Jordan, 11-year-old black male

- ED: 20 cc / kg bolus & Antipyretics
- Hospital Course:
 - Hospital Day #1 – Infectious Disease confirms MIS-C; 2 g/kg intravenous immunoglobulin (IVIG) & 30 mg/kg methylprednisolone; Echo normal
 - Hospital Day #2 – hypotensive, ↑tachycardia increasing
 - Hospital Day #3 – 2-20 cc/kg bolus due to hypotension & tachycardia with some improvement; repeat echo shortening fraction 28% (was 36%). Transferred to Pediatric Intensive Care Unit (PICU)

Component	Latest Ref Rng & Units	2/4/2021	2/4/2021	2/5/2021	2/6/2021	2/7/2021
		1:27 AM	11:30 PM			
Band Neutrophil	5 - 11 %	43 (H)		36 (H)	4 (L)	43 (H)
Segmented Neutrophils	33 - 61 %	30 (L)		45	86 (H)	48
Lymphocytes	28 - 48 %	22 (L)		12 (L)	8 (L)	9 (L)
Atypical Lymphocytes	0 - 8 %			3		
% Monocytes	3 - 6 %	5		4	2 (L)	
% Metamyelocytes	0 - 0 %	0		0	0	0
% Myelocytes	0 - 0 %	0		0	0	0
% Promyelocytes	0 - 0 %	0		0	0	0
Absolute Neutrophil No.	1.6 - 7.6 10E3/uL	6.6		7.5	10.1 (H)	13.9 (H)
Anisocytosis	NA	Slight		Slight		
Poikilocytosis	NA			Slight	Occasional	
Hypochromia	NA			Occasional	Slight	
Polychromasia	NA			Occasional		
RBC Inclusions	NA			Occasional		
WBC Inclusions	NA	Slight				
C-Reactive Protein	0.0 - 1.0 mg/dL	13.3 (H)	14.6 (H)		16.7 (H)	19.3 (H)
B-Type Natr Peptide	0.0 - 125.0 pg/mL	74.0	608.0 (H)	1,219.0 (H)	4,975.0 (H)	14,594.0 (H)

IVIG
Steroids
↓

Steroids
↓

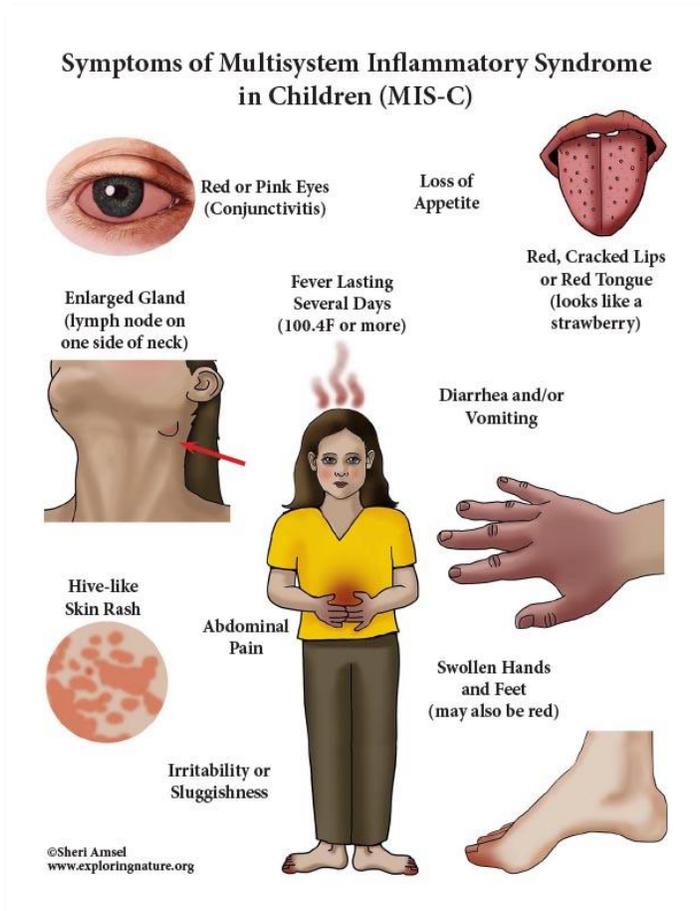
Steroids
PICU
↓



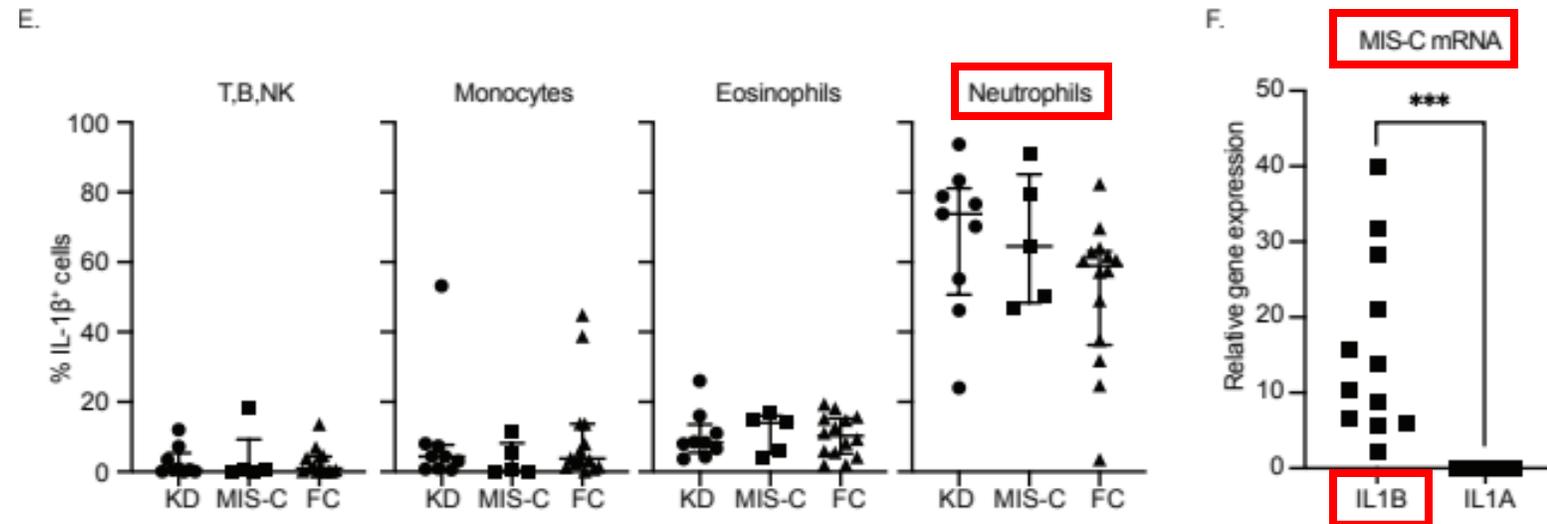
**WHAT
HAPPENED?**



MIS-C results from neutrophil dysregulation



- ↑ # Neutrophils
- ↑ Increased immature neutrophils
- ↑ Interleukin-1b (IL-1b) production



Zhu et al. Immune response to intravenous immunoglobulin in patients with Kawasaki disease and MIS-C. J Clin Invest. 2021 Aug 31.

MIS-C treatment must address neutrophil dysregulation & IL-1b



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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

ACR MIS-C Treatment Recommendation Legend

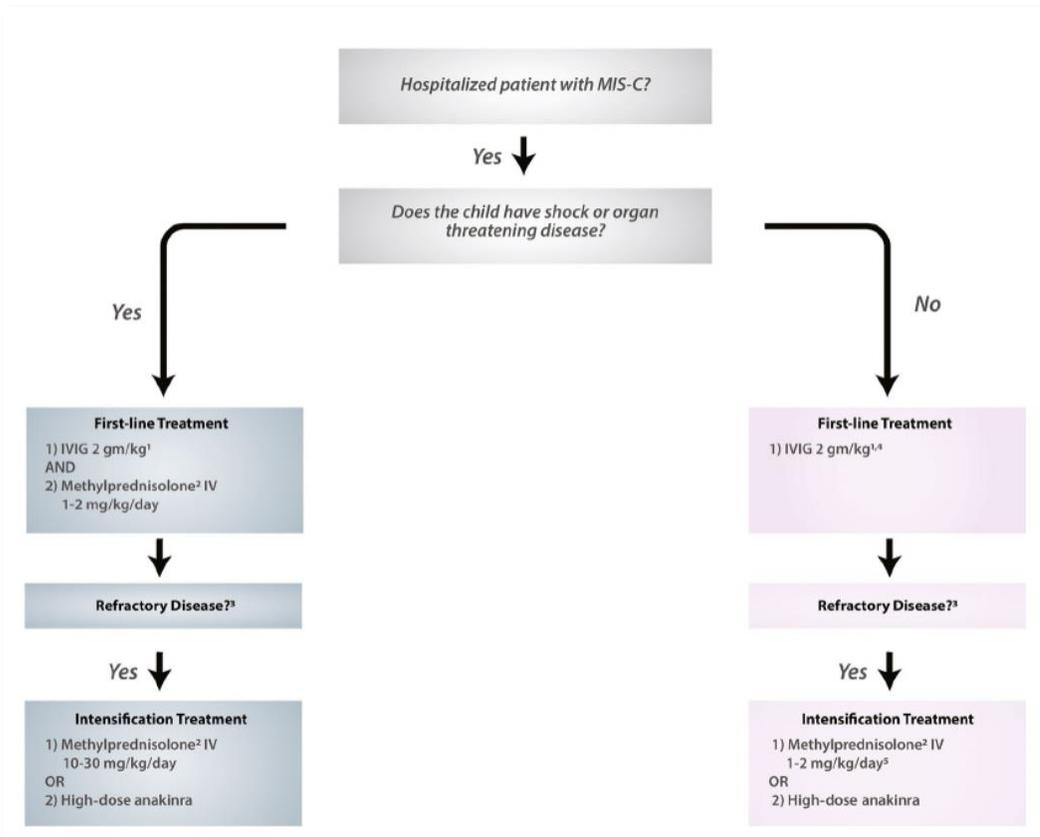
- = intravenous immunoglobulin
- = glucocorticoids
- = anakinra



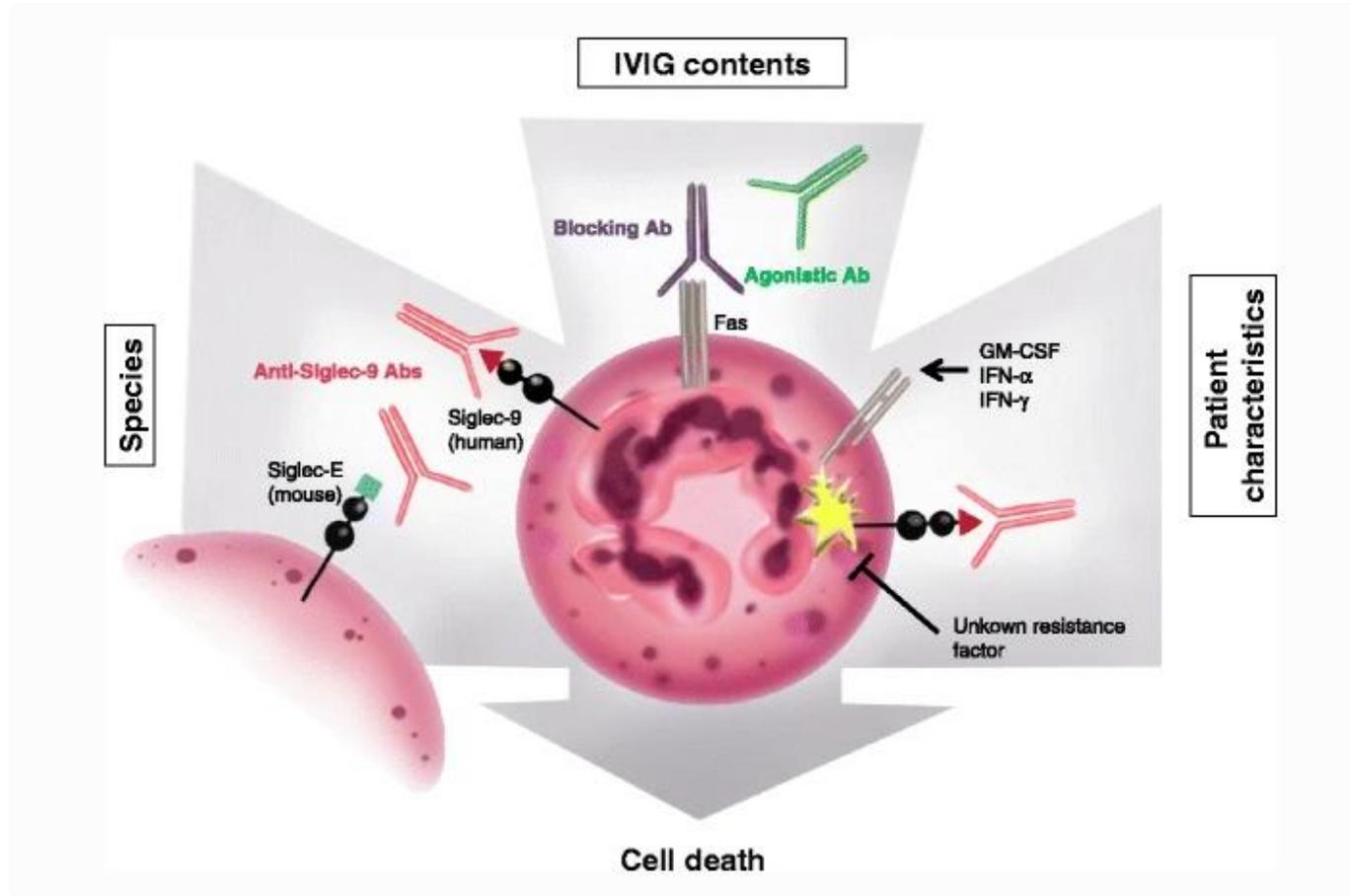
Table 5. Immunomodulatory treatment in MIS-C*

Guidance statement	Level of consensus
Patients under investigation for MIS-C without life-threatening manifestations should undergo diagnostic evaluation for MIS-C as well as other possible infections and non-infection-related conditions 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 only require close monitoring without immunomodulatory treatment. The panel noted uncertainty around the empiric use of IVIG to prevent CAAs in this setting.	Moderate
A stepwise progression of immunomodulatory therapies should be used to treat MIS-C with IVIG considered first-tier therapy. Glucocorticoids should be used as adjunctive therapy in patients with severe disease or as intensification therapy in patients with refractory disease.	High
IVIG should be given to MIS-C patients who are hospitalized and/or fulfill KD criteria.	High
High-dose IVIG (typically 2 gm/kg, based on ideal body weight) should be used for treatment of MIS-C.	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
In some patients with cardiac dysfunction, IVIG may be given in divided doses (1 gm/kg daily over 2 days).	Moderate
Low-to-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-to-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
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
Low-to-moderate-dose steroids (1–2 mg/kg/day) may also be considered in patients with milder forms of MIS-C who are persistently febrile and symptomatic despite a single dose of IVIG.	Moderate
Anakinra (>4 mg/kg/day IV or SC) may be considered for treatment of MIS-C refractory to IVIG and glucocorticoids in patients with MIS-C and features of macrophage activation syndrome or in patients with contraindications to long-term use of glucocorticoids.	Moderate
Serial laboratory testing and cardiac assessment should guide immunomodulatory treatment response and tapering. Patients may require a 2–3-week, or even longer, taper of immunomodulatory medications.	High

* MIS-C = multisystem inflammatory syndrome in children; IVIG = intravenous immunoglobulin; CAAs = coronary artery aneurysms; SC = subcutaneous.

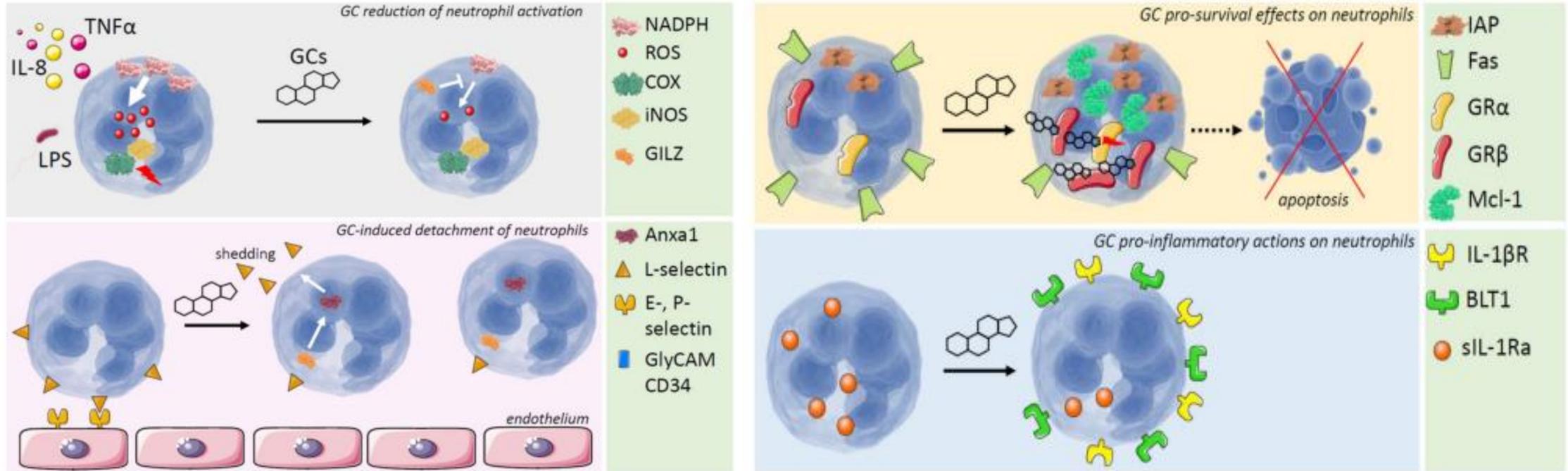


Intravenous immunoglobulin induces neutrophil death.



“increased neutrophil cytotoxicity of IVIG in a cytokine-rich environment may contribute to the antiinflammatory effects of IVIG in the broad range of inflammatory diseases associated with causative neutrophil participation.”

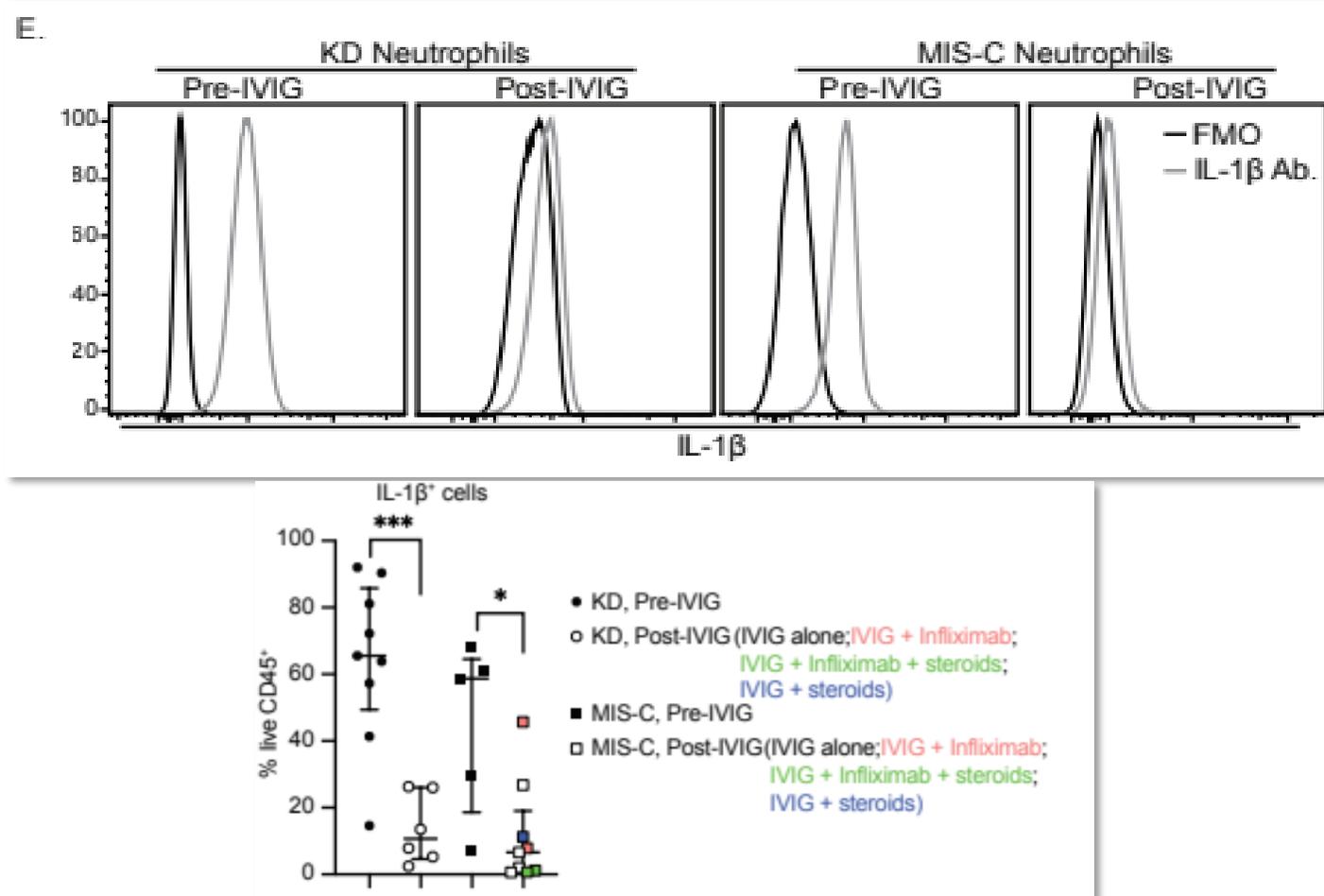
Glucocorticoids reduce neutrophil activation.



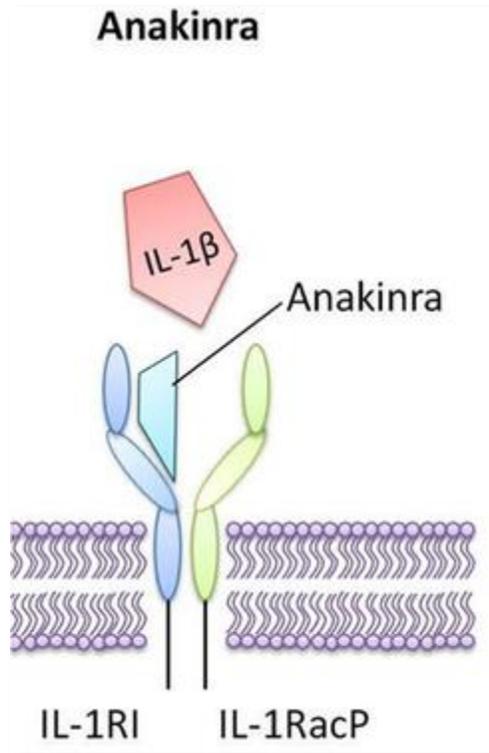
Ronchetti S, Ricci E, Migliorati G, Gentili M, Riccardi C. How Glucocorticoids Affect the Neutrophil Life. Int J Mol Sci. 2018 Dec 17;19(12).



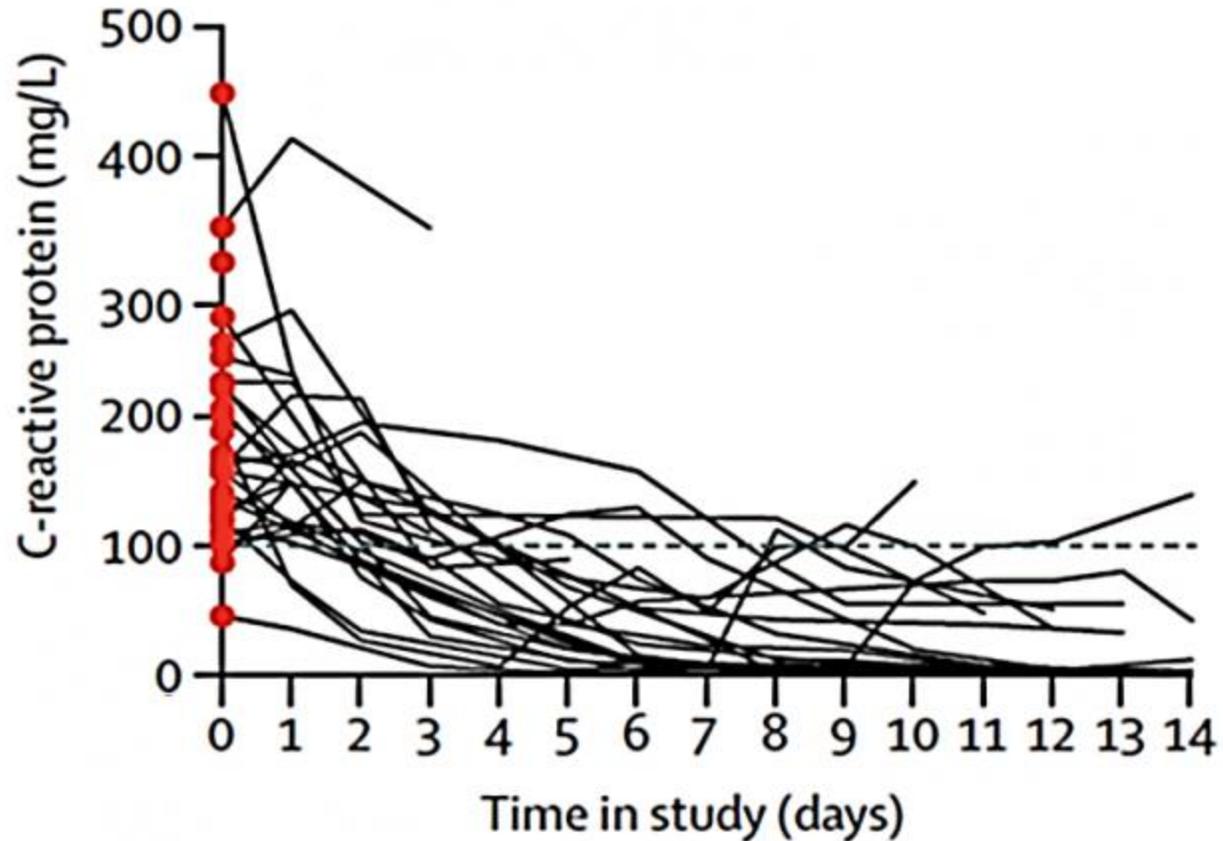
IVIg & glucocorticoids decrease number and activity of neutrophils.



Anakinra blocks Interleukin-1 receptors



- Anakinra – start 6 mg/kg/day IV divided q6 hours; may need 15-20 mg/kg/day
- Use CRP as indicator of response (≥40% reduction within 48 hours)



Cavalli et al., Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: A retrospective cohort study, *Lancet Rheumatology*, Vol 2, Pages e325 -e331, Copyright Elsevier 2020.

Case: Jordan, 11-year-old black male

Hospital Day #3

- Moved to PICU due to declining cardiac function
- Started anakinra 8 mg/kg/ day divided q6 hours
- Steroids continued

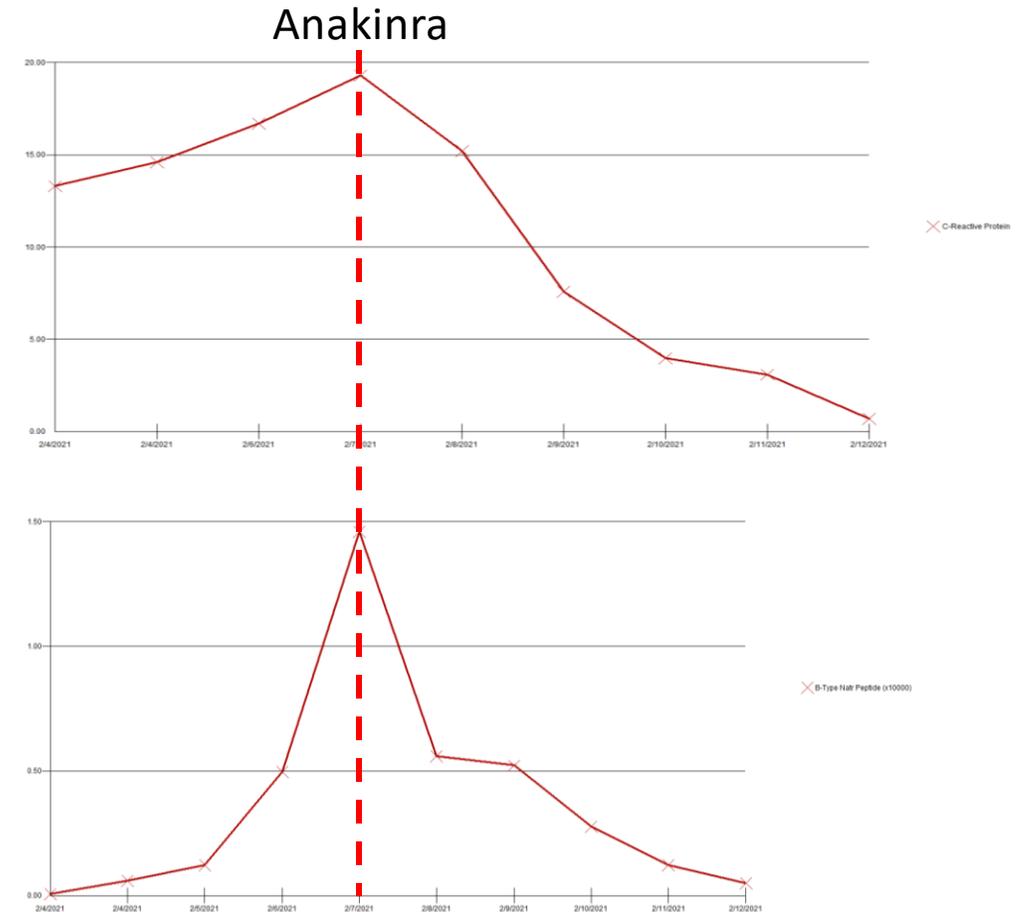
Hospital Day #5

- Echo normalized, cardiac indices down-trending

Hospital Day #7

- Anakinra discontinued & discharged to home

Echocardiograms normal 2 weeks and 6 weeks after discharge



Question #1

- You are seeing a 9-year-old white female for fever, abdominal pain, hive-like rash, and eye redness which started 3 days ago. Four weeks prior to the onset of this illness, her 12-year-old sister and mother tested positive for SARS-CoV-2. As part of the evaluation, you are obtaining screening labs for Multisystem Inflammatory Syndrome in Children (MIS-C). Which of the following lab results would you expect to see if your patient has MIS-C?
 - A. C-reactive protein <2 mg/dL
 - B. Higher percentage of lymphocytes than neutrophils on manual differential
 - C. Platelet count <150 x 10⁹/L
 - D. Creatine Kinase >2,000 units/L
 - E. Antinuclear antibody titer >1:640



Question #2

- Your patient has lab findings consistent with MIS-C. She is admitted to the hospital and treatment for mild MIS-C without shock or organ-threatening disease is initiated. What is the main cellular effect of the immunomodulatory drug recommended for use as 1st therapy in this clinical scenario?
 - A. Down regulation of Interleukin-1 receptors
 - B. Up regulation of interferon-gamma transcription
 - C. Blockade of Interleukin-1 receptors
 - D. Inhibition of IL-6 binding activity
 - E. Neutrophil apoptosis



Question #3

- Following 1st line treatment for MIS-C, your patient remains febrile and develops fluid refractory hypotension and tachycardia. An echocardiogram reveals her ejection fraction is 15% and her Brain Natriuretic Peptide level is 10x upper limit of normal. She is transferred to the Pediatric Intensive Care Unit for myocarditis. What is the main cellular effect of the immunomodulatory drug recommended in this clinical scenario?
 - A. Down regulation of Interleukin-1 receptors
 - B. Up regulation of interferon-gamma transcription
 - C. Blockade of Interleukin-1 receptors
 - D. Inhibition of IL-6 binding activity
 - E. Neutrophil apoptosis

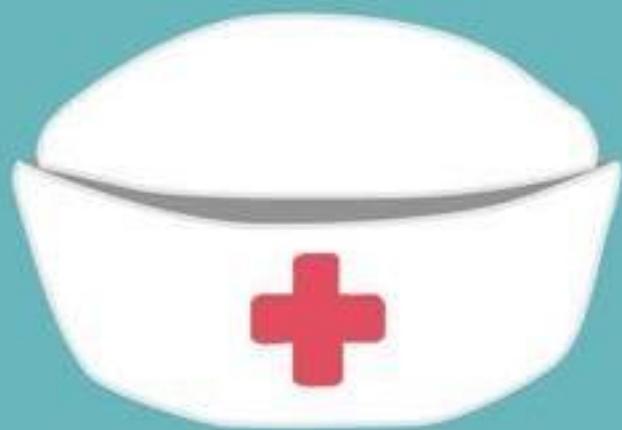


Conclusions

- MIS-C results from dysregulation of neutrophils and overproduction of IL-1b.
- IVIG and glucocorticoids reduce neutrophil activity over 3-5 days.
- Anakinra blocks effects of interleukin-1b resulting in measurable biochemical changes in 24-48 hours.



THANK YOU



FOR ALL YOU DO