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.

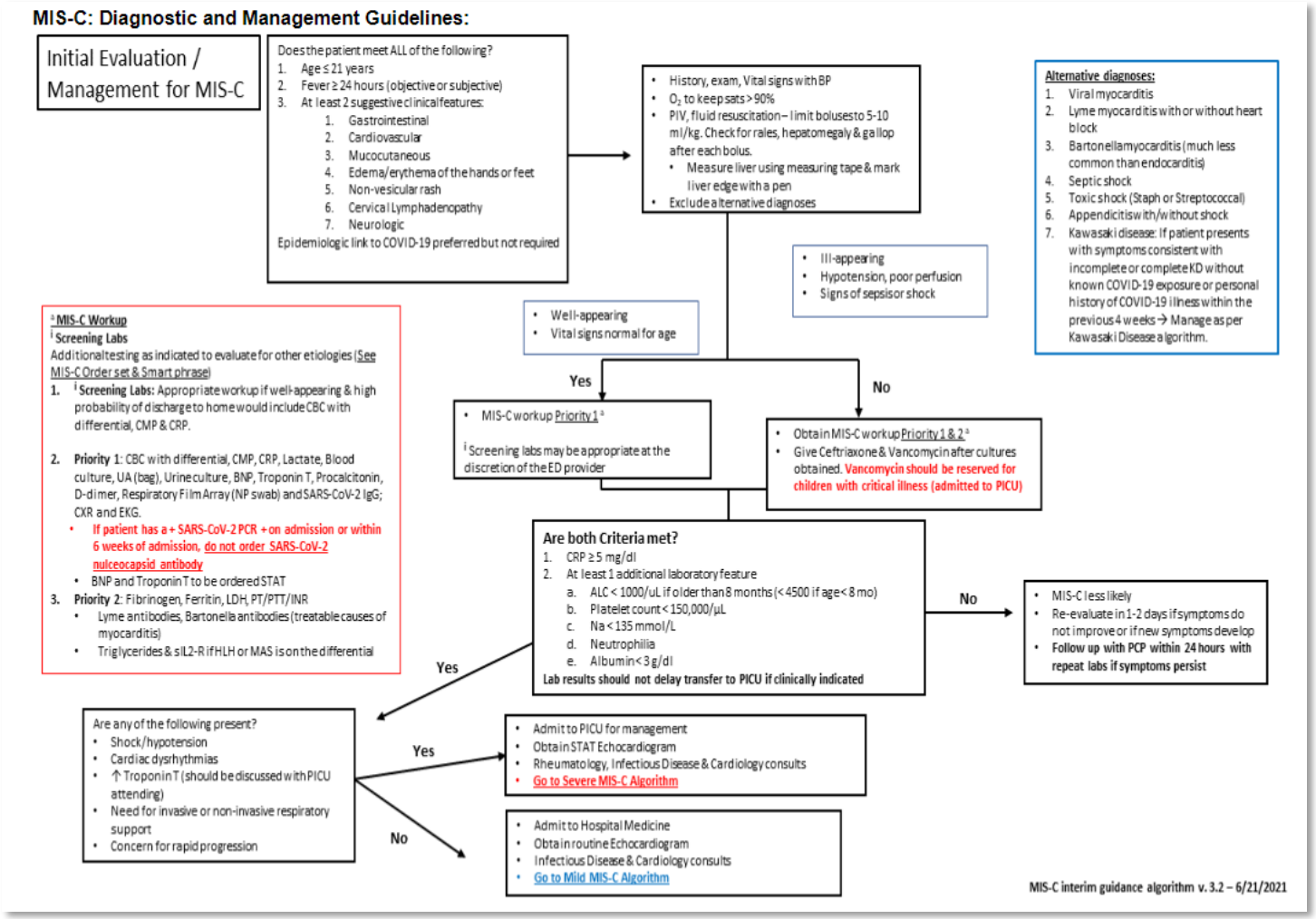
1/1/2021: SARS-CoV-2 RT-PCR +

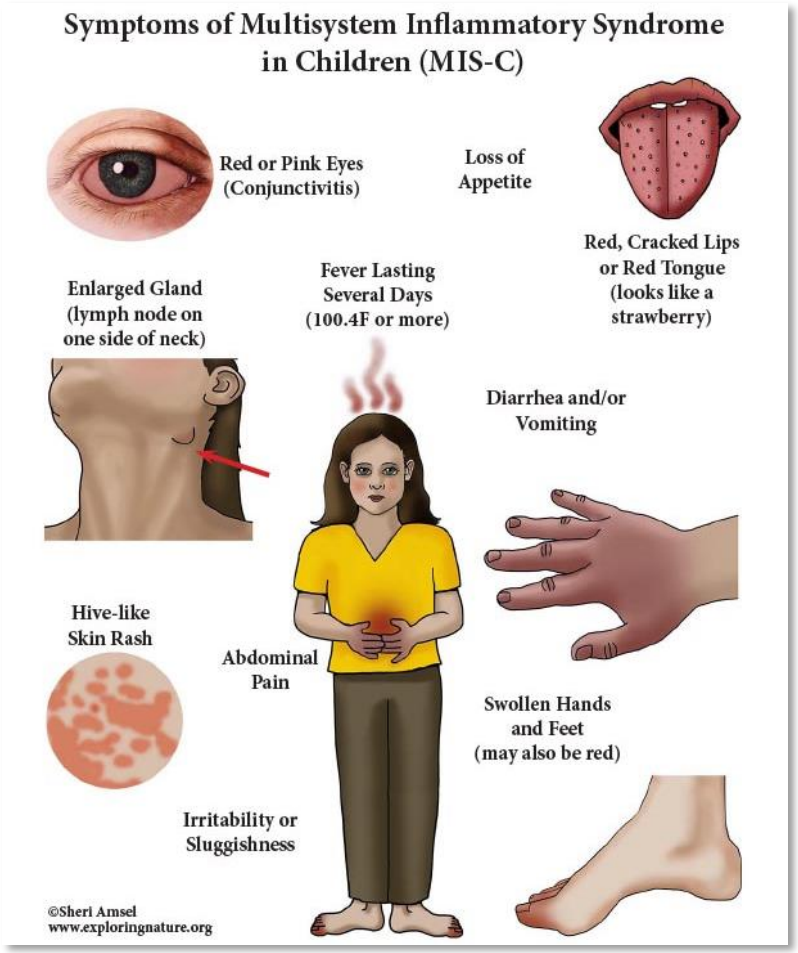
1/31/2021: Fevers, dizziness, fatigue, poor appetite, emesis, and myalgias

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 x 10^9/L

Evaluation of Children with Suspected MIS-C





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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)

IVIG Steroids | Steroids | Steroids PICU

Component	Latest Ref Rng & Units	2/4/2021 1:27 AM	2/4/2021 11:30 PM	2/5/2021	2/6/2021	2/7/2021
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)**

WHAT HAPPENED?

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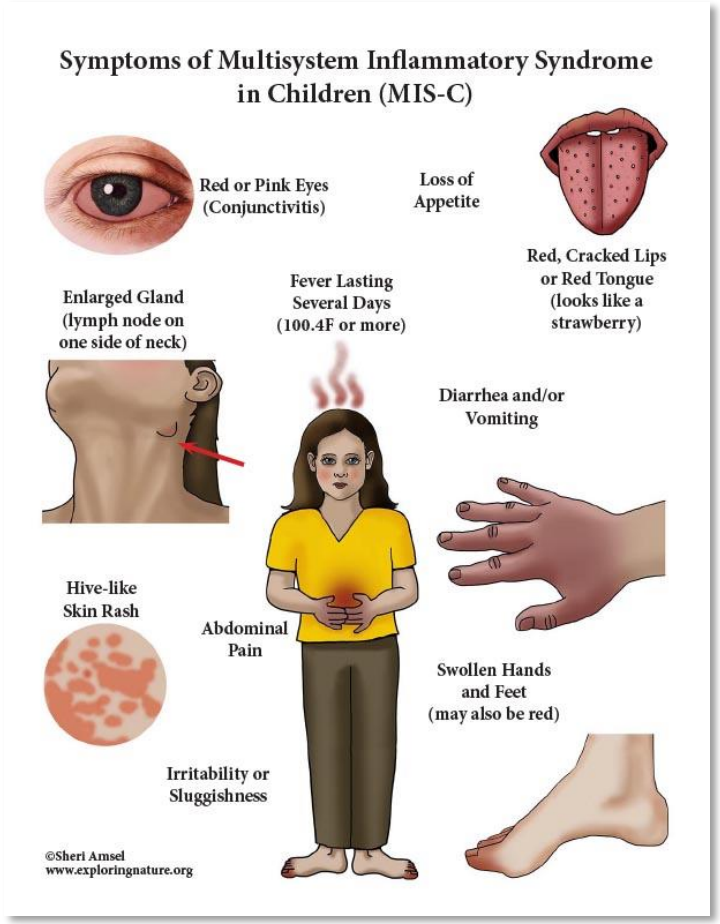
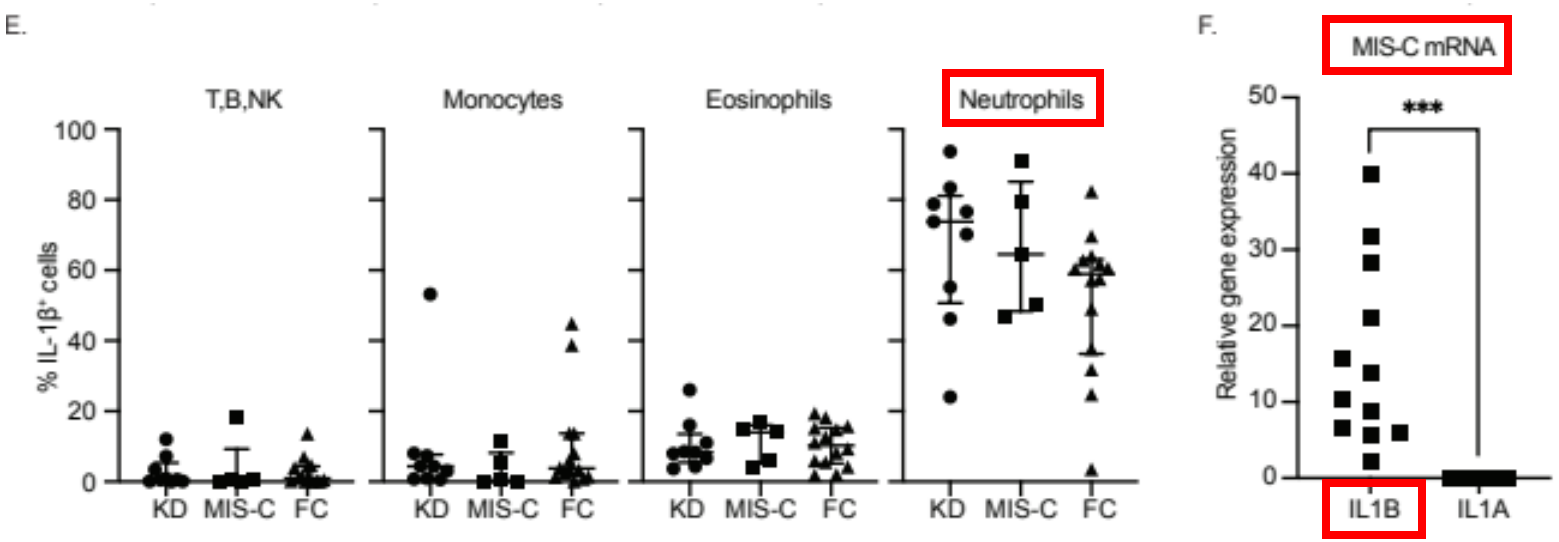
MIS-C results from neutrophil dysregulation



- ↑ # 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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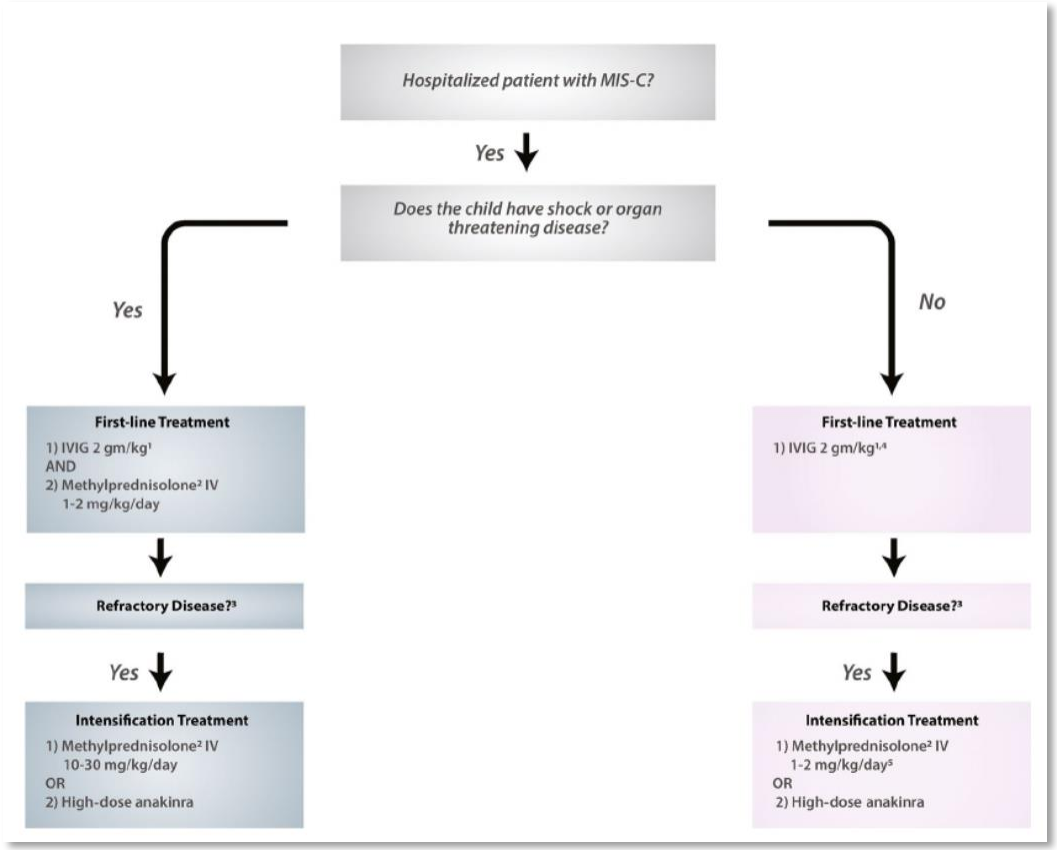
DOI 10.1002/art.41616

American College of Rheumatology
Empowering Rheumatology Professionals

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.

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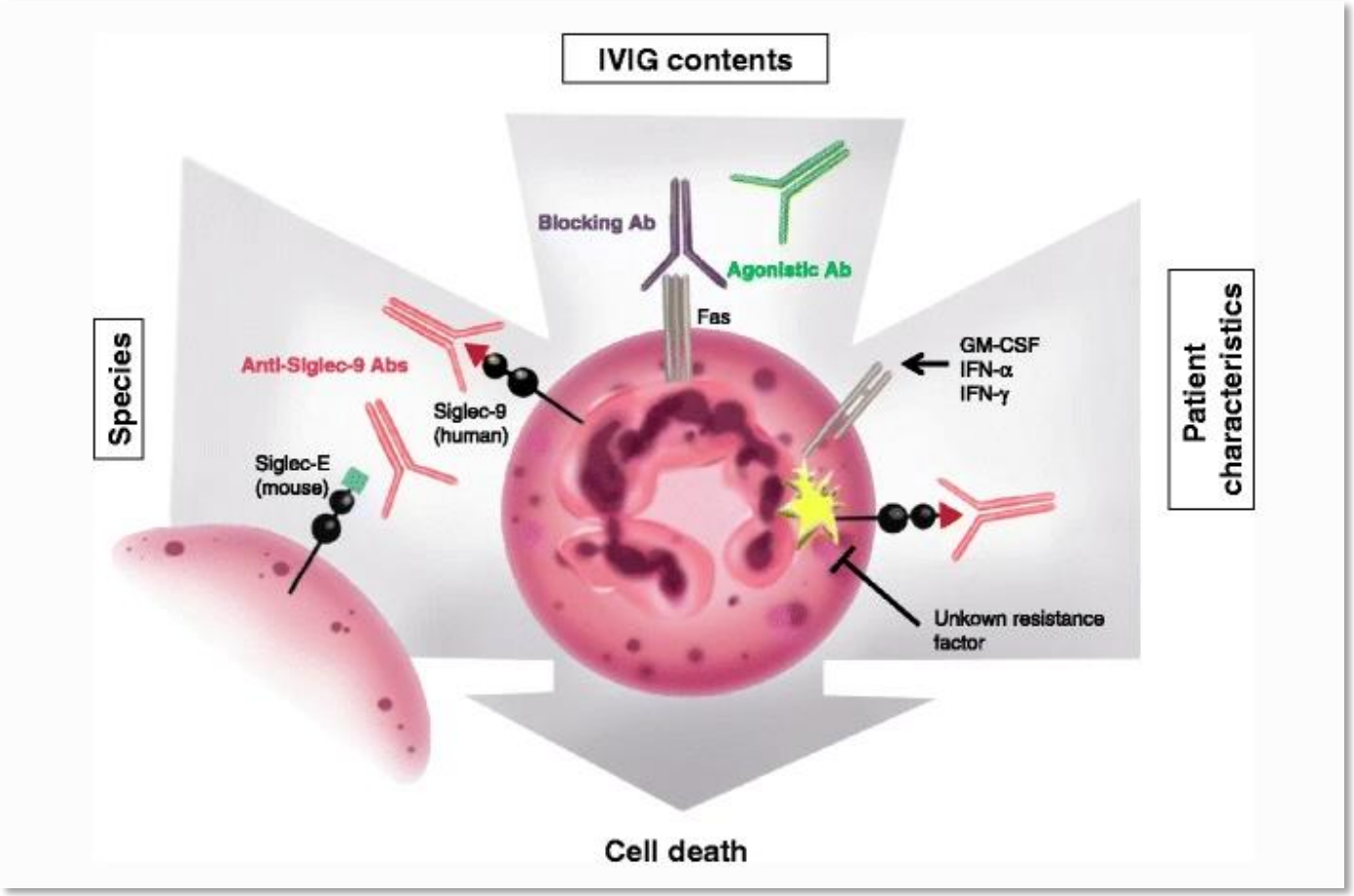
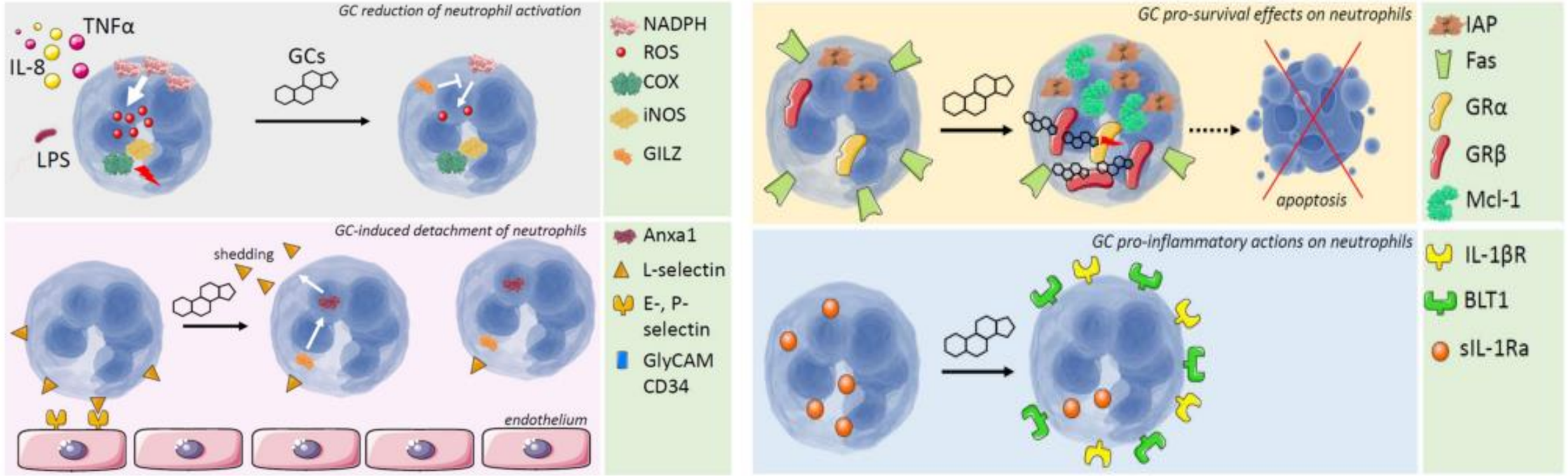
Intravenous immunoglobulin induces neutrophil death.



"***<u>increased neutrophil cytotoxicity of IVIG in a cytokine-rich environment</u>*** may contribute to the antiinflammatory effects of IVIG in the broad range of inflammatory diseases associated with causative neutrophil participation."

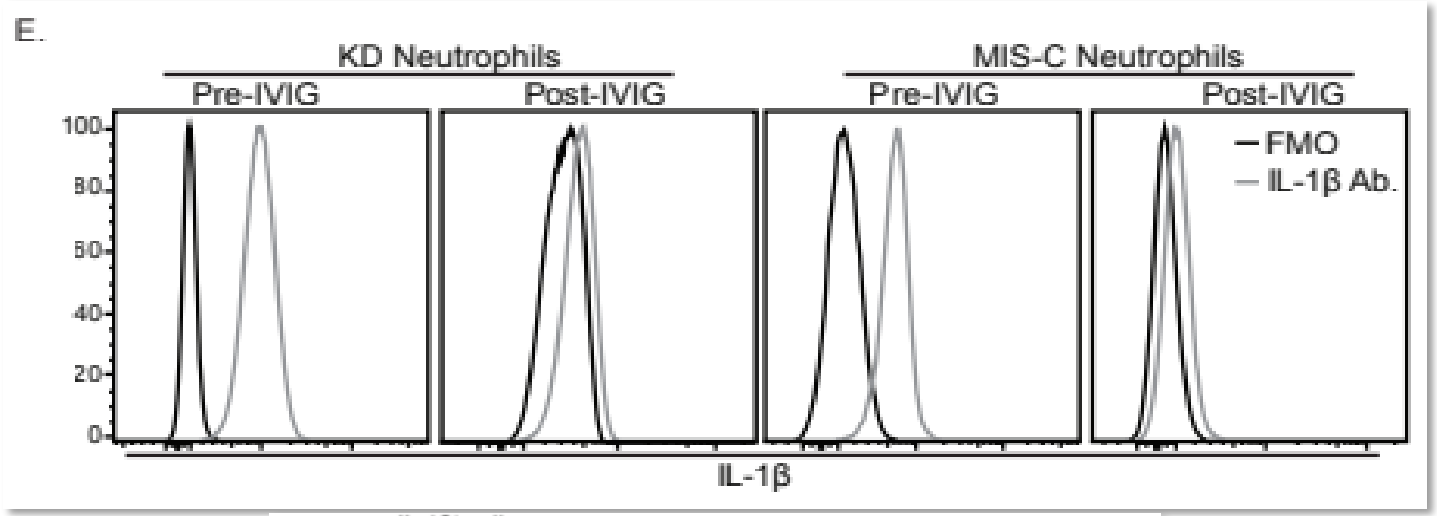
von Gunten S, Simon HU. Cell death modulation by intravenous immunoglobulin. J Clin Immunol. 2010 May;30 Suppl 1:S24-30. doi: 10.1007/s10875-010-9411-8. PMID: 20405180

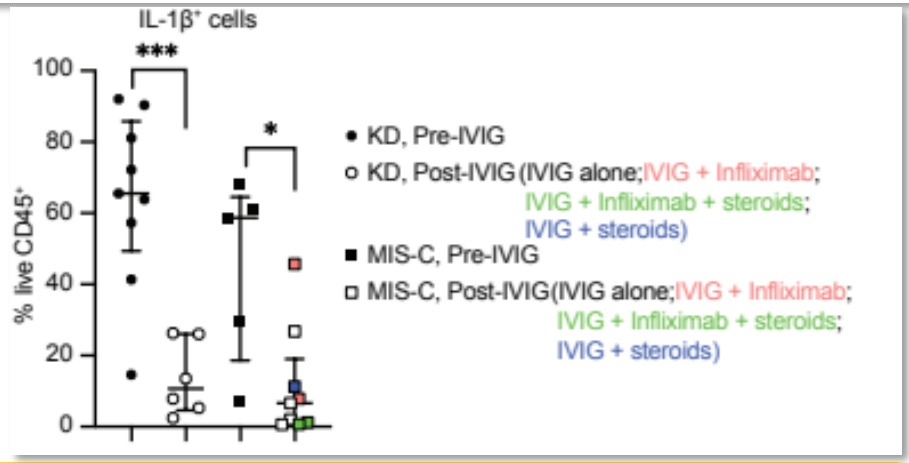
Glucocorticoids reduce neutrophil activation.



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.





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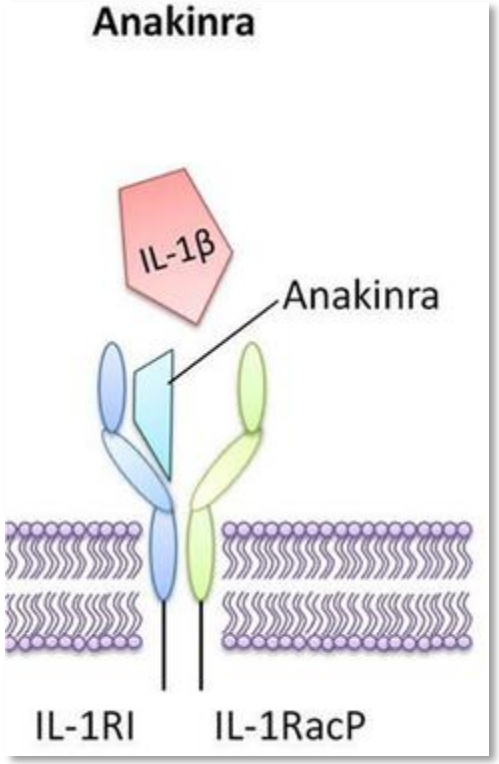
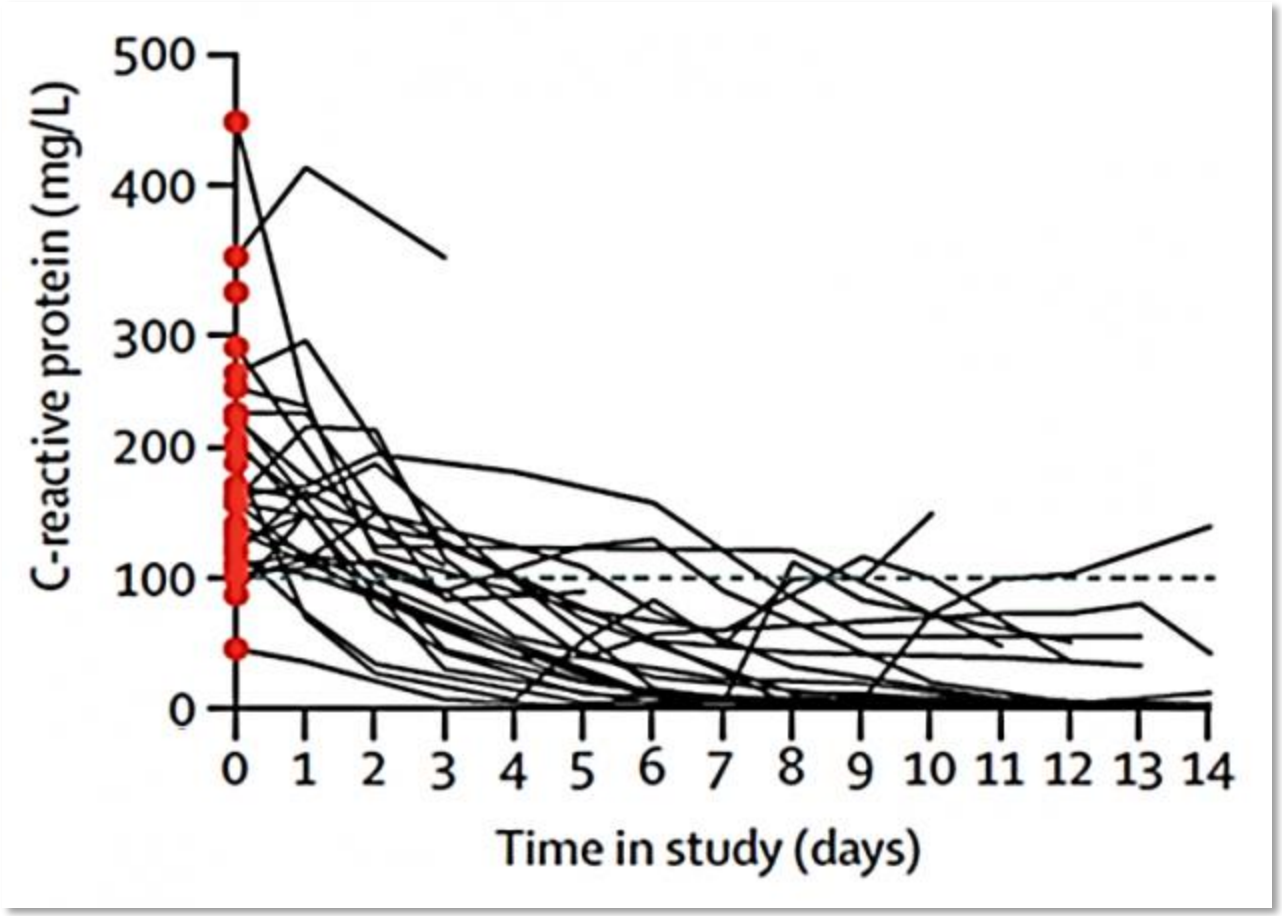
Anakinra blocks Interleukin-1 receptors



- **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.

Phadke O, Rouster-Stevens K, Giannopoulos H, Chandrakasan S, Prahalad S. Intravenous administration of anakinra in children with macrophage activation syndrome. Pediatr Rheumatol Online J. 2021;19(1):98. Published 2021 Jun 29.

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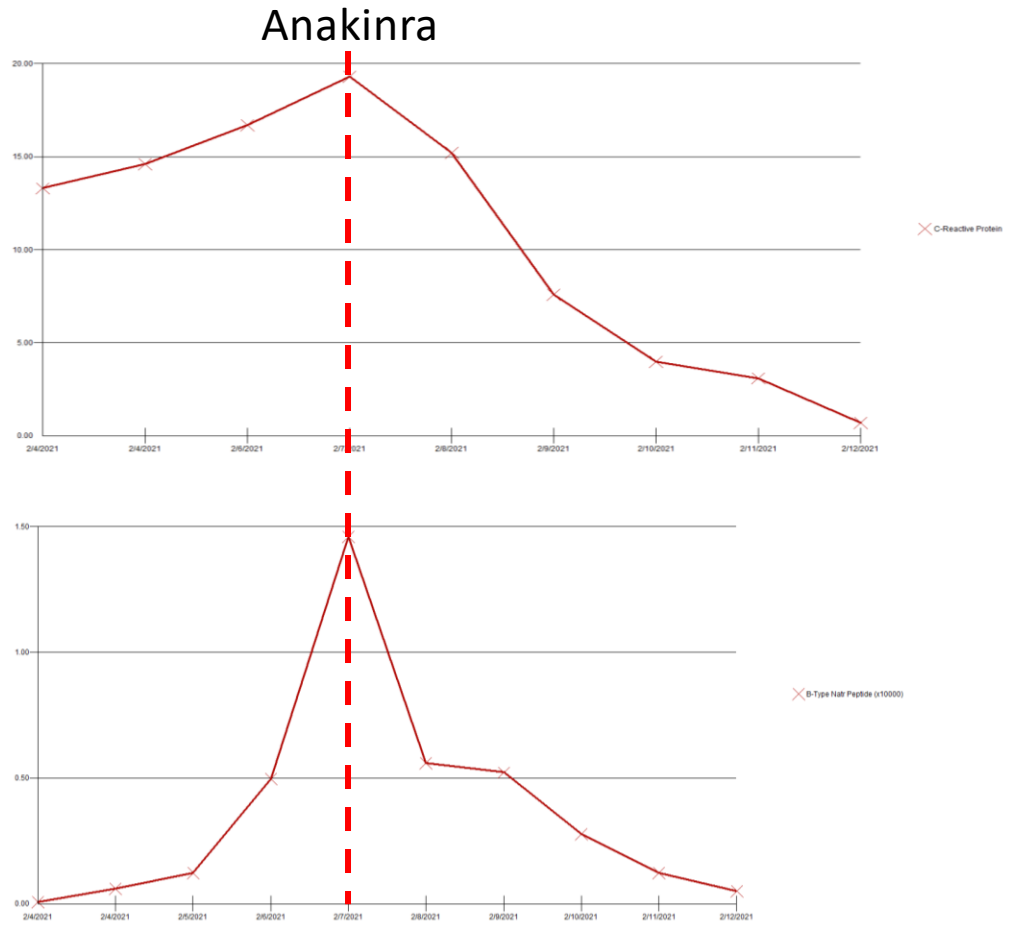
Case: Jordan, 11-year-old black male

Hospital Day #3
- Moved to PICU due to declining cardiac function
- Started anakina 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 10^9/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 immunodulatory 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 Natiuretic 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