



# (s)TICK season



**CLINID conference**  
Hunter Ratliff  
05/21/2026



*Ages, dates, and other identifying information may have been changed  
I have no conflict of interest in relation to this presentation*





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# Shortcuts



**Case**: Start | Summary 1 | prior to X-fer | H-score ||| final labs

Similar labs to anaplasmosis (HGA) HLH

**HLH intro**: Gentle intro | infectious triggers (start) | Dx criteria | treatment

**Pathophys**: Normal Th1 | +loop | w/ triggers | MΦ & ferritin | relation to Hscore

**HGA-HLH**: Cytokine levels | cellular activity | which ticks cause HLH

A man with a beard, wearing a patterned short-sleeved shirt and light-colored pants, stands in a wooded area. He is playing an acoustic guitar. Behind him is a rustic wooden cabin with a gabled roof. The scene is surrounded by lush green trees and foliage. The text "Season of the Ticks" is overlaid in yellow at the bottom of the image.

# Season of the Ticks

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# Case #1

# Case 1: HPI

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A **33 y/o M** with PMH including obesity, OSA p/w **five days of fever**, cough, myalgias, diarrhea

- USOH until 4 days PTA when he developed a nonproductive cough and myalgias
  - Despite cough, no dyspnea
  - Did feel like heart was racing/was having tachycardia (he is a medic)
- Shortly after → fever & diarrhea
  - Diarrhea most bothersome
  - Really loose bowel movements with fecal incontinence (due to coughing).
- He can not recall any rashes or skin changes, nor urinary changes

## Case 1: Social history, exposures, & risk factors

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<b>Geographic &amp; Travel</b>	<ul style="list-style-type: none"><li>• Lives 15 minutes NW of <b>Uniontown, PA</b> with female partner of many years</li><li>• No travel outside of country or recent domestic travel</li></ul>
<b>Occupational</b>	<ul style="list-style-type: none"><li>• Works as EMT</li></ul>
<b>Substance &amp; needles</b>	<ul style="list-style-type: none"><li>• <b>Former heavy EtOH</b> a few years ago, rare EtOH now that on GLP-1</li><li>• Never smoker, no drugs</li></ul>
<b>Animals</b>	<ul style="list-style-type: none"><li>• Indoor <b>cats</b></li><li>• Had <b>construction</b> in his home a few months ago and <b>his cats find mice</b> (but no exposure to rodent urine/feces)</li></ul>
<b>Exposures</b>	When not working, <b>loves to spend time outdoors</b> , including hiking, freshwater activities, and caves

## Case 1: Social history, exposures, & risk factors

<b>Geographic &amp; Travel</b>	Lives northwest of <b>Uniontown</b> with female partner. Never international, no recent travel
<b>Occupational</b>	Works as EMT
<b>Substances</b>	<b>Remote heavy EtOH</b> , rare EtOH now that on GLP-1. Never smoker, no drugs
<b>Animals</b>	Indoor cats. Recent <b>construction</b> . <b>Cats will find mice</b> , but no exposure to urine/feces
<b>Exposures</b>	<ul style="list-style-type: none"><li>• <u>Hiking</u>: Does not regularly use bug spray when hiking, but can not recall finding any embedded ticks (but has seen ticks that were not embedded)</li><li>• <u>Water</u>: kayaking and canoeing - in freshwater</li><li>• <u>Caves</u>: A month ago, went to commercialized cave, might have been bats there</li></ul>

## Case 1: Physical exam

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<b>BP</b>	127/84	<b>Pulse</b>	<b>138</b>	<b>SpO2</b>	<b>91 %</b>
<b>Temp</b>	<b>39.7 °C (103.5 °F)</b>	<b>RR</b>	20	<b>BMI</b>	37 kg/m <sup>2</sup>
<b>General</b>	Alert and oriented, NAD, vitals reviewed				
<b>HEENT</b>	NCAT; trachea appears midline, no gross LAD; EOMI				
<b>Resp</b>	Normal respiratory effort, symmetric chest rise				
<b>CV</b>	RRR; extremities perfused				
<b>GI</b>	Non-distended; no TTP				
<b>Extremities</b>	No clubbing, cyanosis, or edema				
<b>Neuro/MSK</b>	Moves extremities				
<b>Psych</b>	Normal mood; appropriate affect				

## Case 1: Labs

CBC	Result
WBC	<b>3.0</b>
Hgb	17.0
Platelets	<b>72</b>
Neut %	80%
Lymph %	15%
Eos %	0%

Other	Result
CRP	<b>215</b>
Procal	<b>30.7</b>

Chem7	Result
Na	<b>125</b>
K	3.5
HCO3	<b>17</b>
BUN	20
Cr	<b>1.7</b>

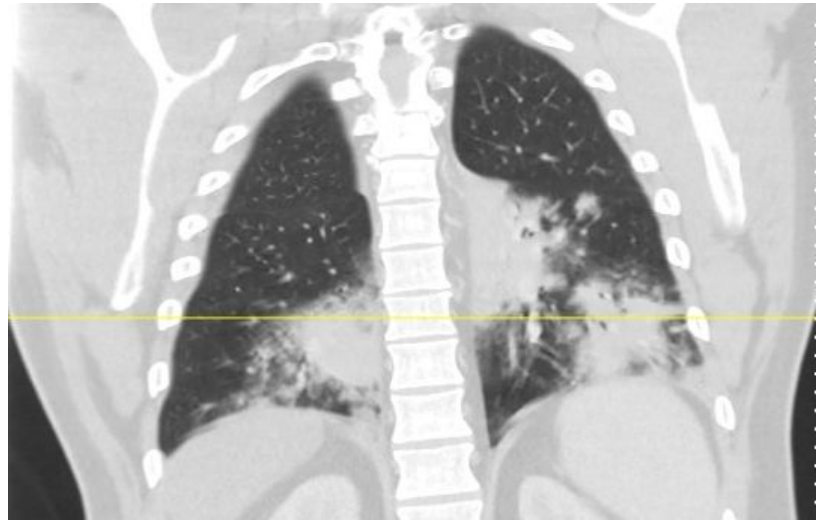
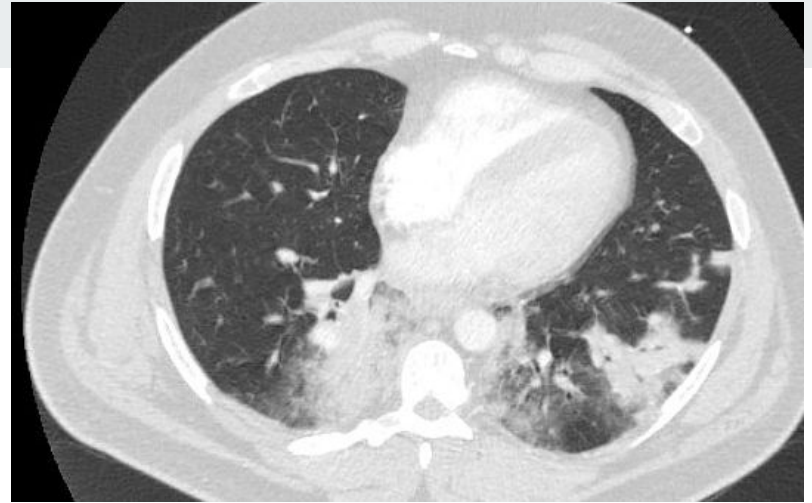
Other	Result
CK	<b>16,100</b>

LFTs	Result
AST	<b>335</b>
ALT	<b>104</b>
Alk Phos	55
Bili	1.1
Albumin	3.5

Urine	Result
Heme	<b>Pos</b>
LeukEst	Neg
Protein	<b>&gt;1000</b>
RBC	0-2
WBC	3-5

# Case 1: Imaging

CT C/A/P w/wo (ED)

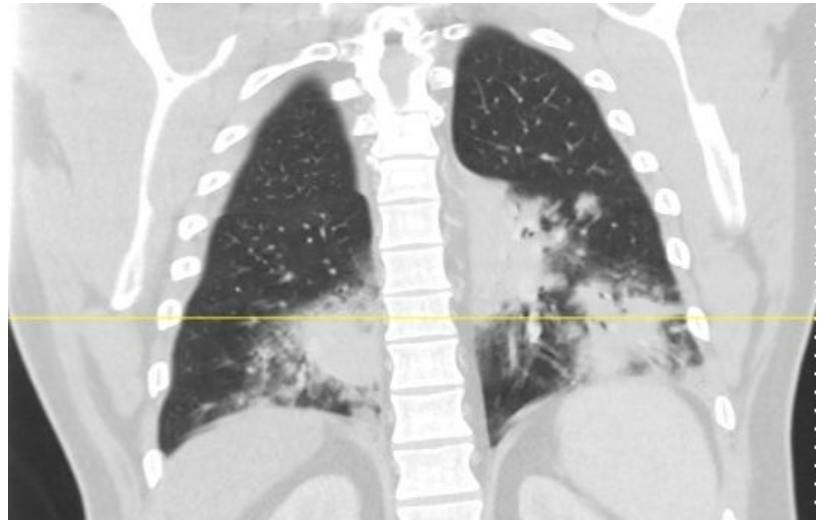
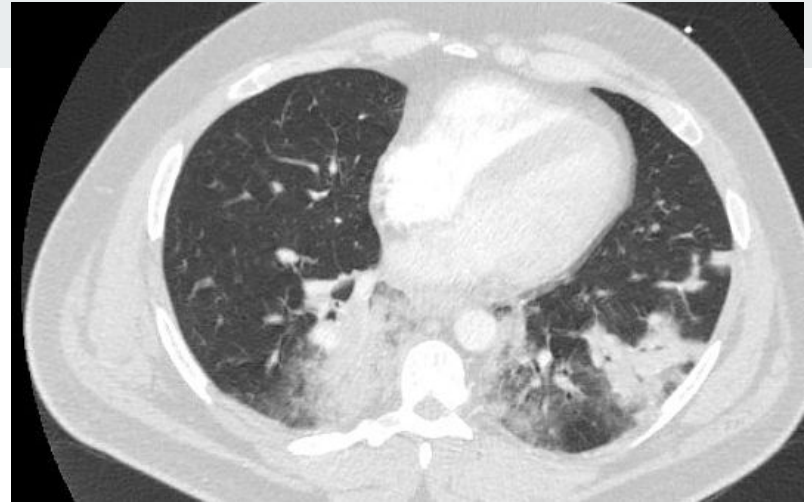


## Case 1: Imaging

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### CT C/A/P w/wo (ED)

1. Multifocal airspace **consolidation in the lower lobes** concerning for atypical infection versus aspiration.
2. Hepatic steatosis.



## Case 1: Imaging

### CT C/A/P w/wo (ED)

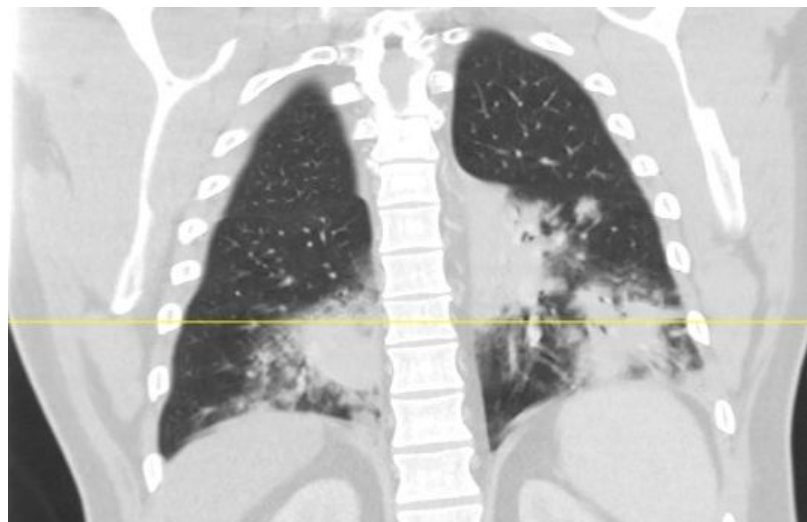
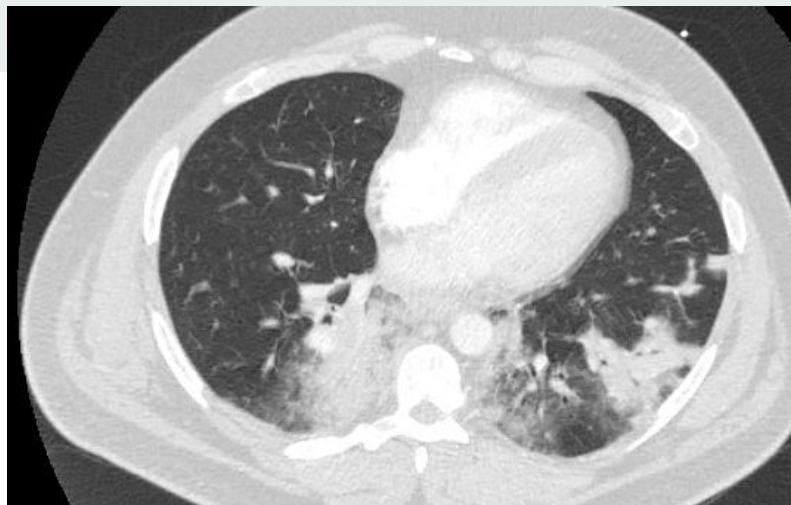
1. Multifocal airspace **consolidation in the lower lobes** concerning for atypical infection versus aspiration.
2. Hepatic steatosis.

**Lungs:** Multifocal airspace consolidation in the lower lobes c/f atypical infection versus aspiration

**Liver:** Diffuse hypodensity of the liver suggesting hepatic steatosis

**GI:** Fibrofatty changes in the terminal ileitis suggesting chronic inflammation

**Unremarkable:** gallbladder, pancreas, spleen, adrenal glands, kidneys, GU, lymph nodes



## Case 1: Summary

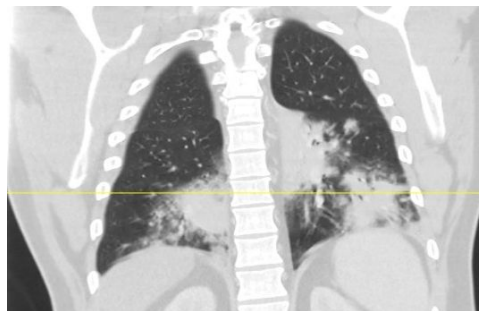
A **33 y/o M** with PMH including obesity, OSA p/w **five days** of **cough + myalgias** → **high (103.5) fever** + **diarrhea**. Stable vitals, non-toxic. CT C/A/P shows bilateral lower lobe pneumonia & terminal ileitis

Work=EMT, but play is...

- **Hiking** (no bug spray), ?ticks
- **Freshwater** (kayaking)
- **Caves** (1 month ago), ?bats
- **Cats** (mice?)

CBC/Inflm	Result
WBC	<b>3.0</b>
Hgb	17.0
Platelets	<b>72</b>
CRP	<b>215</b>
Procal	<b>30.7</b>

Chem7	Result
Na	<b>125</b>
K	3.5
HCO3	<b>17</b>
BUN	20
Cr	<b>1.7</b>
CK	<b>16k</b>



LFTs	Result
AST	<b>335</b>
ALT	<b>104</b>
Alk Phos	55
Bili	1.1
Albumin	3.5

## Case 1: Outside ED course

A **33 y/o M** with PMH including obesity, OSA p/w **five days** of **cough + myalgias** → **high (103.5) fever + diarrhea**. Stable vitals, non-toxic. CT C/A/P shows bilateral lower lobe pneumonia & terminal ileitis

	Result
COVID/Flu/RSV	Neg
Drug screen	Neg
EtOH	Neg
HIV screen	Neg

	Result
Urine legionella	Neg
Hepatitis A	Neg
Hep B	Neg
Hep C	Neg

	Result
GI biofire	Neg
Resp BF	<b>Adenovirus</b>
C diff	Neg

## Case 1: Outside ED course

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While in the ED, fever **103.5 °F** (39.7 °C) → **106.3 °F** (41.3 °C)

- Rest of his vitals stable (still sinus tachycardia)

Nursing insists on taking tylenol

- Patient **declines tylenol** or motrin
  - They try to give **IV toradol** → still says that he doesn't need it
  - Recall, he **works as EMT**
- **This escalates...ends up in four point restraints**

# Case 1: Outside hospital course

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A 33 y/o M with PMH including obesity, OSA p/w **five days** of **cough + myalgias** → **high (103.5) fever + diarrhea**. Stable vitals, non-toxic. CT C/A/P shows bilateral lower lobe pneumonia & terminal ileitis

- Mildly low O2 sats → started **nasal cannula**
- **Continues to fever**, but otherwise no new symptoms

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CBC/Inflm	ED	#2	#3	#4
WBC	<b>3.0</b>			
Hgb	17			
Platelets	<b>72</b>			
# Lymph	0.45			
CRP	<b>215</b>			
Procal	<b>30.7</b>			
CK	<b>16k</b>			

CMP	ED	#2	#3	#4
Na	<b>125</b>			
K	3.5			
HCO3	<b>17</b>			
BUN	20			
Cr	<b>1.7</b>			
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CBC/Inflm	ED	#2	#3	#4
WBC	<b>3.0</b>	4.1		
Hgb	17	15.4		
Platelets	<b>72</b>	75		
# Lymph	<b>0.45</b>	0.41		
CRP	<b>215</b>	---		
Procal	<b>30.7</b>	---		
CK	<b>16k</b>	18k		

CMP	ED	#2	#3	#4
Na	<b>125</b>			
K	3.5			
HCO3	<b>17</b>			
BUN	20			
Cr	<b>1.7</b>			
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CBC/Inflm	ED	#2	#3	#4
WBC	<b>3.0</b>	4.1	<b>2.5</b>	
Hgb	17	15.4	14.3	
Platelets	<b>72</b>	75	<b>46</b>	
# Lymph	<b>0.45</b>	0.41	0.73	
CRP	<b>215</b>	---	215	
Procal	<b>30.7</b>	---	---	
CK	<b>16k</b>	18k	<b>21k</b>	

CMP	ED	#2	#3	#4
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CBC/Inflm	ED	#2	#3	#4
WBC	<b>3.0</b>	4.1	<b>2.5</b>	3.4
Hgb	17	15.4	14.3	12.5
Platelets	<b>72</b>	75	<b>46</b>	<b>42</b>
# Lymph	<b>0.45</b>	0.41	0.73	0.65
CRP	<b>215</b>	---	215	<b>345</b>
Procal	<b>30.7</b>	---	---	<b>59.9</b>
CK	<b>16k</b>	18k	<b>21k</b>	19k

CMP	ED	#2	#3	#4
Na	<b>125</b>			
K	3.5			
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Procal	<b>30.7</b>	---	---	<b>59.9</b>
CK	<b>16k</b>	18k	<b>21k</b>	19k

CMP	ED	#2	#3	#4
Na	<b>125</b>	132		
K	3.5	3.4		
HCO3	<b>17</b>	14		
BUN	20	18		
Cr	<b>1.7</b>	1.4		
AST	<b>335</b>	<b>334</b>		
ALT	<b>104</b>	105		
ALkP	55	49		
Bili	1.1	0.7		

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CK	<b>16k</b>	18k	<b>21k</b>	19k

CMP	ED	#2	#3	#4
Na	<b>125</b>	132	135	
K	3.5	3.4	4.4	
HCO3	<b>17</b>	14	16	
BUN	20	18	23	
Cr	<b>1.7</b>	1.4	1.27	
AST	<b>335</b>	<b>334</b>	<b>481</b>	
ALT	<b>104</b>	105	<b>135</b>	
ALkP	55	49	41	
Bili	1.1	0.7	1.1	

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A 33 y/o M with PMH including obesity, OSA p/w **five days** of **cough + myalgias** → **high (103.5) fever + diarrhea**. Stable vitals, non-toxic. CT C/A/P shows bilateral lower lobe pneumonia & terminal ileitis

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Procal	<b>30.7</b>	---	---	<b>59.9</b>
CK	<b>16k</b>	18k	<b>21k</b>	19k

CMP	ED	#2	#3	#4
Na	<b>125</b>	132	135	133
K	3.5	3.4	4.4	3.4
HCO3	<b>17</b>	14	16	<b>17</b>
BUN	20	18	23	25
Cr	<b>1.7</b>	1.4	1.27	0.98
AST	<b>335</b>	<b>334</b>	<b>481</b>	<b>538</b>
ALT	<b>104</b>	105	<b>135</b>	<b>125</b>
ALkP	55	49	41	37
Bili	1.1	0.7	1.1	1.2

## Case 1: Outside hospital course

A 33 y/o M with PMH including obesity, OSA p/w **five days** of **cough + myalgias** → **high (103.5) fever + diarrhea**. Stable vitals, non-toxic. CT C/VP shows bilateral lower lobe pneumonia & terminal ileitis

CBC/Inflm	ED	#2	#3	#4
WBC				
Hgb				
Platelet				
# Lymph				
CRP				
Procalc	30.7	---	---	59.9
CK	16k	18k	21k	19k

		Result
Ferritin		7,088
Triglycerides		173
LDH		1,501

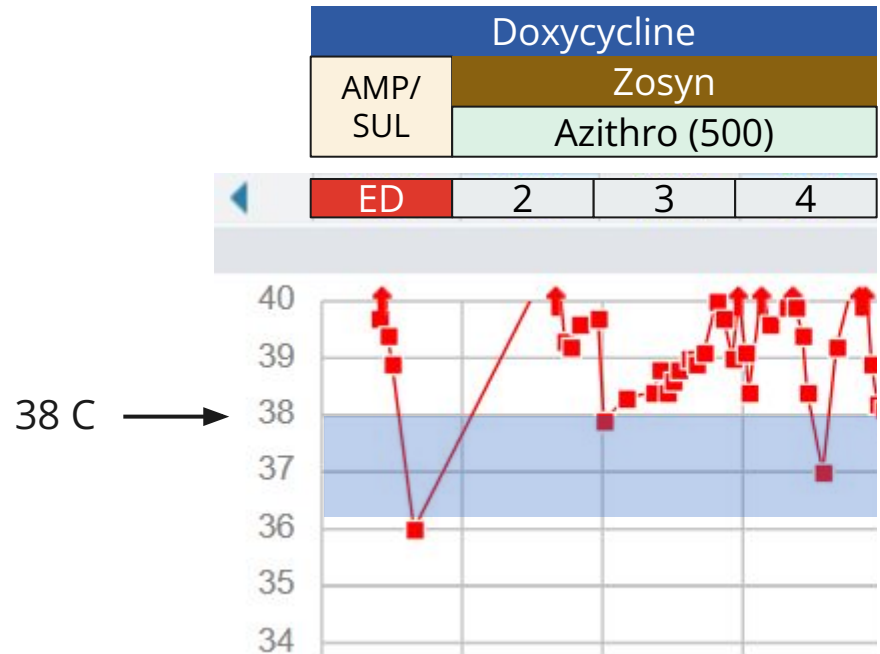
CMP	ED	#2	#3	#4
Na	125	132	135	133
K	3.5	3.4	4.4	3.4
HCO3	17	14	16	17
BUN	20	18	23	25
Cr	1.7	1.4	1.27	0.98
AST	335	334	481	538
ALT	104	105	135	125
ALkP	55	49	41	37
Bili	1.1	0.7	1.1	1.2

# Case 1: Outside hospital course

Continues to fever despite:

- Unasyn → Zosyn
- Doxycycline
- Azithro

Then **SpO2** begins to **worsen**



# Case 1: Summary

A **33 y/o M** with PMH including obesity, OSA p/w **five days** of **cough + myalgias** → **high (103.5) fever** + **diarrhea**. Stable vitals, non-toxic. CT C/A/P shows bilateral lower lobe pneumonia & terminal ileitis

**Continues to fever**, worsening O2

u-Legionella	Neg
GI biofire	Neg
Cv/Flu/RSV	Neg
HIV & Hep A-C	Neg

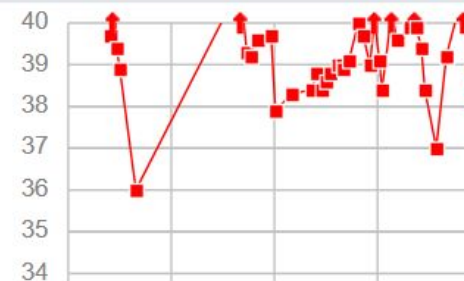
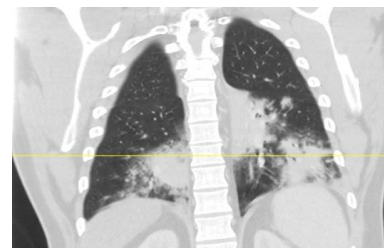
<b>Ferritin</b>	<b>7,088</b>
<b>LDH</b>	<b>1,501</b>

CMP	
Na	<b>125</b> ± 132
K	3's
HCO3	<b>17</b> ± 2
BUN	20s
Cr	<b>1.7</b> → <b>1.0</b>
<b>AST</b>	<b>335</b> → <b>538</b>
<b>ALT</b>	<b>104</b> → <b>125</b>
ALkP	40-50s
Bili	1.0 ± 0.2

CBC/inflammatory	
WBC	<b>3.0</b> ± 1
Hgb	17 → <b>12</b>
PLT	<b>72</b> → <b>42</b>
CRP	<b>215</b> → <b>345</b>
PCT	<b>30.7</b> → <b>59.9</b>
CK	<b>21k</b> (peak)

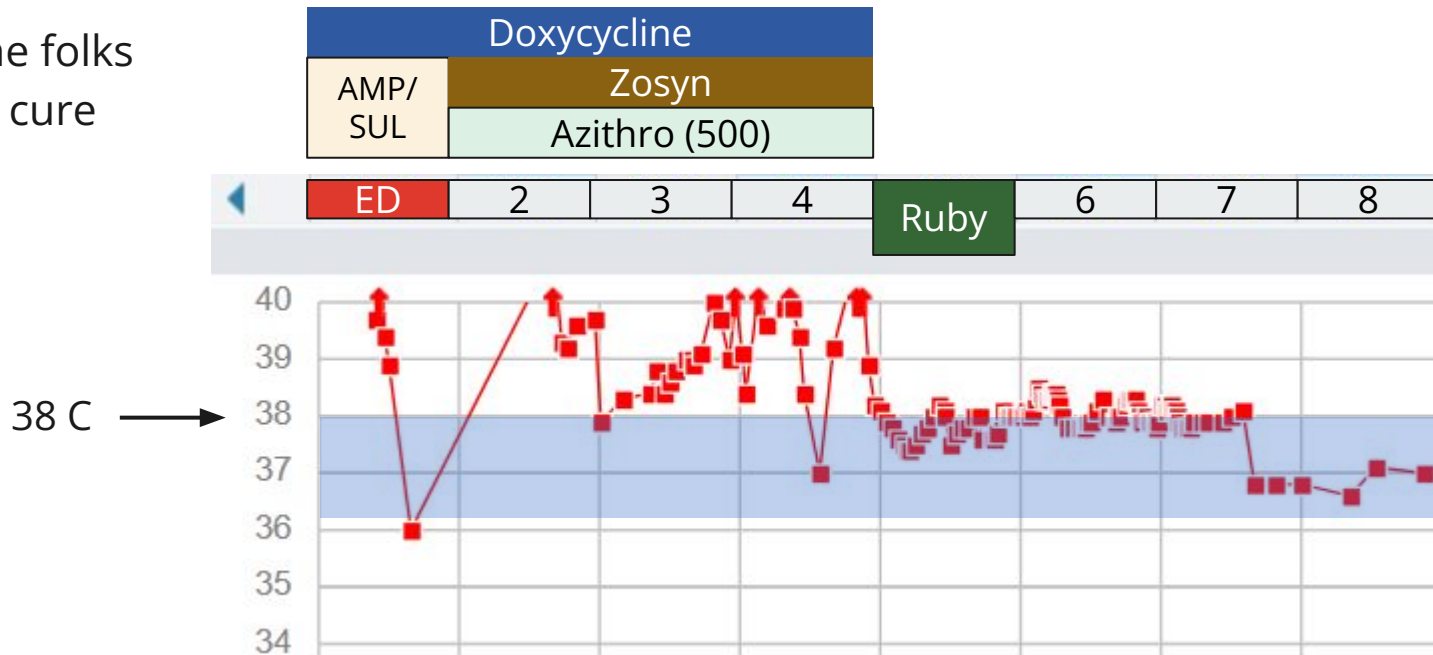
Doxycycline	
AMP/	Zosyn
SUL	Azithro (500)

ED	2	3	4
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# Case 1: Outside hospital course → Ruby MICU

Guess what the folks at Ruby did to cure the fever?







# Case 1: Ruby MICU

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- Just prior to transfer, was started on **high flow** → **BiPap**
- Wheezing on admission to **MICU** → **intubated**

# Case 1: Ruby MICU

- Just prior to transfer, was started on **high flow** → **BiPap**
- Wheezing on admission to **MICU** → **intubated**

Hematology consulted for possible HLH

- H-score is high

HScore for HLH		+0
Known underlying immunosuppression	???	
Temperature, °F	???	
Hepato/spleno-megaly	???	
Number of cytopenias	???	
Ferritin	???	
Triglycerides	???	
Fibrinogen	???	
AST	???	
Bone marrow Bx	???	

# Case 1: Ruby MICU

- Just prior to transfer, was started on **high flow** → BiPap
- Wheezing on admission to **MICU** → **intubated**

Hematology consulted for possible HLH

- H-score is high
  - **70-80%** chance of HLH
- They order some sendout labs

HScore for HLH		+186
Known underlying immunosuppression	No	
<b>Temperature, °F</b>	<b>&gt;102.9</b>	+49
Hepato/spleno-megaly	Neither	
<b>Number of cytopenias</b>	2 lines	+24
<b>Ferritin</b>	<b>&gt;6,000</b>	+50
<b>Triglycerides</b>	132 - 354	+44
Fibrinogen	>250	
<b>AST</b>	<b>≥30</b>	+19
Bone marrow Bx	TBD	

# Case 1: Ruby MICU

- Just prior to transfer, was started on **high flow** → **BiPap**
- Wheezing on admission to **MICU** → **intubated**

Hematology consulted for possible HLH

- H-score is high
  - **70-80%** chance of HLH
- They order some sendout labs

MICU **starts on steroids**

- **Quickly extubated** next day (got tons of IV fluids for treatment of rhabdo)

HScore for HLH		+186
Known underlying immunosuppression	No	
<b>Temperature, °F</b>	<b>&gt;102.9</b>	+49
Hepato/spleno-megaly	Neither	
<b>Number of cytopenias</b>	2 lines	+24
<b>Ferritin</b>	<b>&gt;6,000</b>	+50
<b>Triglycerides</b>	132 - 354	+44
Fibrinogen	>250	
<b>AST</b>	<b>≥30</b>	+19
Bone marrow Bx	TBD	

What's going on?



## Ticks

Anaplasmosis

Lyme

Other

## Viral

ds-DNA  
(HSV, VZV, EBV)

HIV

Other

## Bacterial

Legionella

Spirochete  
(besides lyme)

Other

## Non-infectious

Autoimmune

Malignancy

Drugs

## Other infections

Parasitic

Histoplasmosis

Others

## Case 1: Further workup

Serologies	IgM	IgG
Lyme		
Ehrlichia		
Anaplasma		
RMSF		

Other	
Parasite smear	
Monospot	

CMP	
Na	125 ± 132
K	3's
HCO3	17 ± 2
BUN	20s
Cr	1.7 → 1.0
AST	335 → 538
ALT	104 → 125
ALkP	40-50s
Bili	1.0 ± 0.2

Biofires	Result
GI PCR	Neg
Resp PCR	Adeno

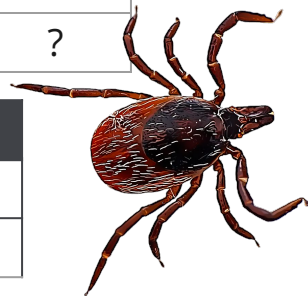
CBC/inflammatory	
WBC	3.0 ± 1
Hgb	17 → 12
PLT	72 → 42
CRP	215 → 345
PCT	30.7 → 59.9
CK	21k (peak)

u-Legionella	Neg
GI biofire	Neg
Cv/Flu/RSV	Neg
HIV & Hep A-C	Neg

# Case 1: Further workup

Serologies	IgM	IgG
<b>Lyme</b>	<b>Pos</b>	Neg
Ehrlichia	?	?
Anaplasma	?	?
RMSF	?	?

Other	
Parasite smear	
Monospot	



CMP	
Na	<b>125</b> ± 132
K	3's
HCO3	<b>17</b> ± 2
BUN	20s
Cr	<b>1.7</b> → <b>1.0</b>
<b>AST</b>	<b>335</b> → <b>538</b>
<b>ALT</b>	<b>104</b> → <b>125</b>
ALkP	40-50s
Bili	1.0 ± 0.2

CBC/inflammatory	
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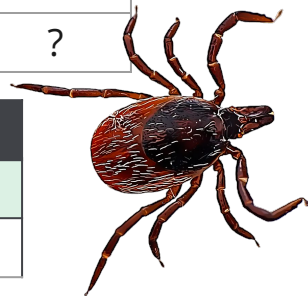
Biofires	Result
GI PCR	Neg
Resp PCR	<b>Adeno</b>

u-Legionella	Neg
GI biofire	Neg
Cv/Flu/RSV	Neg
HIV & Hep A-C	Neg

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Serologies	IgM	IgG
<b>Lyme</b>	Pos	Neg
Ehrlichia	?	?
Anaplasma	?	?
RMSF	?	?

Other	Result
Parasite smear	Neg
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CMP	
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K	3's
HCO3	17 ± 2
BUN	20s
Cr	1.7 → 1.0
AST	335 → 538
ALT	104 → 125
ALkP	40-50s
Bili	1.0 ± 0.2

Biofires	Result
GI PCR	Neg
Resp PCR	Adeno

CBC/inflammatory	
WBC	3.0 ± 1
Hgb	17 → 12
PLT	72 → 42
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CK	21k (peak)

u-Legionella	Neg
GI biofire	Neg
Cv/Flu/RSV	Neg
HIV & Hep A-C	Neg

**Do ticks cause HLH?**

---



## Lit review



When I saw this case, I came across a wonderful case report of **Anaplasmosis-HLH**

## *Open Forum Infectious Diseases*

### ID TEACHING CASES

## Anaplasmosis-Induced Hemophagocytic Lymphohistiocytosis: A Case Report and Review of the Literature

**Jacob Scribner,<sup>1, </sup> Benita Wu,<sup>2</sup> Andre Lamyathong,<sup>2</sup> Victor Arcega,<sup>1</sup> and Daphne-Dominique Villanueva<sup>1</sup>**

<sup>1</sup>Department of Medicine Section of Infectious Diseases, West Virginia University, Morgantown, West Virginia, USA, and <sup>2</sup>Department of Internal Medicine, West Virginia University, Morgantown, West Virginia, USA

## Lit review

---

When I saw this case, I came across a wonderful case report of

### **Anaplasmosis-HLH**

- Case of HLH (confirmed by biopsy) from WVU

So I **compared the labs...**

## *Open Forum Infectious Diseases*

### ID TEACHING CASES

## **Anaplasmosis-Induced Hemophagocytic Lymphohistiocytosis: A Case Report and Review of the Literature**

**Jacob Scribner,<sup>1,®</sup> Benita Wu,<sup>2</sup> Andre Lamyathong,<sup>2</sup> Victor Arcega,<sup>1</sup> and Daphne-Dominique Villanueva<sup>1</sup>**

<sup>1</sup>Department of Medicine Section of Infectious Diseases, West Virginia University, Morgantown, West Virginia, USA, and <sup>2</sup>Department of Internal Medicine, West Virginia University, Morgantown, West Virginia, USA

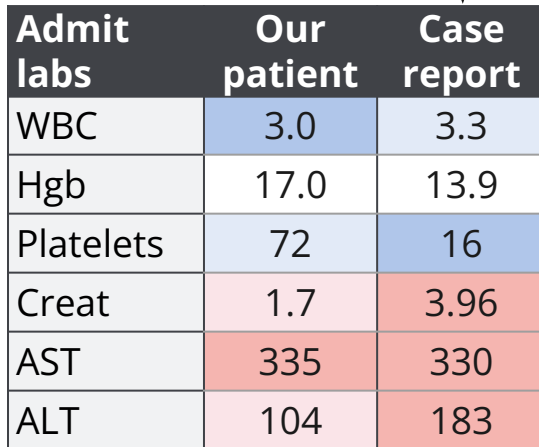
# Comparing with the case report [1]



Admit labs	Our patient
WBC	3.0
Hgb	17.0
Platelets	72
Creat	1.7
AST	335
ALT	104

# Comparing with the case report [1]

ID TEACHING CASES



Admit labs	Our patient	Case report
WBC	3.0	3.3
Hgb	17.0	13.9
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Admission labs	Our patient	Case report	Normal range	In HLH
Ferritin	8,830 (29 x ULN)		20-300	↑↑↑
Triglycerides	173		<150	↑
Fibrinogen	697		200 - 400	↓
LDH	1,501		125 - 220	↑
Soluble IL-2 receptor	6,180 (7 x ULN)		175 - 858	↑↑↑
D-dimer	---		<233	↑

# Comparing with the case report [1]

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WBC	3.0	3.3
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LDH	1,501	1,337	125 - 220	↑
Soluble IL-2 receptor	6,180 (7 x ULN)	31,673 (37 x ULN)	175 - 858	↑↑↑
D-dimer	---	>5000	<233	↑

# Comparing with the case report [1]

Admit labs	Our patient	Case report
WBC	3.0	3.3
Hgb	17.0	13.9
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Also made me wonder how **often** we **only look at these** numbers

Admission labs	Our patient	Case report	Normal range	In HLH
Ferritin	8,830 (29 x ULN)	>33,511 (>110 x ULN)	20-300	↑↑↑
Triglycerides	175	448	<150	↑
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LDH	1,501	1,337	125 - 220	N/A
Soluble IL-2 receptor	6,180 (7 x ULN)	31,673 (37 x ULN)	175 - 858	↑↑↑
D-dimer	---	>5000	<233	N/A



# Hemophagocytic Lympho- Histiocytosis

1. **What is HLH?**
2. **Diagnosis** of HLH
3. **Triggers** for HLH
4. A closer look at the **pathophys**

# What is HLH? [2]



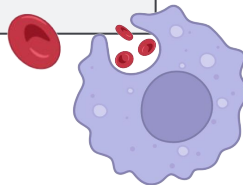
## Med student explanation

- Immune system getting “**stuck in the ON position**”
  - Uncontrolled immune activation →
  - Cytokine storm →
  - Organ damage
- Mediated by NK, cytotoxic T cells, and **macrophages**

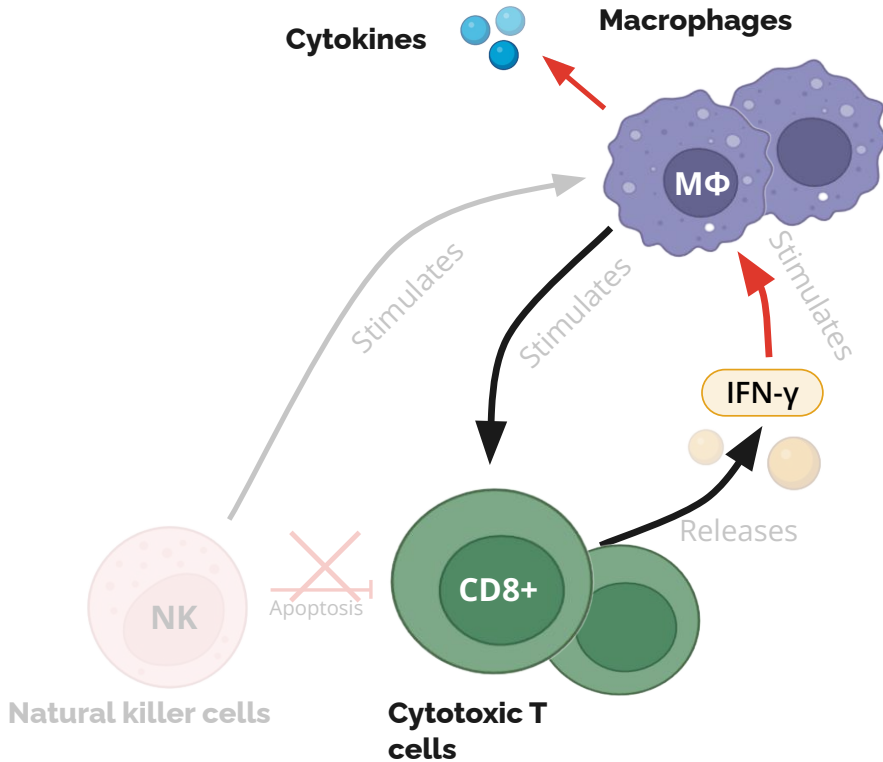
# What is HLH? [2]

## Med student explanation

- Immune system getting “**stuck in the ON position**”
  - Uncontrolled immune activation →
  - Cytokine storm →
  - Organ damage
- Mediated by NK, cytotoxic T cells, and **macrophages**
- Clues: **sky high ferritin**, fevers, cytopenias
- “**Hemophagocytic**” = **macrophages** phagocytosis blood cells in marrow/spleen



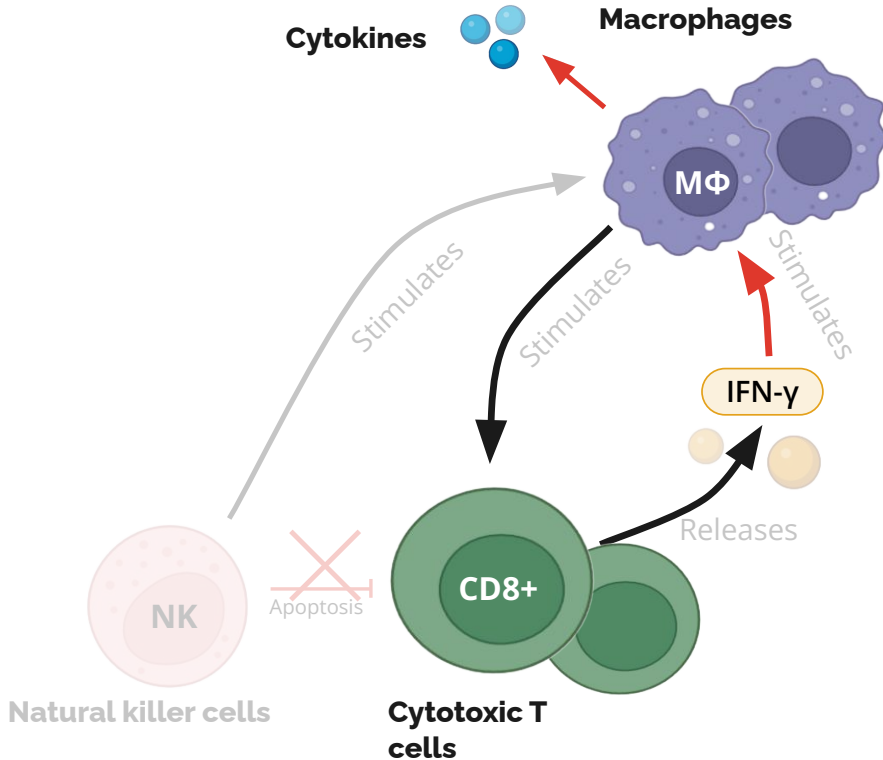
# What is HLH? [2]



## Intern explanation

- Pathophys:
  - Impaired **cytotoxic function** (NK/CD8) → **macrophage activation**
  - Massive cytokine release (IFN-γ, IL-6) that can **mimic sepsis**

# What is HLH? [2]



## Intern explanation

- Pathophys:
  - Impaired **cytotoxic function** (NK/CD8) → **macrophage activation**
  - Massive cytokine release (IFN-γ, IL-6) that can **mimic sepsis**
- Can be **genetic** or **secondary to a trigger**:
  - **Infectious** (viral; not bacteremia)
  - **Malignancy** (lymphoma)
  - **Rheum** (called **macrophage activation syndrome**)
  - Reality: a mix of genes + trigger

# HLH diagnostic criteria [2]

HScore
Known underlying immunosuppression
Temperature, °F
Hepato/spleno-megaly
Number of cytopenias
Ferritin
Triglycerides
Fibrinogen
AST
Bone marrow Bx

## HLH-2004 (need $\geq 5$ )

1. Fever
2. Splenomegaly
3. Cytopenias ( $\geq 2$  lineages)
4. Either (or both)
  - a.  $\uparrow$  triglycerides
  - b.  $\downarrow$  fibrinogen
5. Hemophagocytosis (BMBx, spleen, LN)
6.  $\downarrow$  NK cell activity
7.  $\uparrow$  Ferritin ( $\geq 500$ )
8.  $\uparrow$  Soluble IL-2 receptor

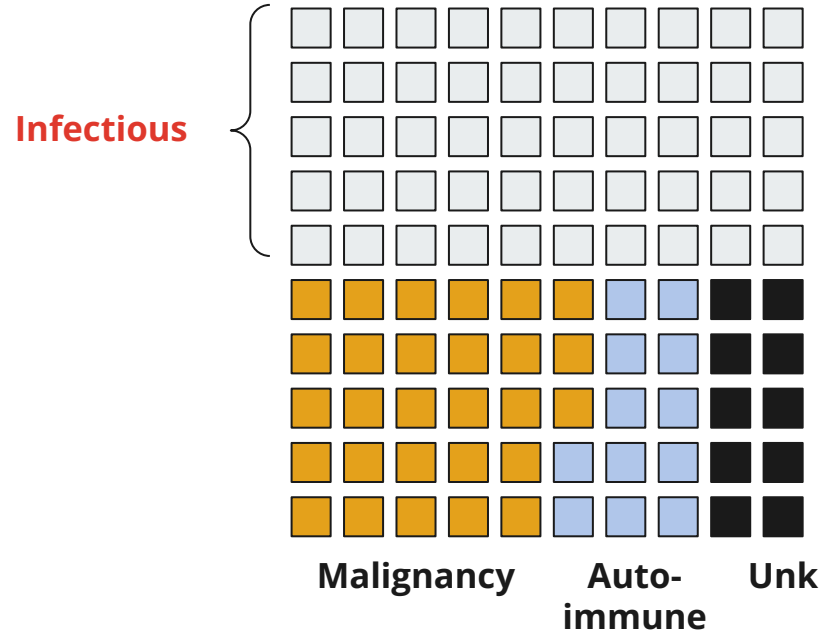
## Included just FYI

The exact measures aren't as important (normally heme who "officially" does the diagnosis)

# What triggers HLH? [7]

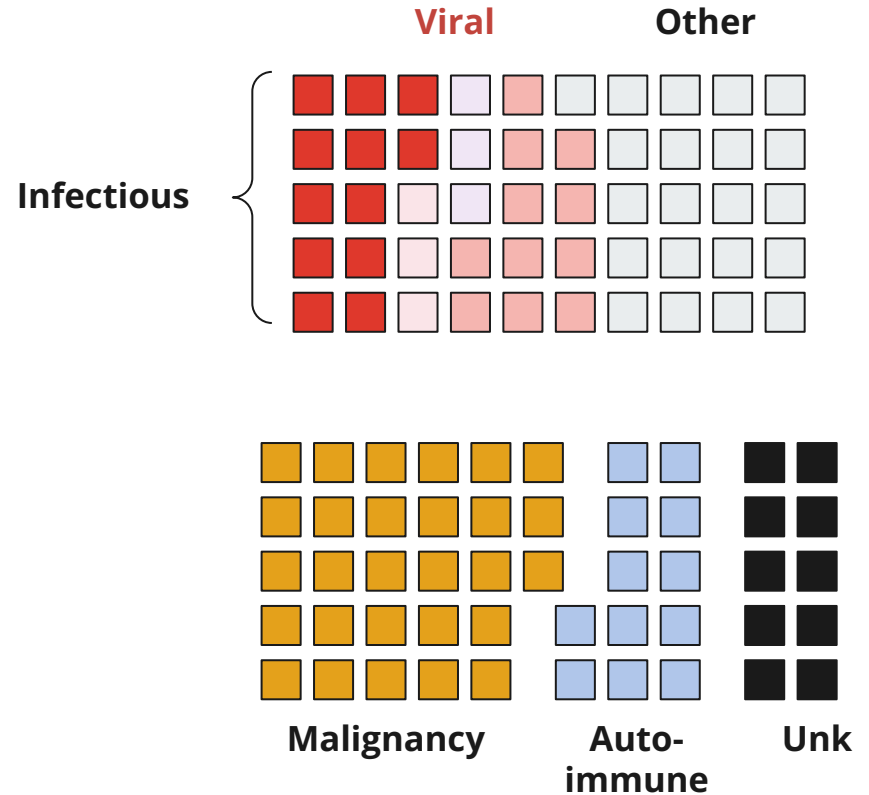
In pooled systematic review of critically ill patients:

- **Half** had an **infectious trigger**
- Malignancy: 28%
- Autoimmune: 12%
- Unknown: 10%



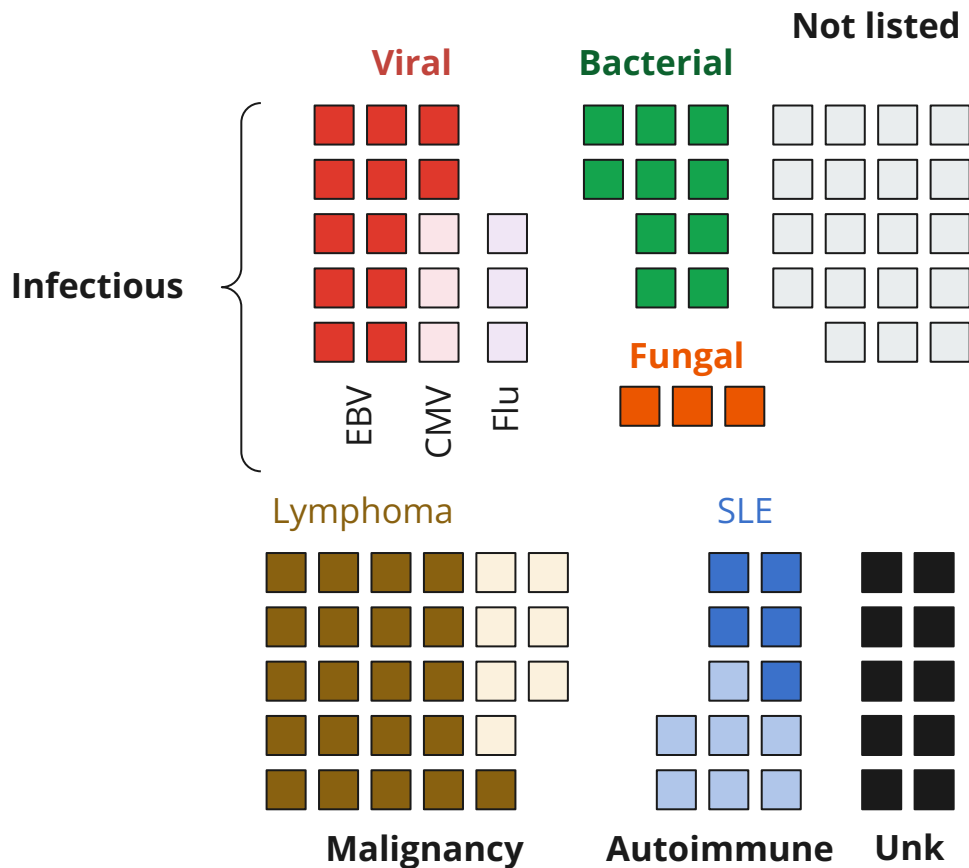
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- **EBV** (12%)
- CMV (3.3%), flu (2.1%)



# What triggers HLH? [7]

- **EBV** (12%)
- CMV (3.3%), flu (2.1%)
- **Bacterial** (10.1%)
  - **Lymphoma** is twice as common (21%)
- **Fungal** (2.9%)
  - On par with Adult-onset Still (2.6%)

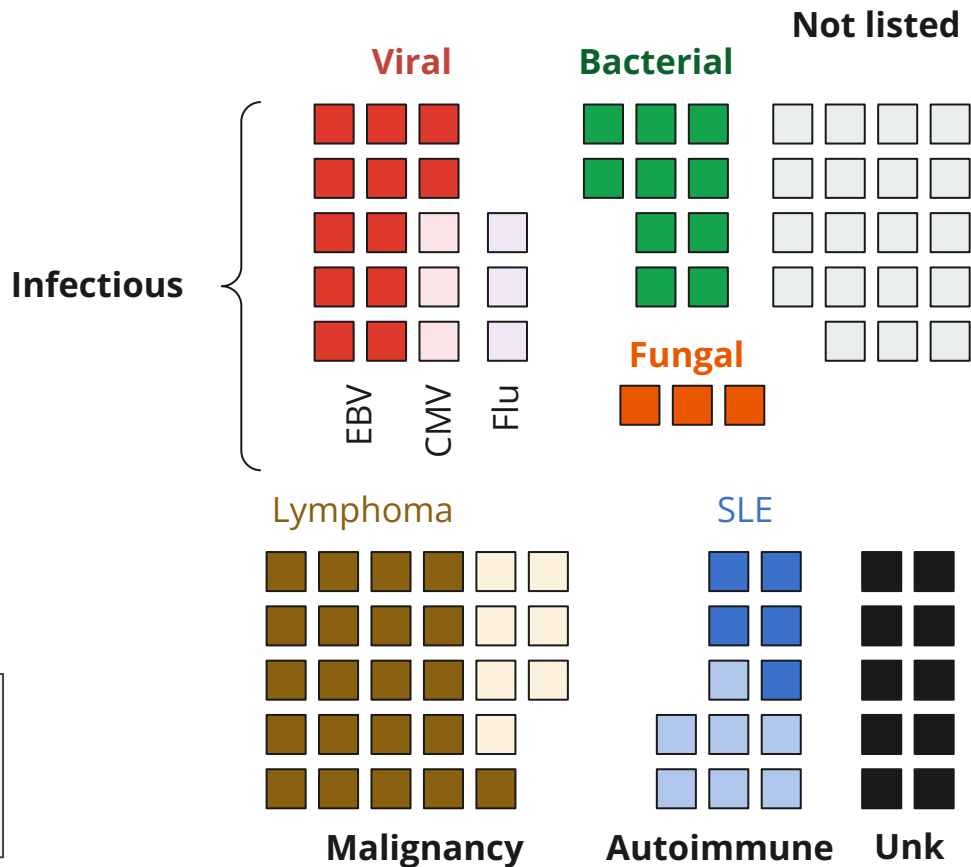


# What triggers HLH? [7]

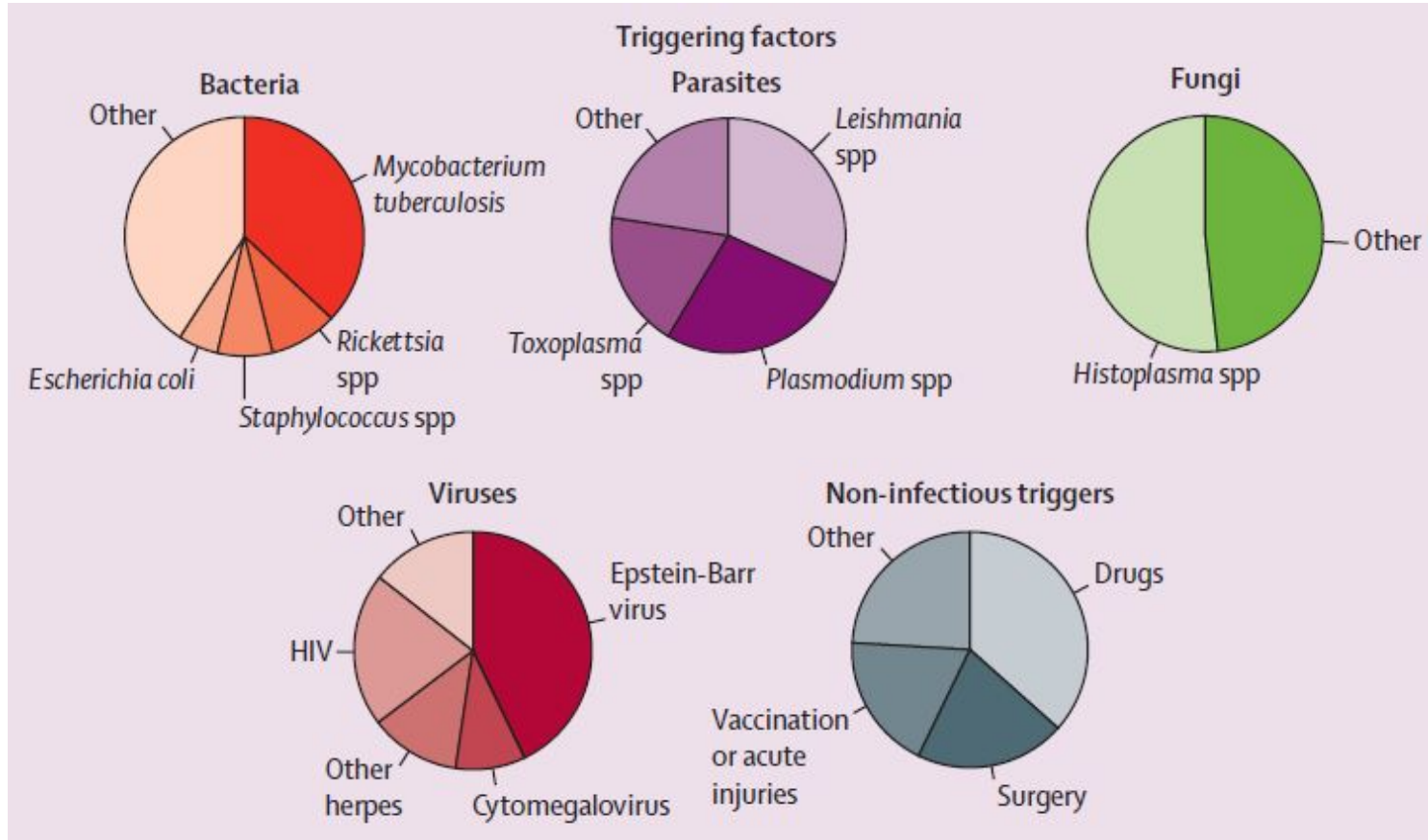
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- **Bacterial** (10.1%)
  - **Lymphoma** is twice as common (21%)
- **Fungal** (2.9%)
  - On par with Adult-onset Still (2.6%)

**Limitation**

They did not give a full breakdown of the infections



# Which infections trigger HLH? [8]

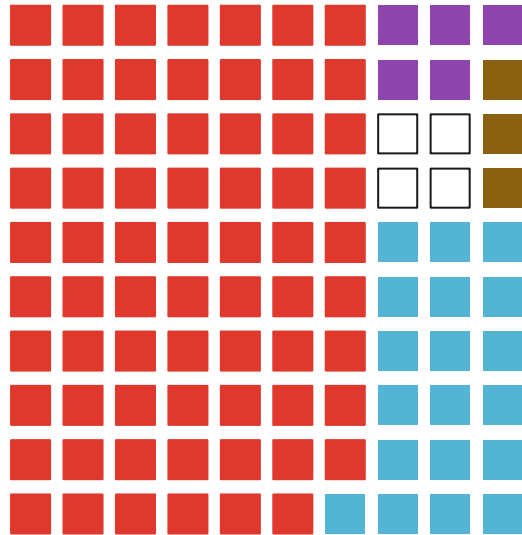


# Which infections trigger HLH? [8]



**Viral (69%)**

Infectious HLH triggers



**Parasites (4.8%)**

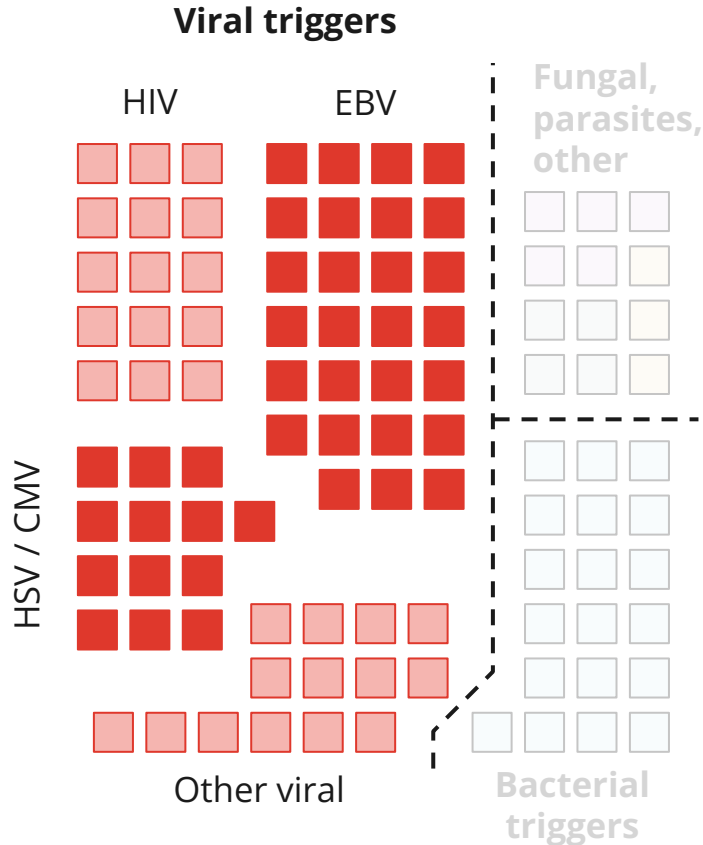
**Fungal (3.3%)**

**Bacterial (18.6%)**

# Which infections trigger HLH? [8]

## Viral (69%)

1. **EBV** (30%)
2. **HIV** (15%)
3. **HSV** (6.7%)
4. **CMV** (6.2%)
5. Other / not specified (6.1%)
6. **Viral hepatitis** (1.8%)
7. Influenza (1.3%)
8. Parvo B19 (1.3%)

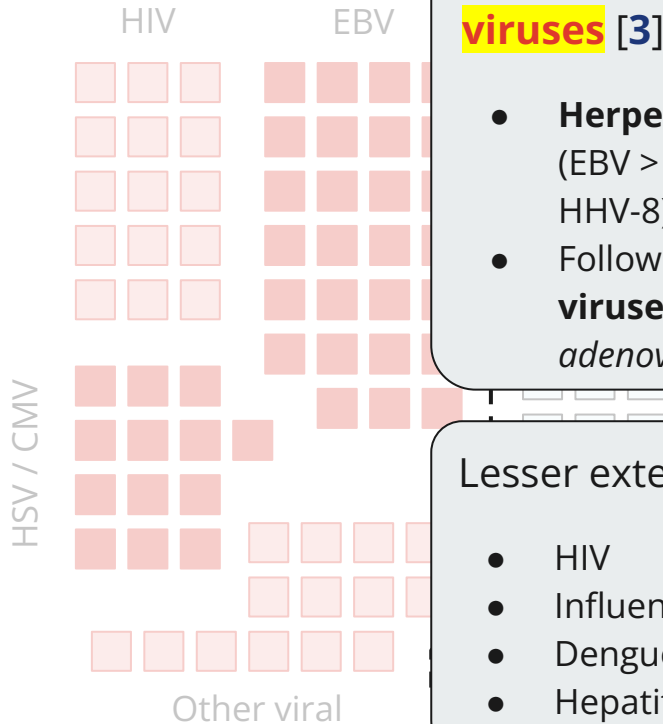


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6. **Viral hepatitis** (1.8%)
7. Influenza (1.3%)
8. **Parvo B19** (1.3%)

## Viral triggers



Strongest association with **DNA viruses** [3]:

- **Herpesviruses**  
(EBV > CMV > VZV, HHV-6, HHV-8)
- Followed by **other DNA viruses** (parvo B19, adenoviruses)

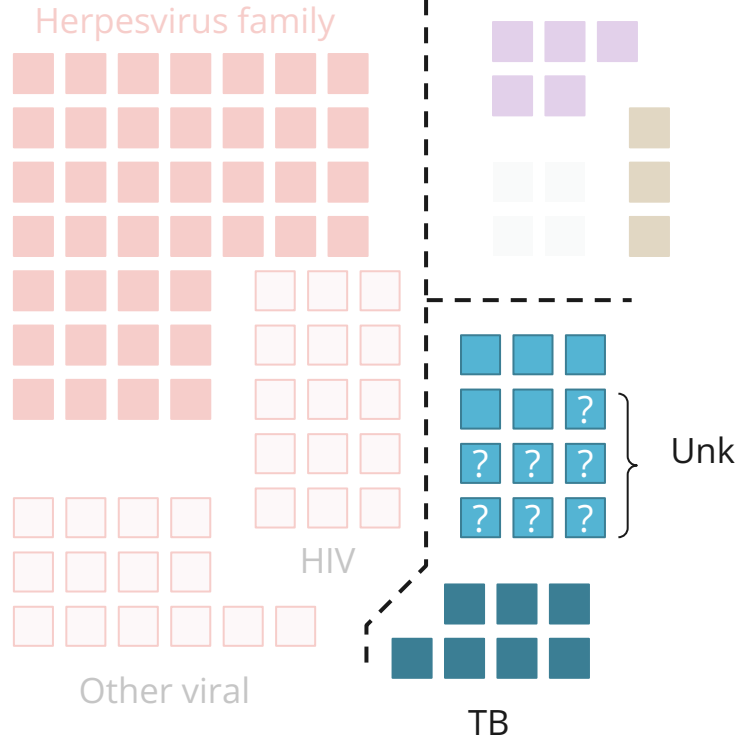
Lesser extent **RNA viruses** [3]:

- HIV
- Influenza
- Dengue
- Hepatitis C

# Which infections trigger HLH? [8]

## Viral (69%)

1. EBV (30%)
2. HIV (15%)
3. HSV / CMV (15%)
4. Other / unk (6.1%)
5. Viral hepatitis (1.8%)
6. Influenza (1.3%)
7. Parvo B19 (1.3%)



## Bacterial (18.6%)

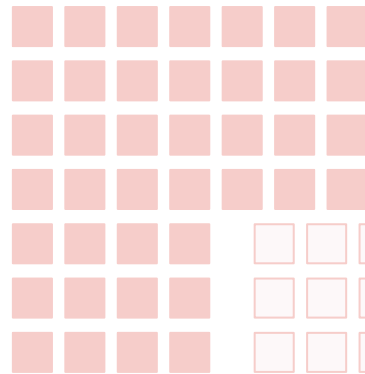
1. TB (7.0%)
2. Other / not specified (7.7%)
3. Rickettsia spp (1.5%)
4. Staph spp (1.4%)
5. E coli (1.0%)

# Which infections trigger HLH? [8]

## Viral (69%)

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2. HIV (15%)
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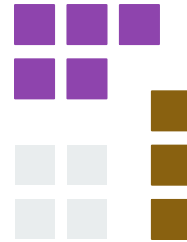
## Herpesvirus family



HIV



Other viral



Unk



TB



## Parasites (4.8%)

1. Leishmania (1.5%)
2. Malaria (1.3%)
3. Toxo (0.9%)

## Fungi (3.3%)

1. Histo (1.6%)
2. Other (1.7%)

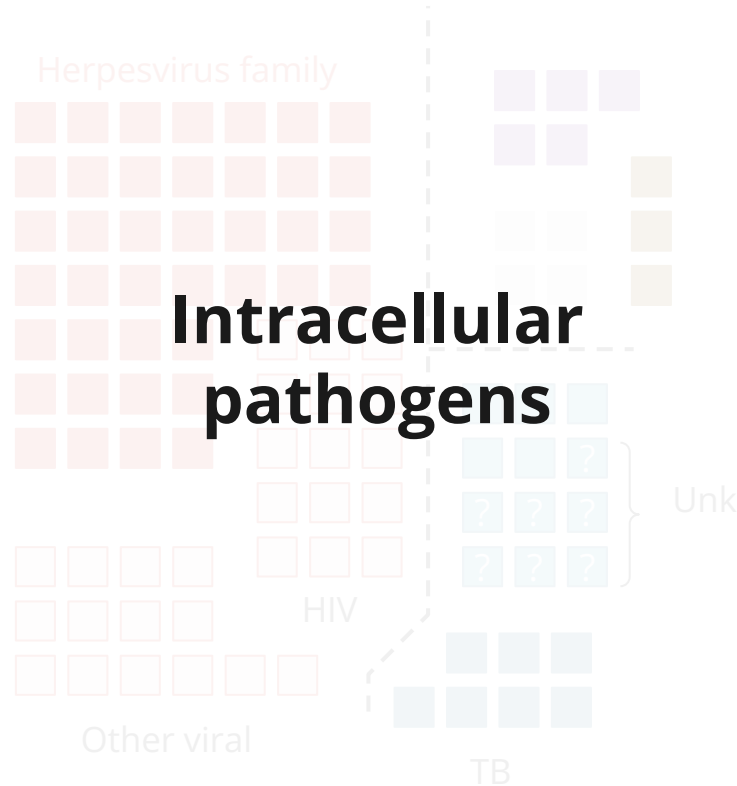
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## Parasites (4.8%)

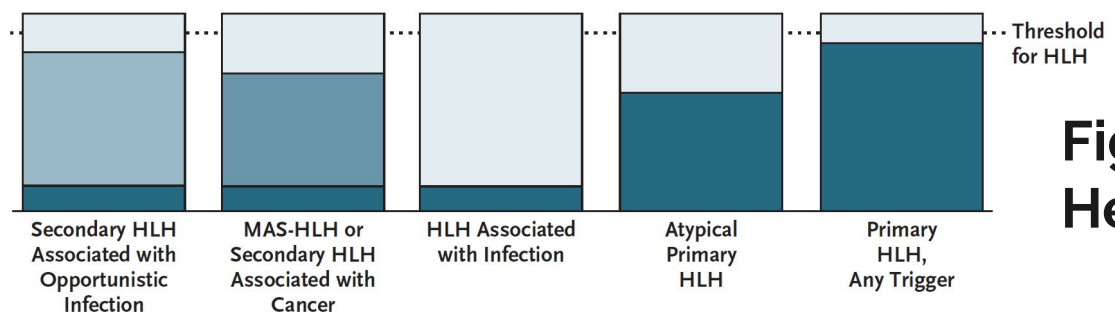
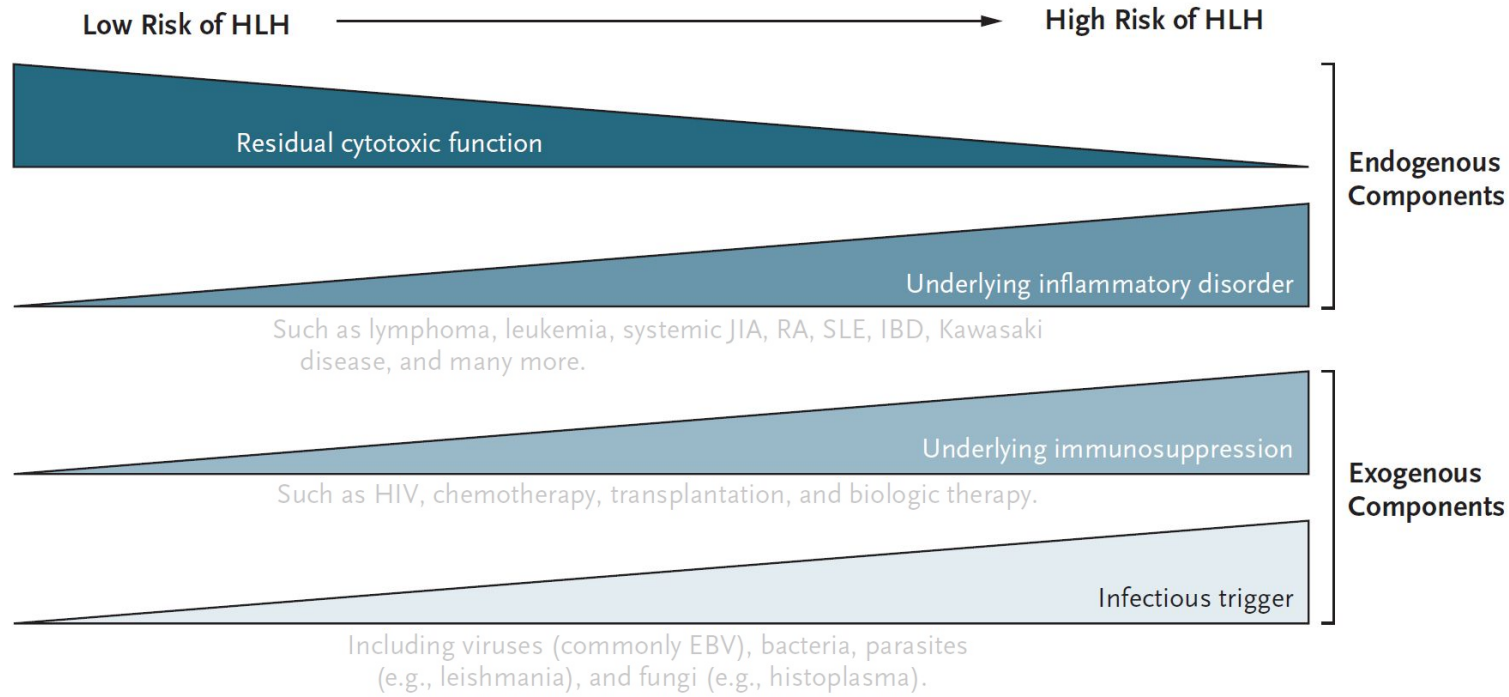
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## Fungi (3.3%)

1. **Histo** (1.6%)
2. Other (1.7%)

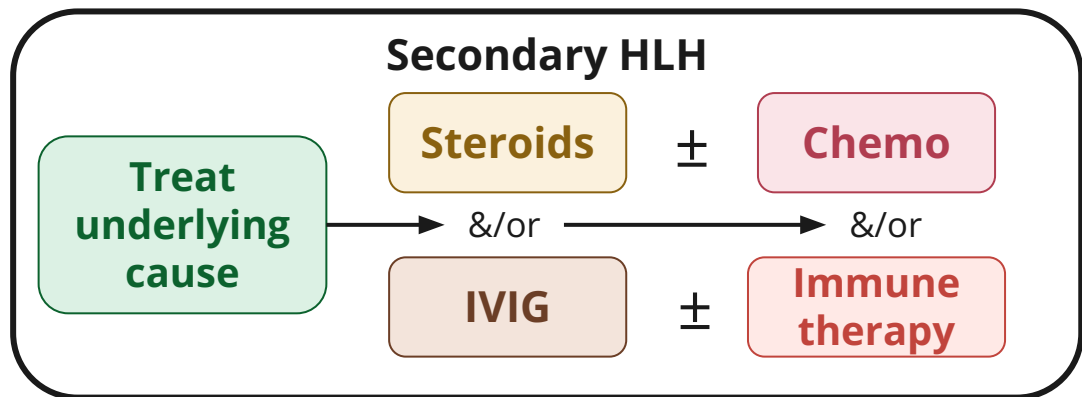
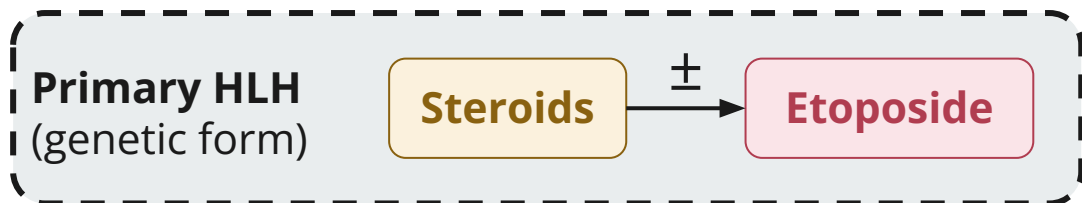
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**Figure 3: [2]  
Henter, 2025**

# Treatment of HLH



Subgroup analysis (of pooled systematic review) [7]

- Infectious: IVIG reduced mortality 45%; chemo 7.6-fold increase
- All others: No change (for better or worse)

Limited data on the role for immunosuppression with anaplasmosis [1]

Sepsis associated HLH, treating sepsis + anakinra has reduced mortality [2]

---

**Refresher on the case...**



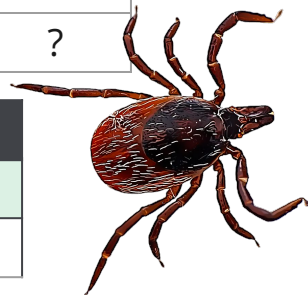
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Serologies	IgM	IgG
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Ehrlichia	?	?
Anaplasma	?	?
RMSF	?	?

Other	Result
Parasite smear	Neg
Monospot	Neg

BMBx	
CMV PCR	?
EBV PCR	?
Flow cyto	?

Serum PCRs
Pending



CMP	
Na	125 ± 132
K	3's
HCO3	17 ± 2
BUN	20s
Cr	1.7 → 1.0
AST	335 → 538
ALT	104 → 125
ALkP	40-50s
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Biofires	Result
GI PCR	Neg
Resp PCR	Adeno

CBC/inflammatory	
WBC	3.0 ± 1
Hgb	17 → 12
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CRP	215 → 345
PCT	30.7 → 59.9
CK	21k (peak)

u-Legionella	Neg
GI biofire	Neg
Cv/Flu/RSV	Neg
HIV & Hep A-C	Neg



# Pathophysiology of “HLH”

The focus is full-blown HLH, but would think of it as “**broken loop of Th1 cytokine storm**”, including:

- HLH
- Macrophage activation syndrome
- Cytokine release syndrome

Normal Th1 response

Positive loops

HLH triggers

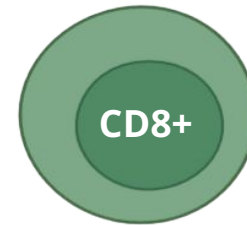
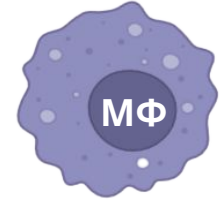
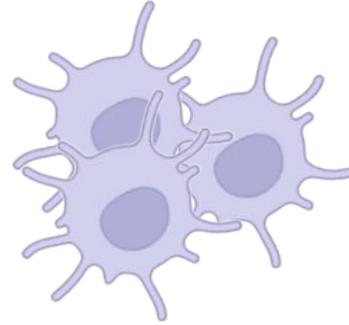
MΦ & ferritin

Clinical manifestations

## Normal Th1 response [2]

Antigen presenting cells

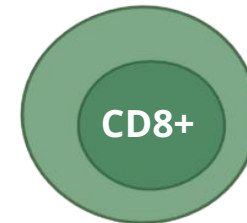
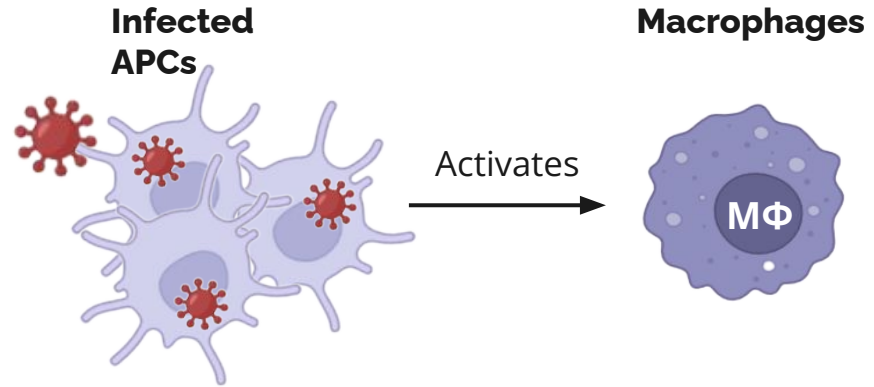
Macrophages



Cytotoxic T cells

## Normal Th1 response [2]

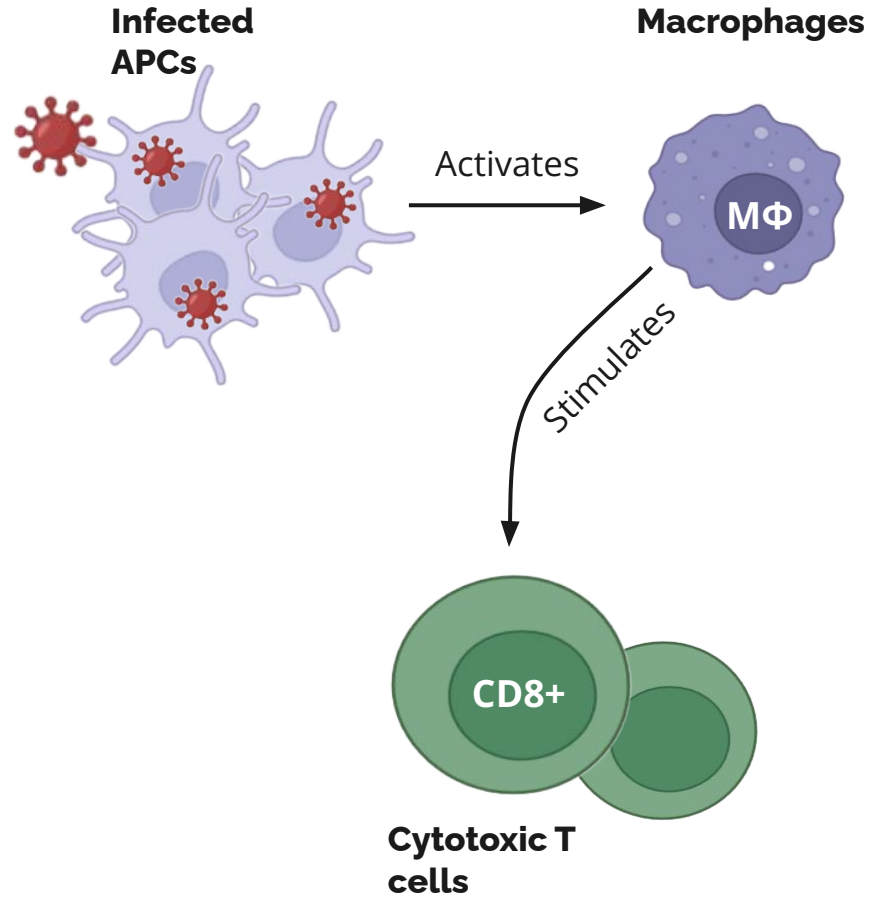
1. **Infected cells present antigens** and **activate macrophages** via **PAMPs** (pathogen-associated molecular patterns)



**Cytotoxic T cells**

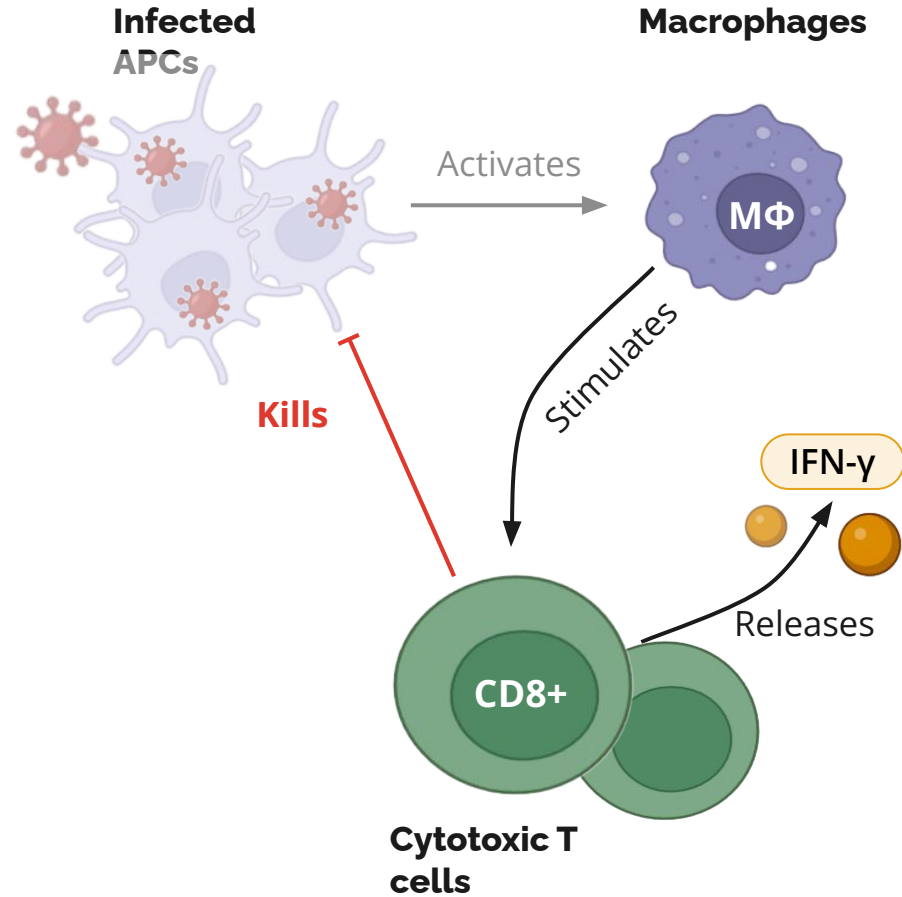
## Normal Th1 response [2]

1. **Infected cells present antigens** and **activate macrophages** via **PAMPs** (pathogen-associated molecular patterns)
2. **Antigen-specific CD8+ T cells** are recruited and...



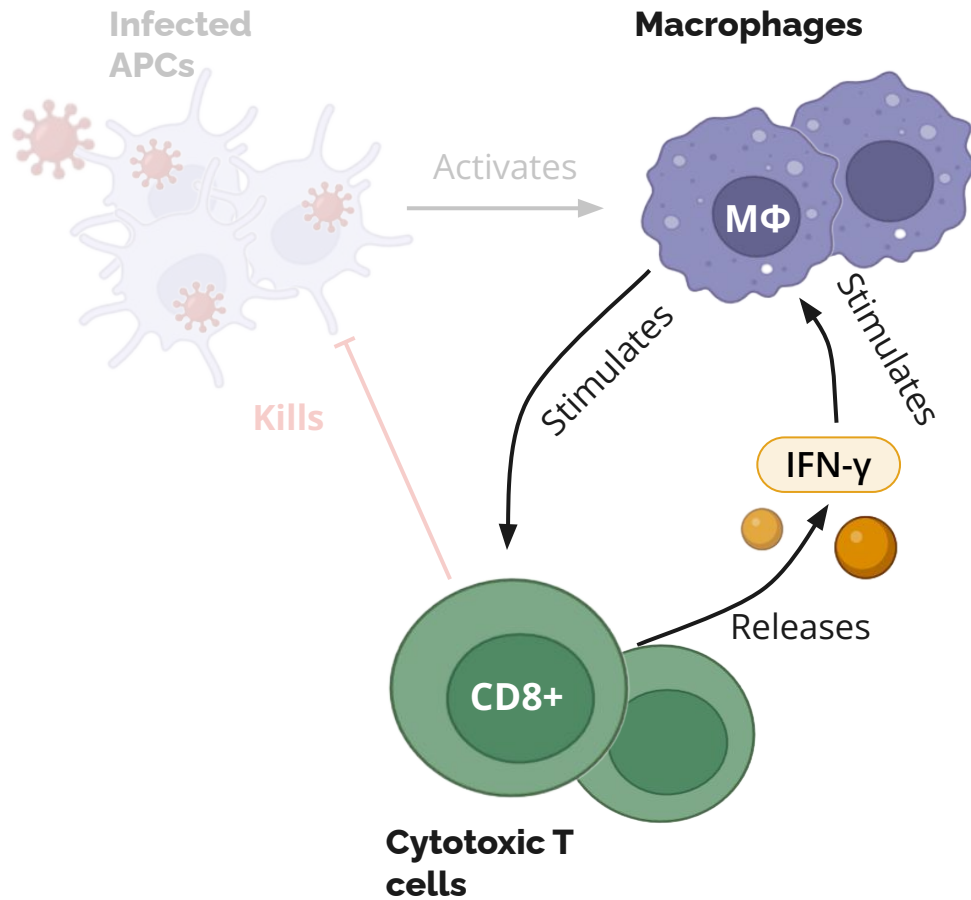
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  - a. **Kill infected cells** directly
  - b. Secrete **interferon gamma**



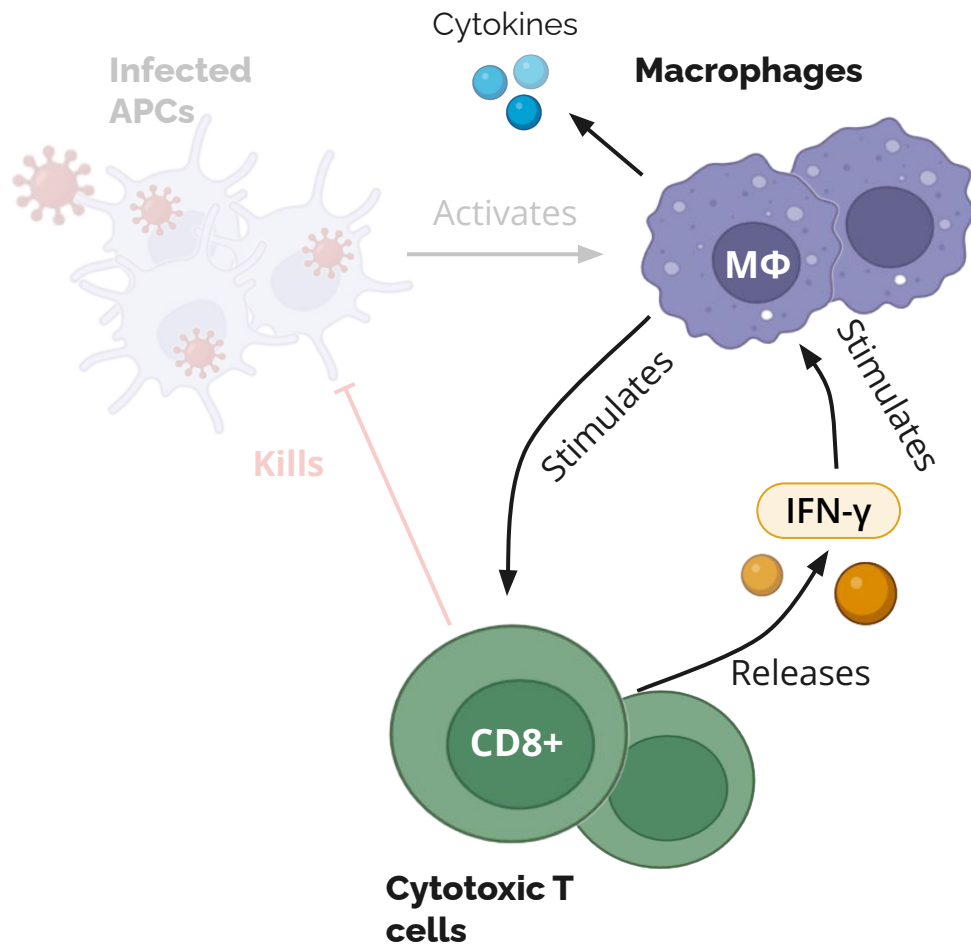
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3. **IFN-γ** in turn will...
  - a. Potent **activator of macrophages**



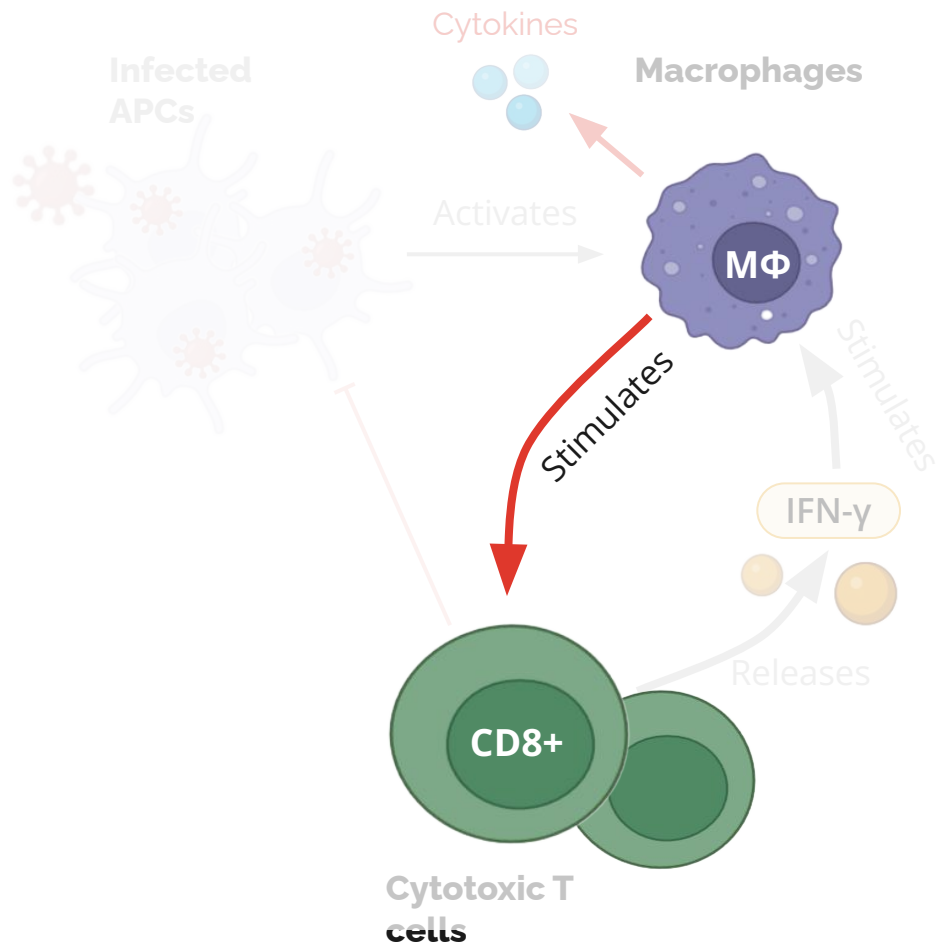
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2. **Antigen-specific CD8+ T cells** are recruited and...
  - a. **Kill infected cells** directly
  - b. Secrete **interferon gamma**
3. **IFN-γ** in turn will...
  - a. Potent **activator of macrophages**
  - b. Induces MΦ to **produce more cytokines**



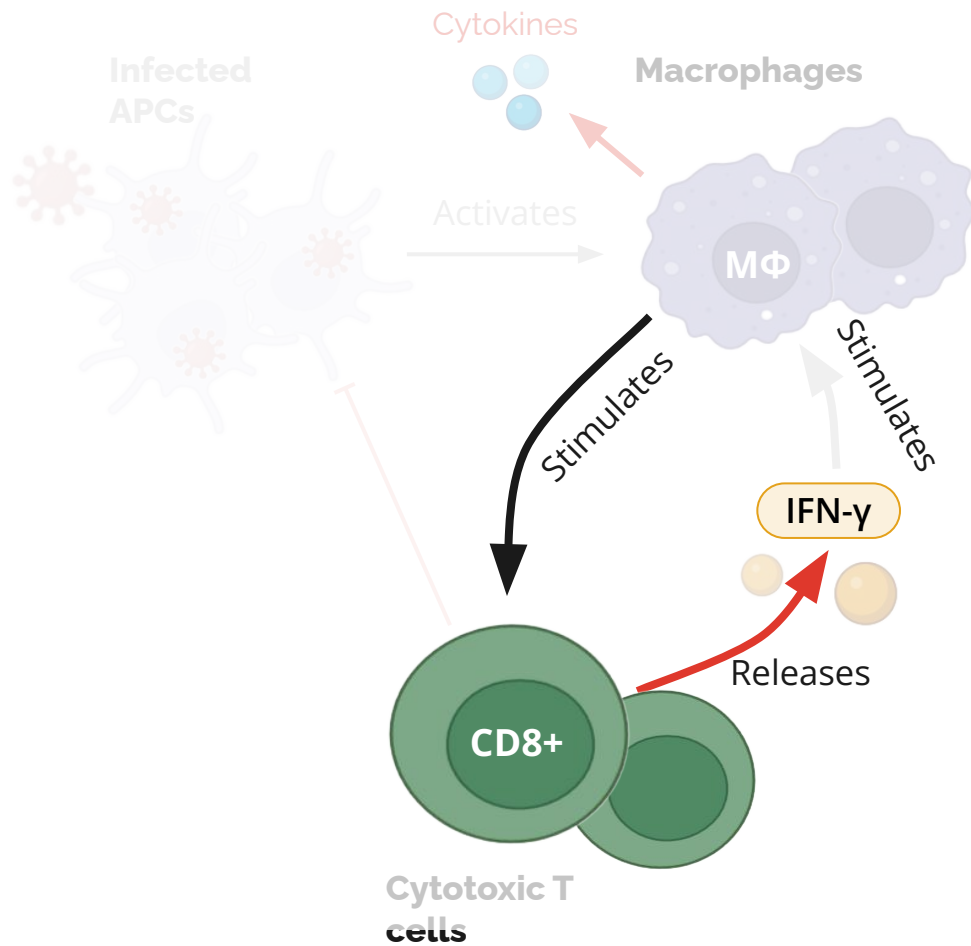
## Positive feedback loop

1. **Activated macrophages** activate **cytotoxic T cells**



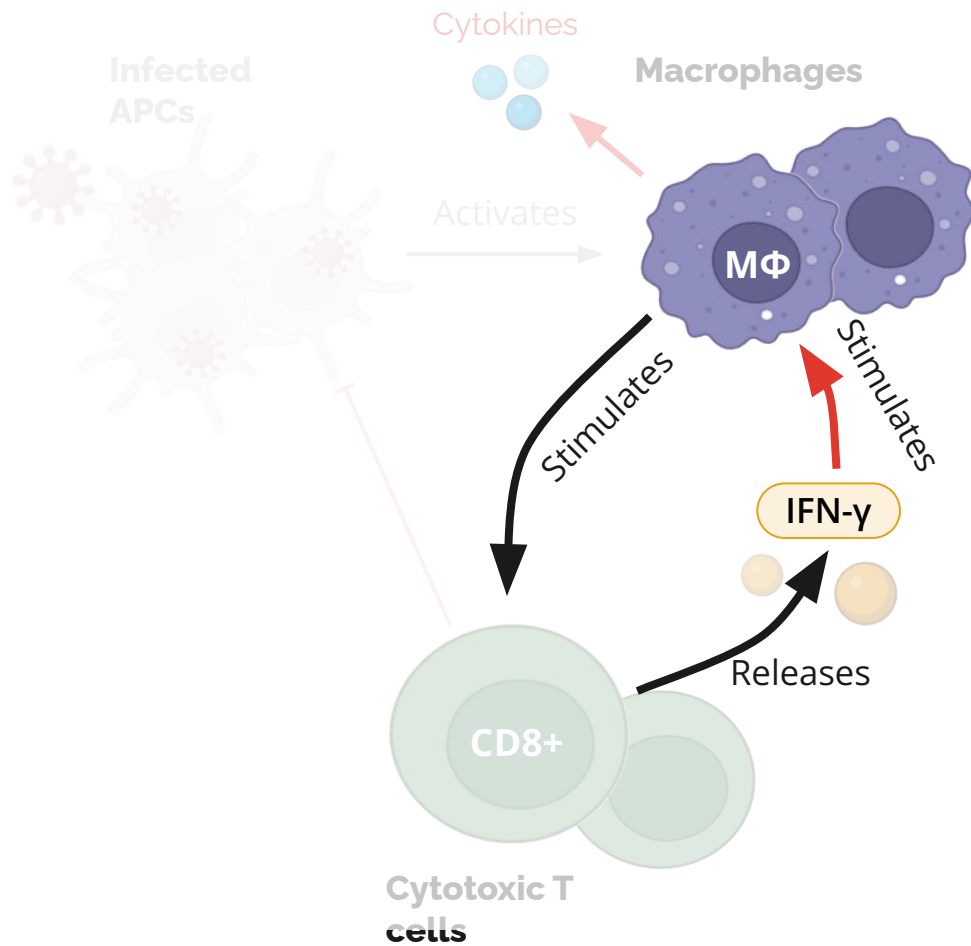
## Positive feedback loop

1. **Activated macrophages** activate **cytotoxic T cells**
2. **Cytotoxic T cells** secrete **IFN- $\gamma$**



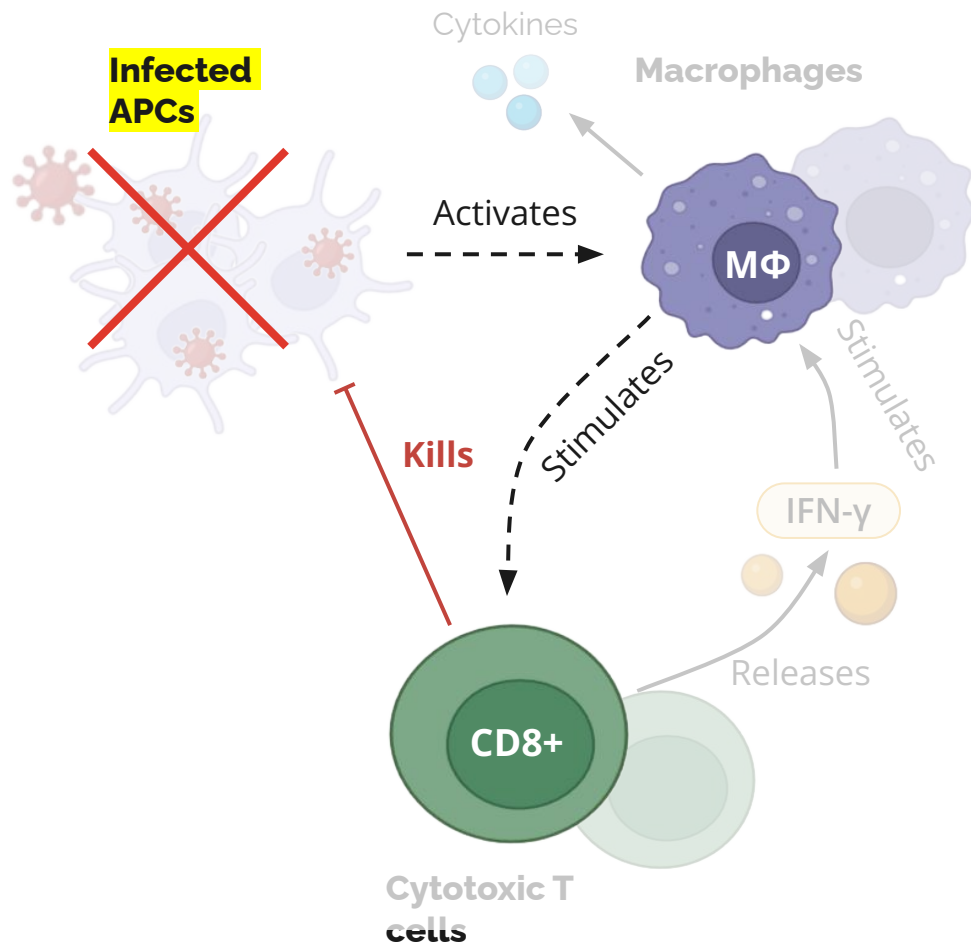
## Positive feedback loop

1. **Activated macrophages** activate **cytotoxic T cells**
2. **Cytotoxic T cells** secrete **IFN-γ**
3. **IFN-γ** activates **macrophages**



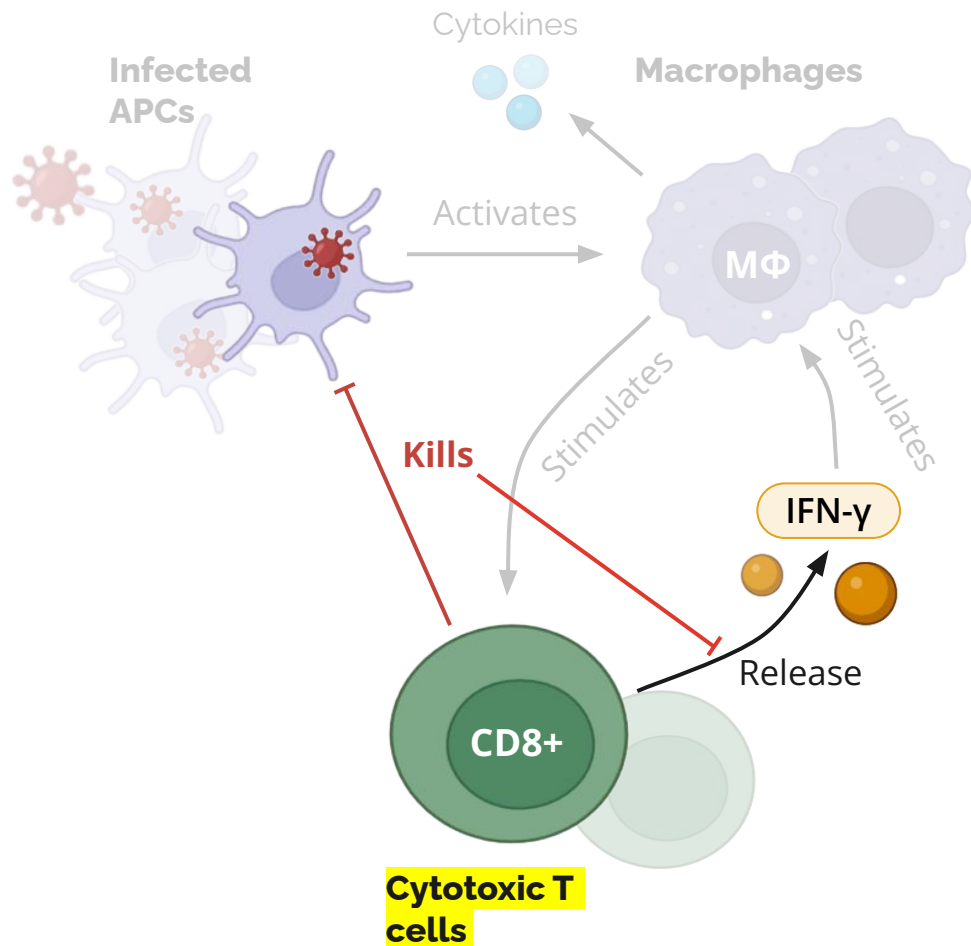
## What stops this cycle?

1. Successfully **eliminating the infection**
  - a. If infection is removed, **PAMPs** are **not activating** the **macrophages**



## What stops this cycle?

1. Successfully **eliminating the infection**
  - a. If infection is removed, **PAMPs** are **not activating** the **macrophages**
  - b. When **CD8+ successfully kill** their target, they are able to **disengage from the target synapse** → can **stop releasing** cytokines



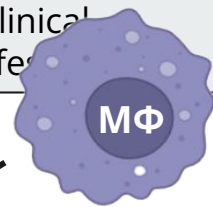
Normal Th1 response

Positive loops

HLH triggers

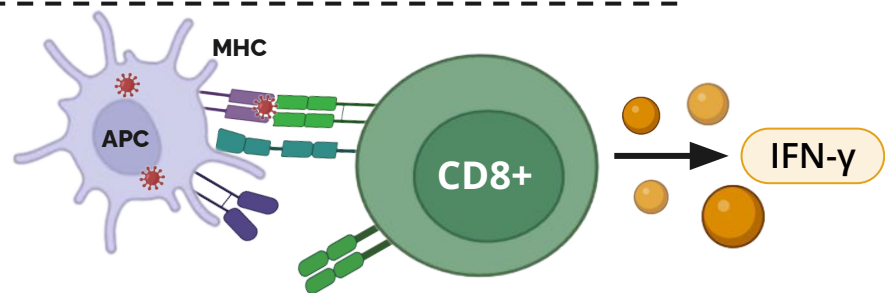
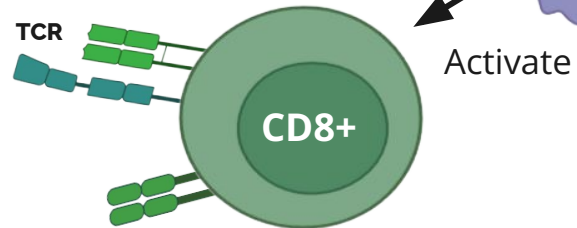
MΦ & ferritin

Clinical  
manifestation



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## More specifically [3]

- When the cytotoxic T cell **finds an infected APC**, it **secretes cytokines**

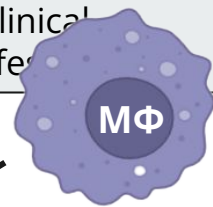
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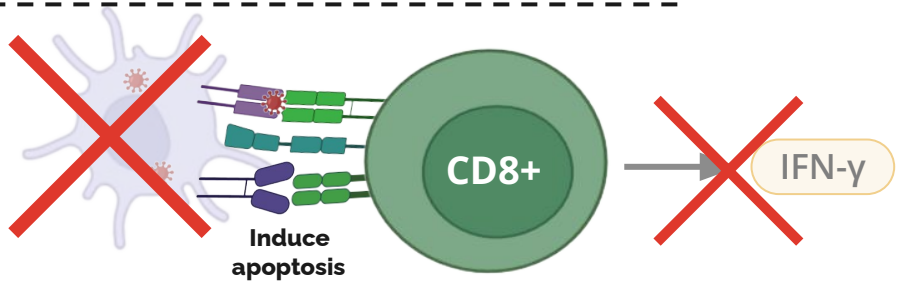
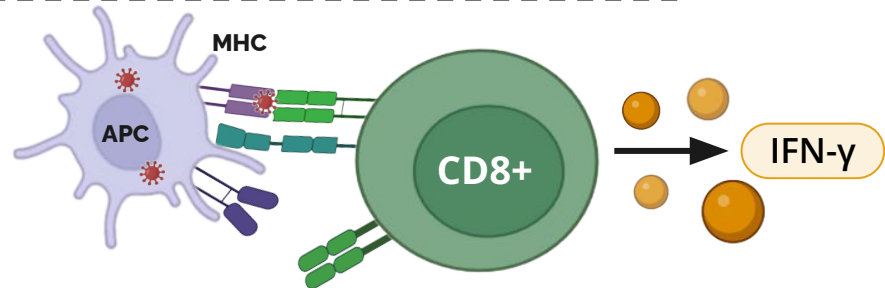
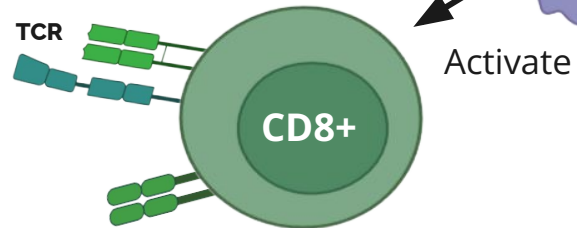
MΦ & ferritin

Clinical  
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# What stops this cycle?

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**More specifically [3]**

- When the cytotoxic T cell **finds an infected APC**, it **secretes cytokines**
- It **stops secreting** cytokines when it **induces apoptosis** successfully

Normal Th1 response

Positive loops

HLH triggers

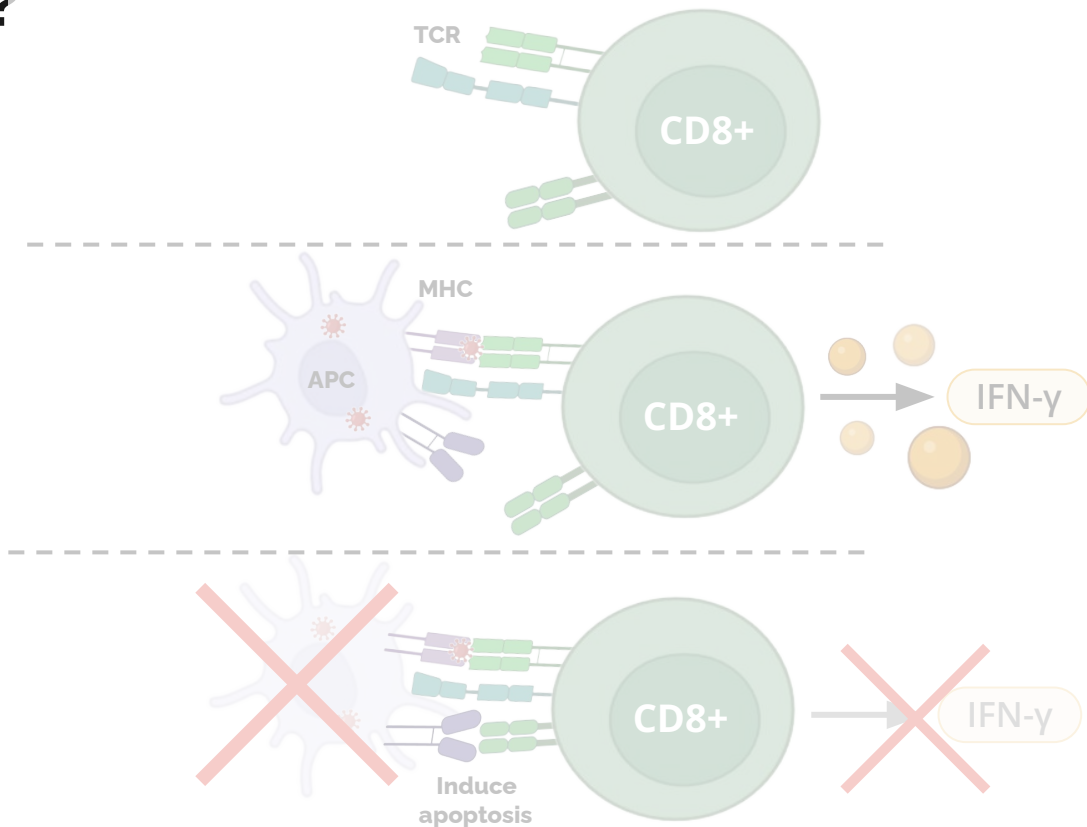
MΦ & ferritin

Clinical manifestations

## What stops this cycle?

### Why it matters to us [3]

- The most common infectious **cause of HLH are viruses**, namely large DNA viruses (**herpesvirus family**)
- Over half of their genome is dedicated to **immunomodulation**



Normal Th1 response

Positive loops

HLH triggers

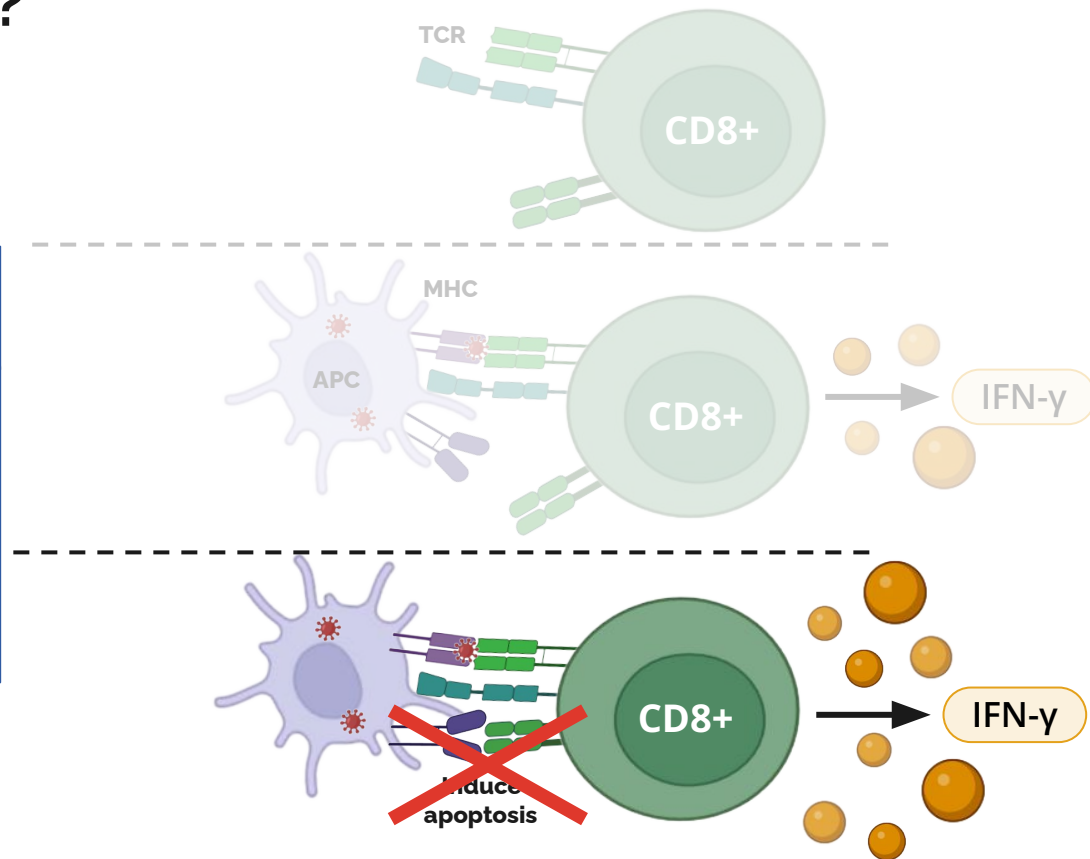
MΦ & ferritin

Clinical manifestations

## What stops this cycle?

### Why it matters to us [3]

- The most common infectious **cause of HLH are viruses**, namely large DNA viruses (**herpesvirus family**)
- Over half of their genome is dedicated to **immunomodulation**
- When they are found → **preventing successful apoptosis**



Normal Th1 response

Positive loops

HLH triggers

MΦ & ferritin

Clinical manifestations

## What stops this cycle?

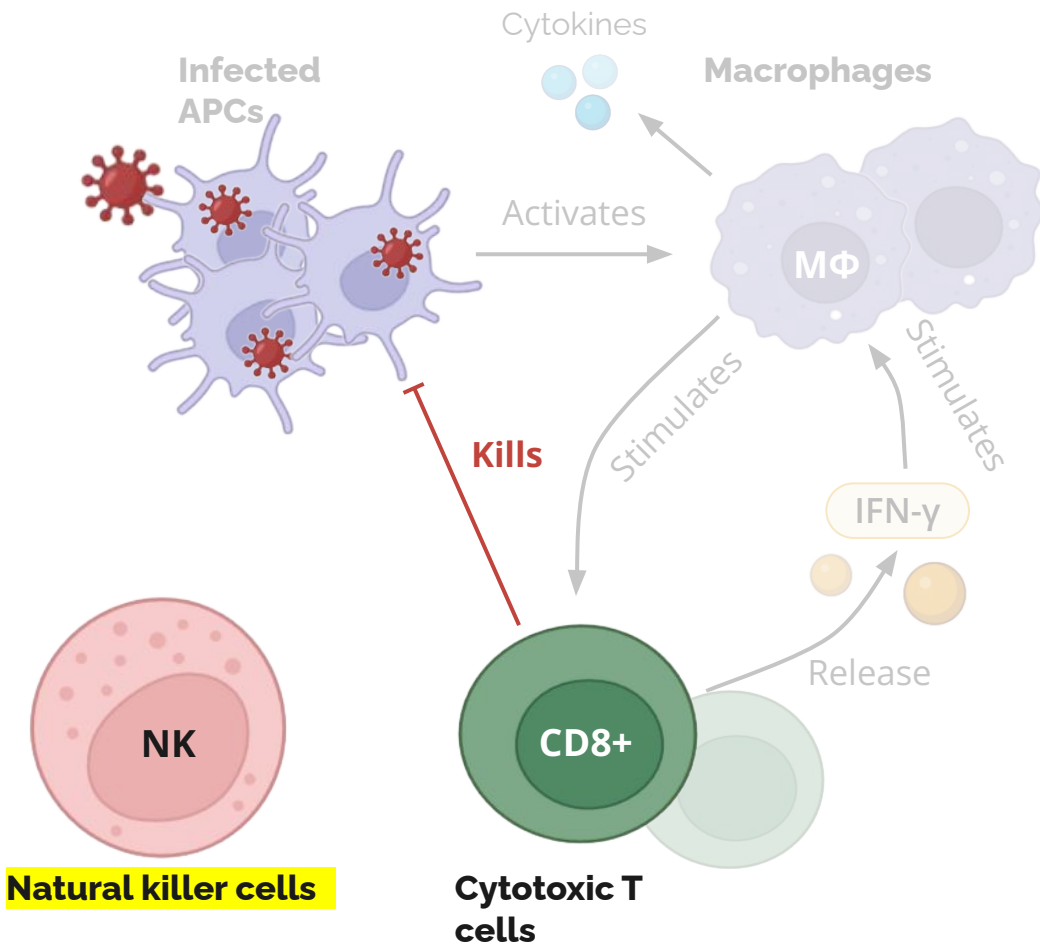


Successfully **eliminating the infection**

1. **Macrophages** stop activating CD8+
2. **CD8+ successfully killing** stops releasing **cytokines**



**Natural killer cells** regulate CD8+



Normal Th1 response

Positive loops

HLH triggers

MΦ & ferritin

Clinical manifestations

## What stops this cycle?



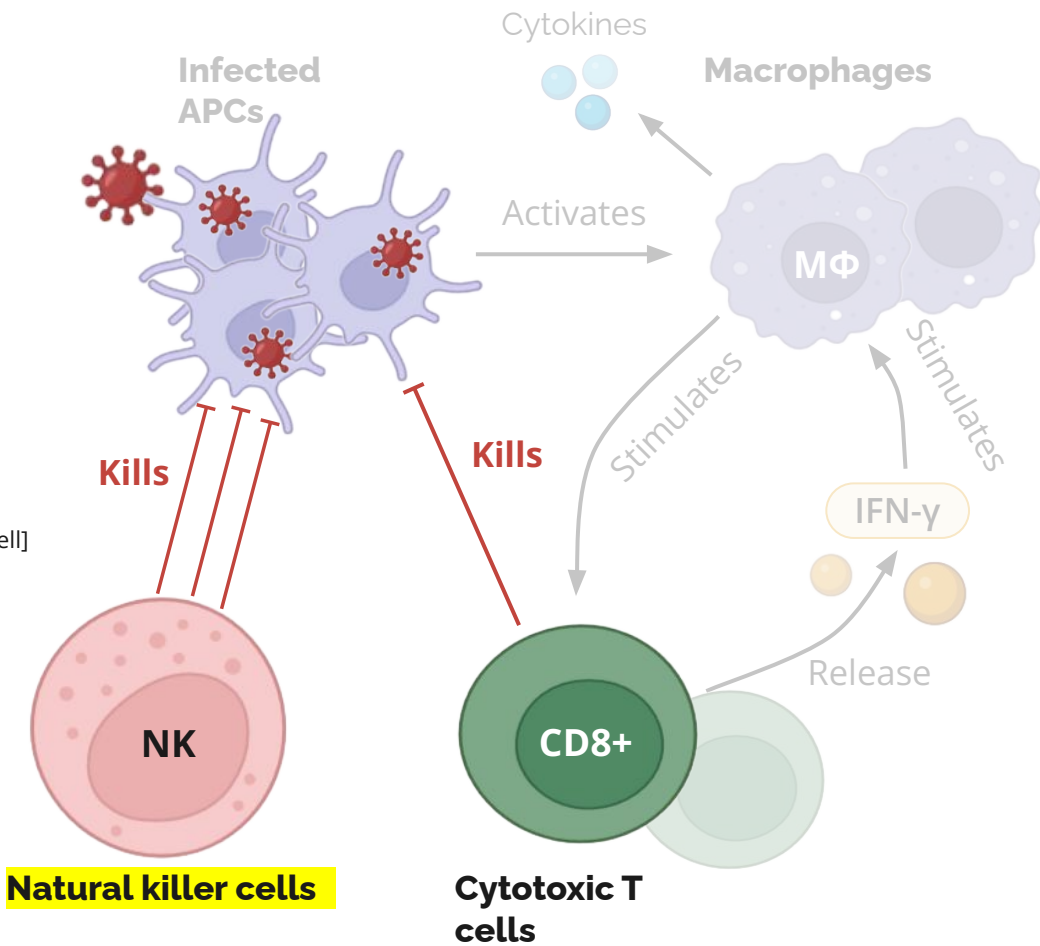
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**Natural killer cells** regulate CD8+

- When pathogens exist, NK cells are **focused on infected APCs** [best I can tell]



Normal Th1 response

Positive loops

HLH triggers

MΦ & ferritin

Clinical manifestations

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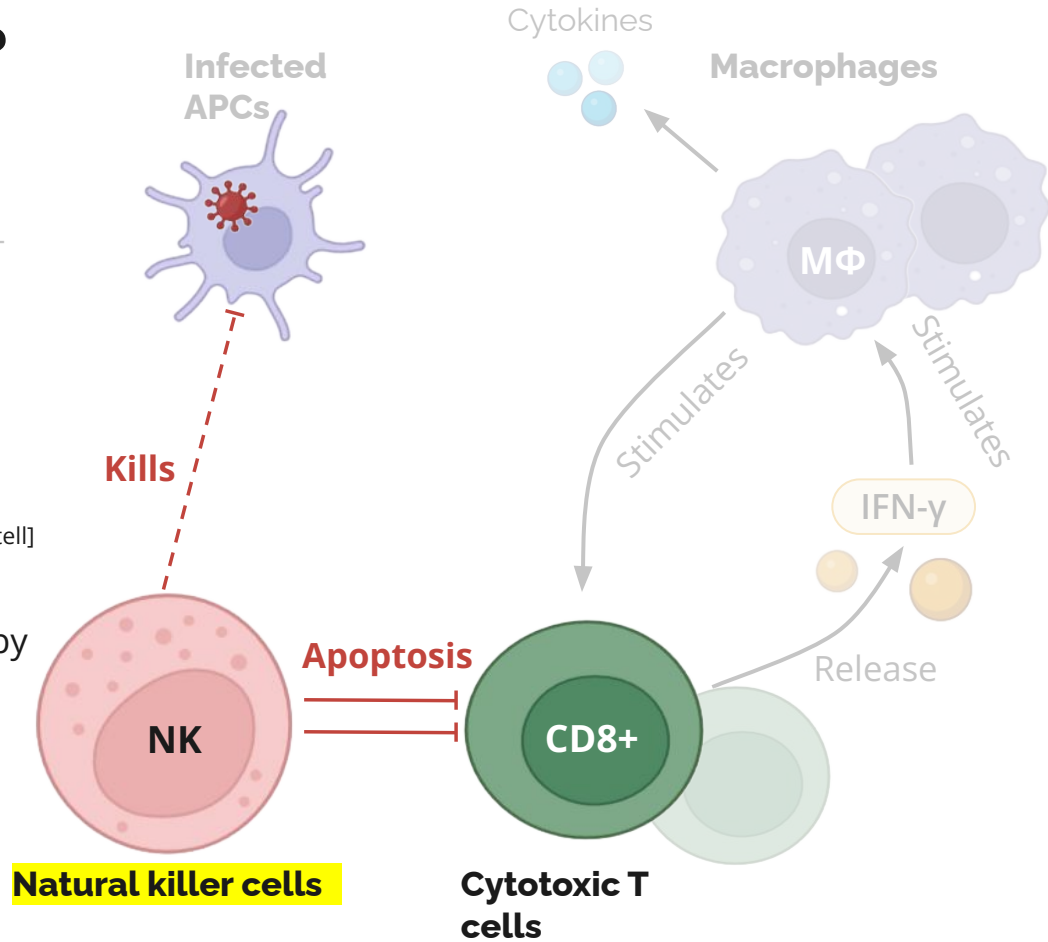
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**Natural killer cells** regulate CD8+

- When pathogens exist, NK cells are **focused on infected APCs** [best I can tell]
- When the infected APCs are gone, **NK cells regulate cytotoxic cells** by inducing apoptosis



Normal Th1 response

Positive loops

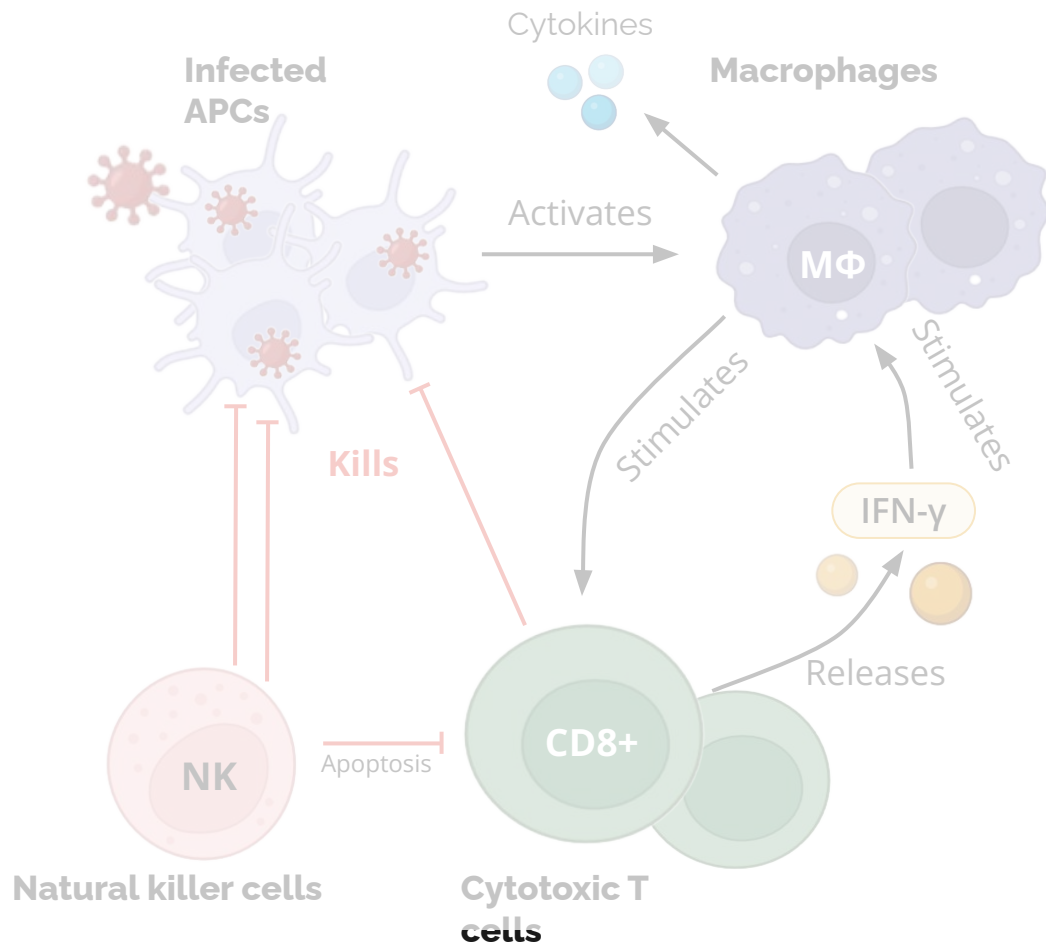
HLH triggers

MΦ & ferritin

Clinical manifestations

# Th1 hyperactivation

Revisiting the causes of HLH (and related syndromes)



Normal Th1 response

Positive loops

HLH triggers

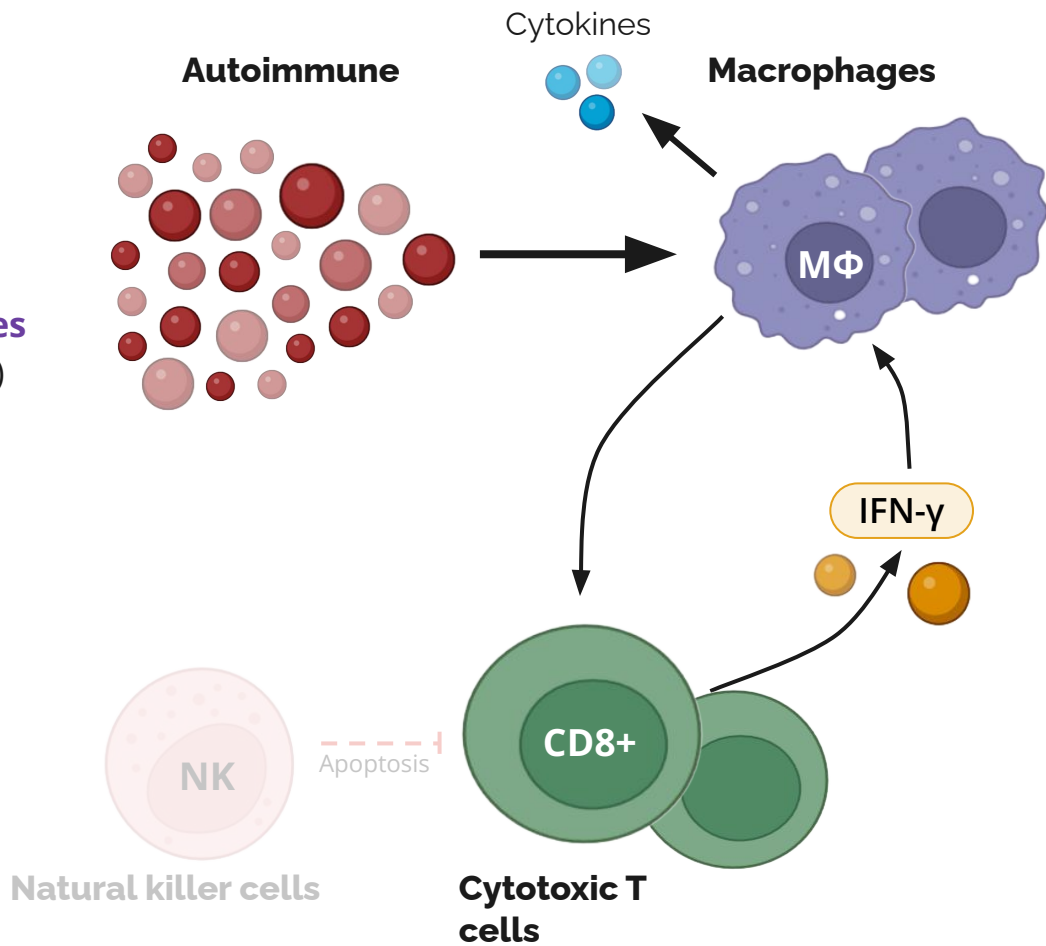
MΦ & ferritin

Clinical manifestations

## Th1 hyperactivation

Revisiting the causes of HLH (and related syndromes)

**Autoimmune:** Key player is **macrophages** (hence macrophage activation syndrome)



Normal Th1 response

Positive loops

HLH triggers

MΦ & ferritin

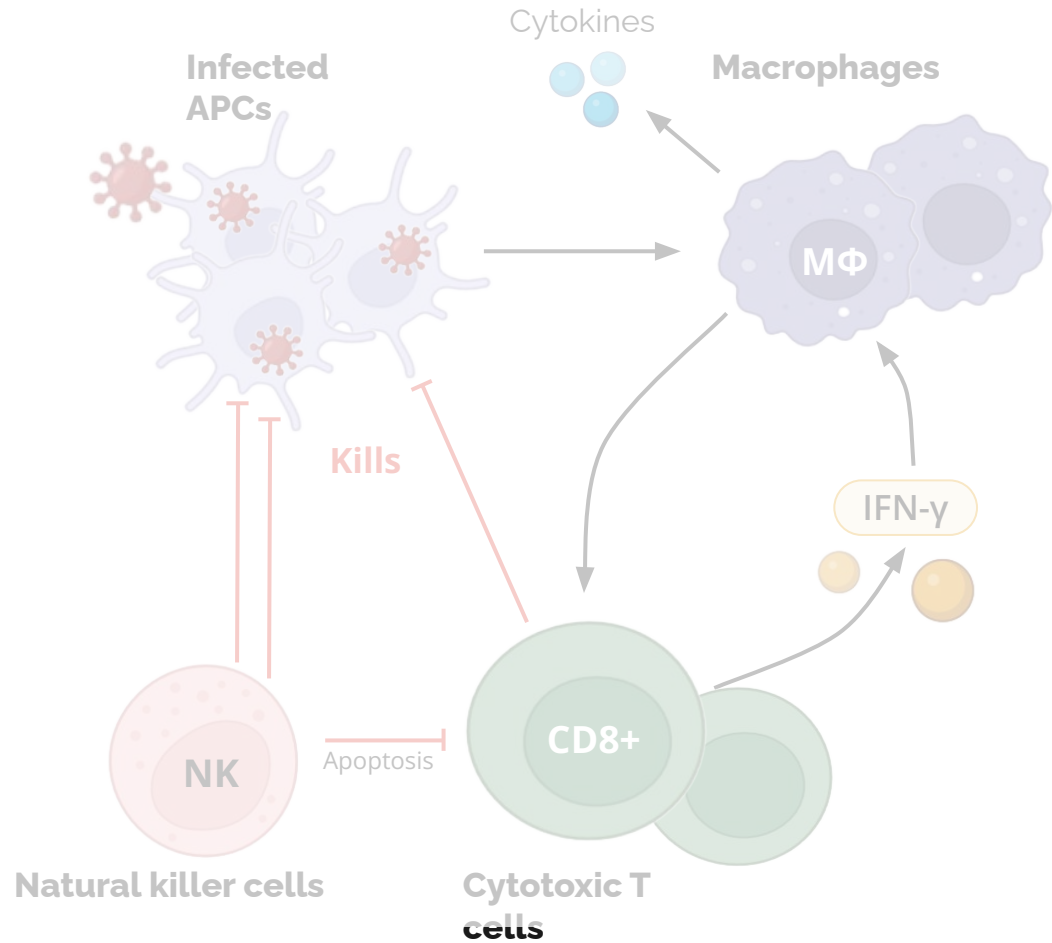
Clinical manifestations

# Th1 hyperactivation

Revisiting the causes of HLH (and related syndromes)

**Autoimmune:** Macrophages

**Malignancy:**



Normal Th1 response

Positive loops

HLH triggers

MΦ & ferritin

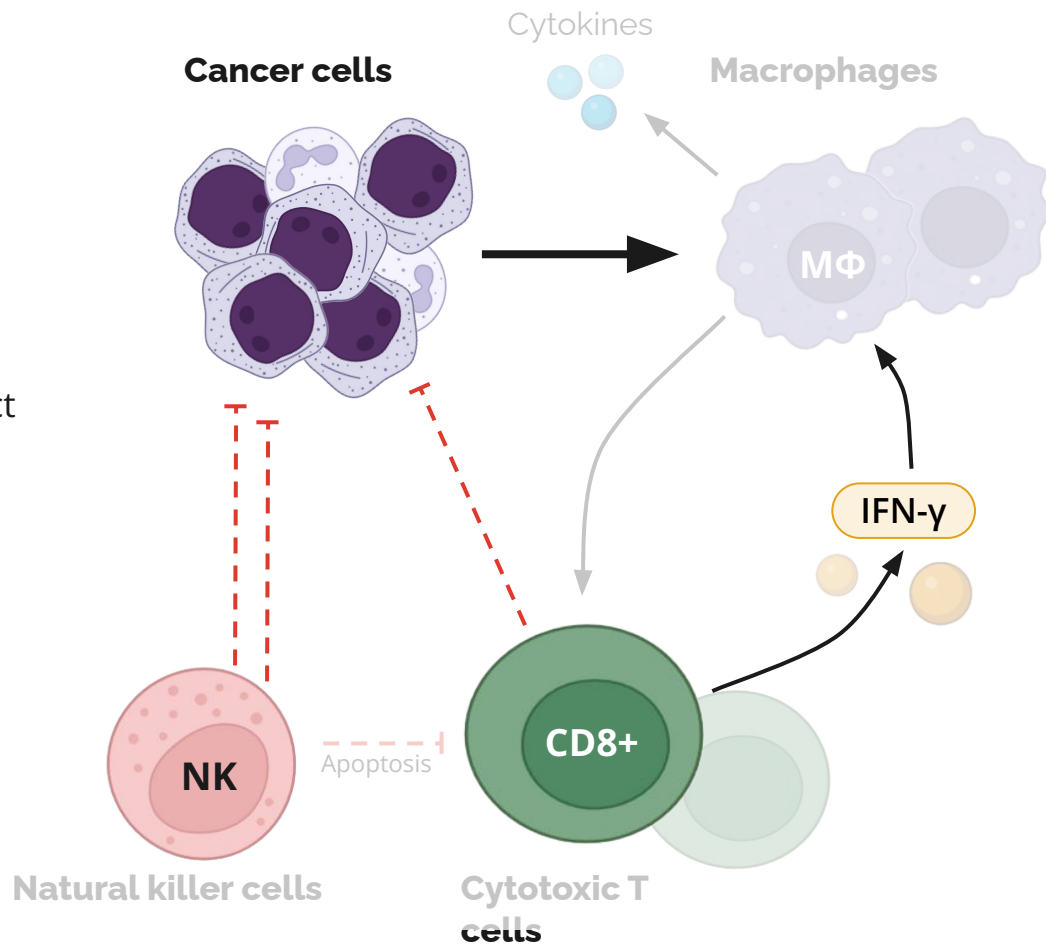
Clinical manifestations

## Th1 hyperactivation

Revisiting the causes of HLH (and related syndromes)

**Autoimmune:** Macrophages

**Malignancy:** Lymphomas (and others) act as a persistent **source of "antigens"**



Normal Th1 response

Positive loops

HLH triggers

MΦ & ferritin

Clinical manifestations

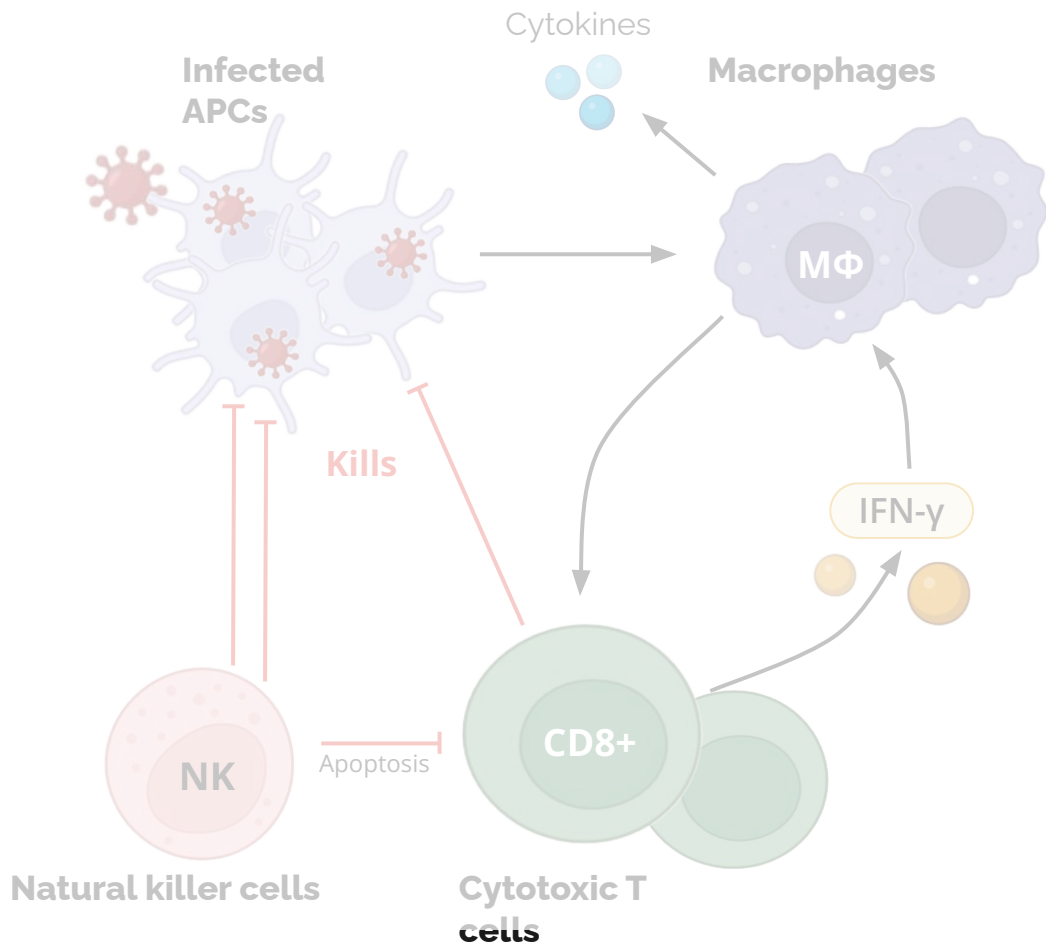
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Revisiting the causes of HLH (and related syndromes)

**Autoimmune:** Macrophages

**Malignancy:** Persistent antigens

**CAR-T:**



Normal Th1 response

Positive loops

HLH triggers

MΦ & ferritin

Clinical manifestations

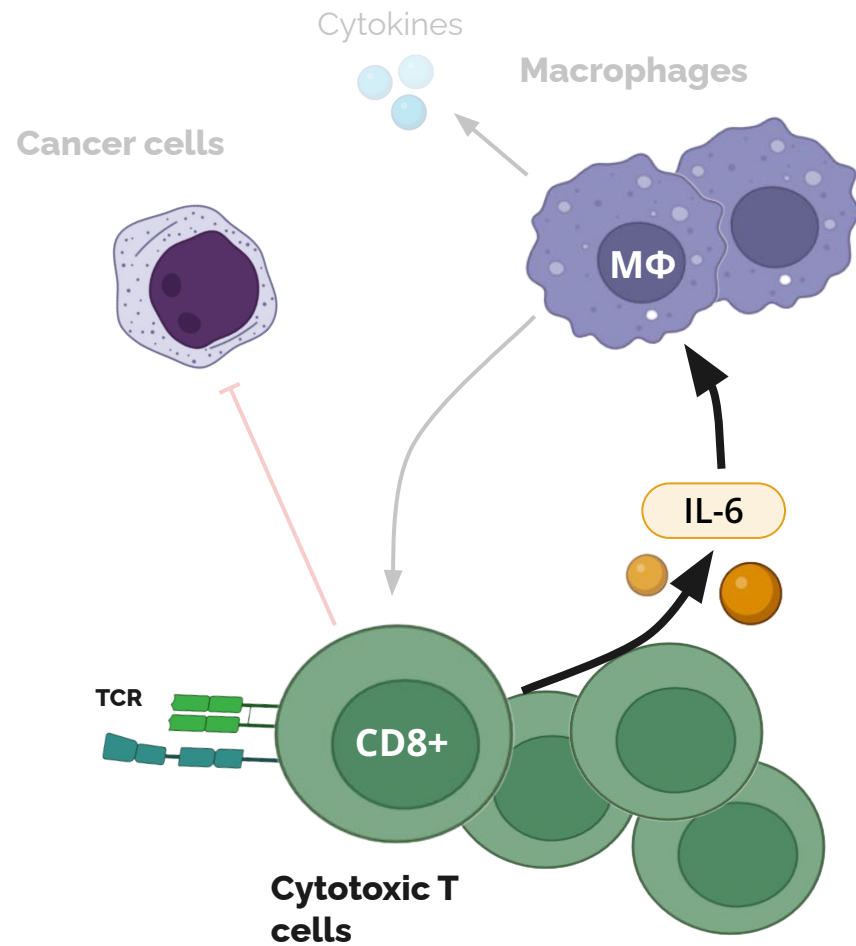
## Th1 hyperactivation

Revisiting the causes of HLH (and related syndromes)

**Autoimmune:** Macrophages

**Malignancy:** Persistent antigens

**CAR-T:** Cytokine release syndrome from **chimeric T-cell receptor therapy** can cause massive activation of T cells



Normal Th1 response

Positive loops

HLH triggers

MΦ & ferritin

Clinical manifestations

## Th1 hyperactivation

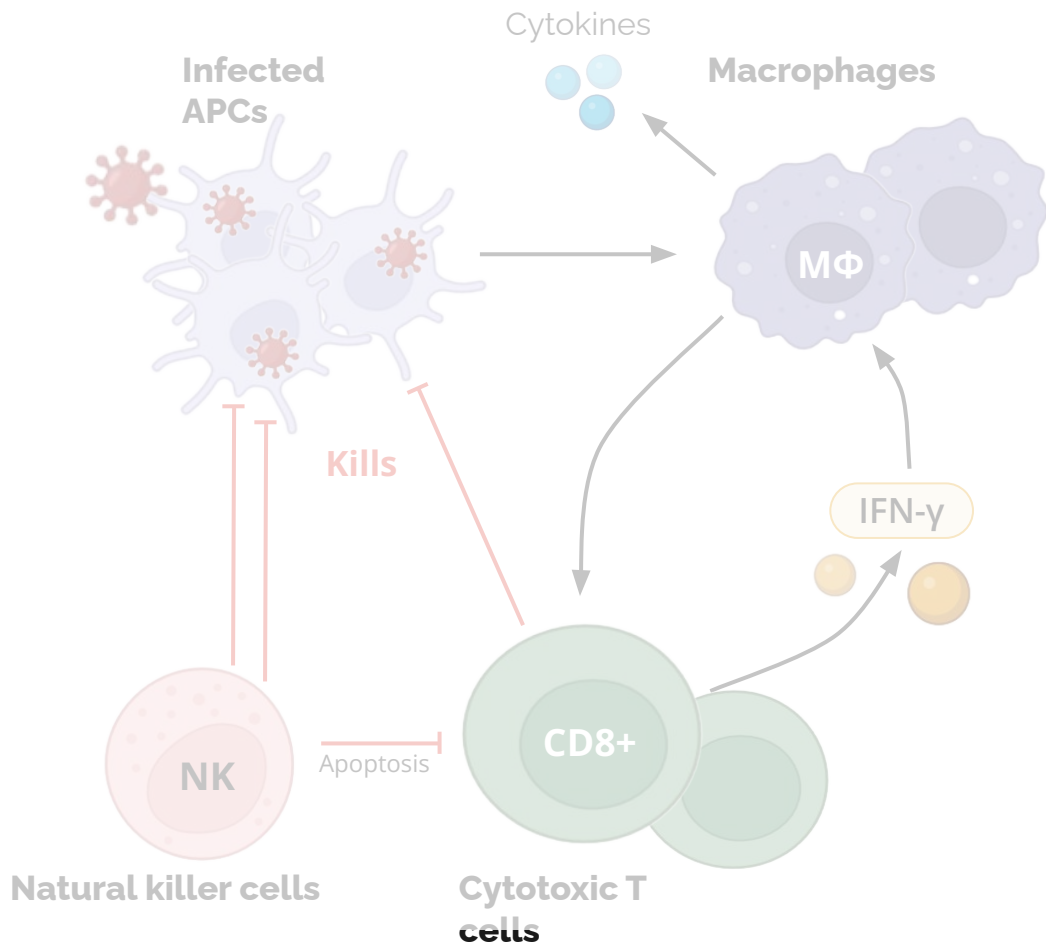
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**Infections:**





Normal Th1 response

Positive loops

HLH triggers

MΦ & ferritin

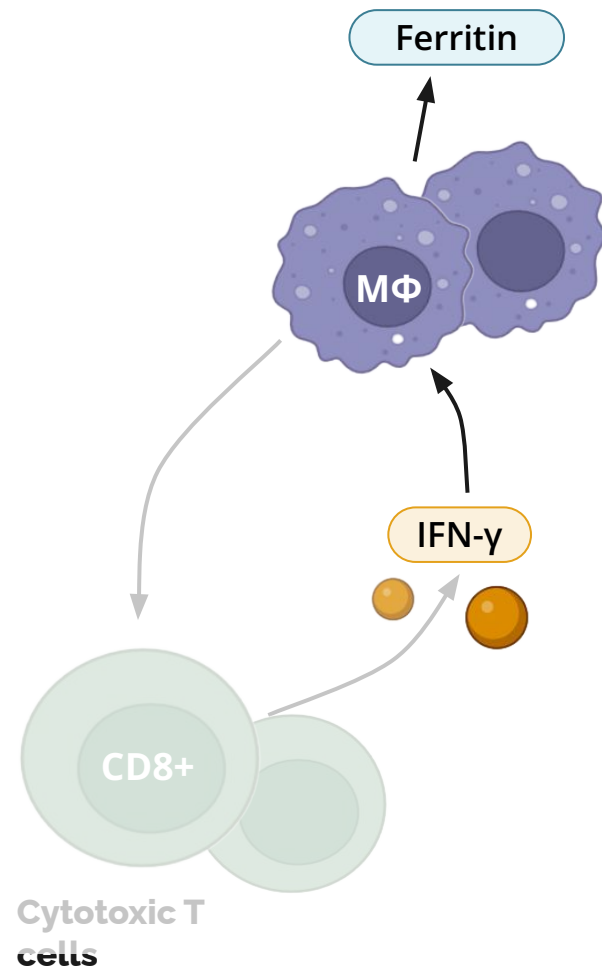
Clinical manifestations

## Macrophages & ferritin

### IFN- $\gamma$ $\rightarrow$ M $\Phi$ $\rightarrow$ Ferritin axis

In all these conditions, the **common downstream** effector cells are **macrophages**

Although IFN- $\gamma$  is one of the stronger inducers of ferritin release (mainly from macrophages), **there are other mechanisms** that can cause **ferritin release too** (e.g. ischemic hepatitis)



Normal Th1 response

Positive loops

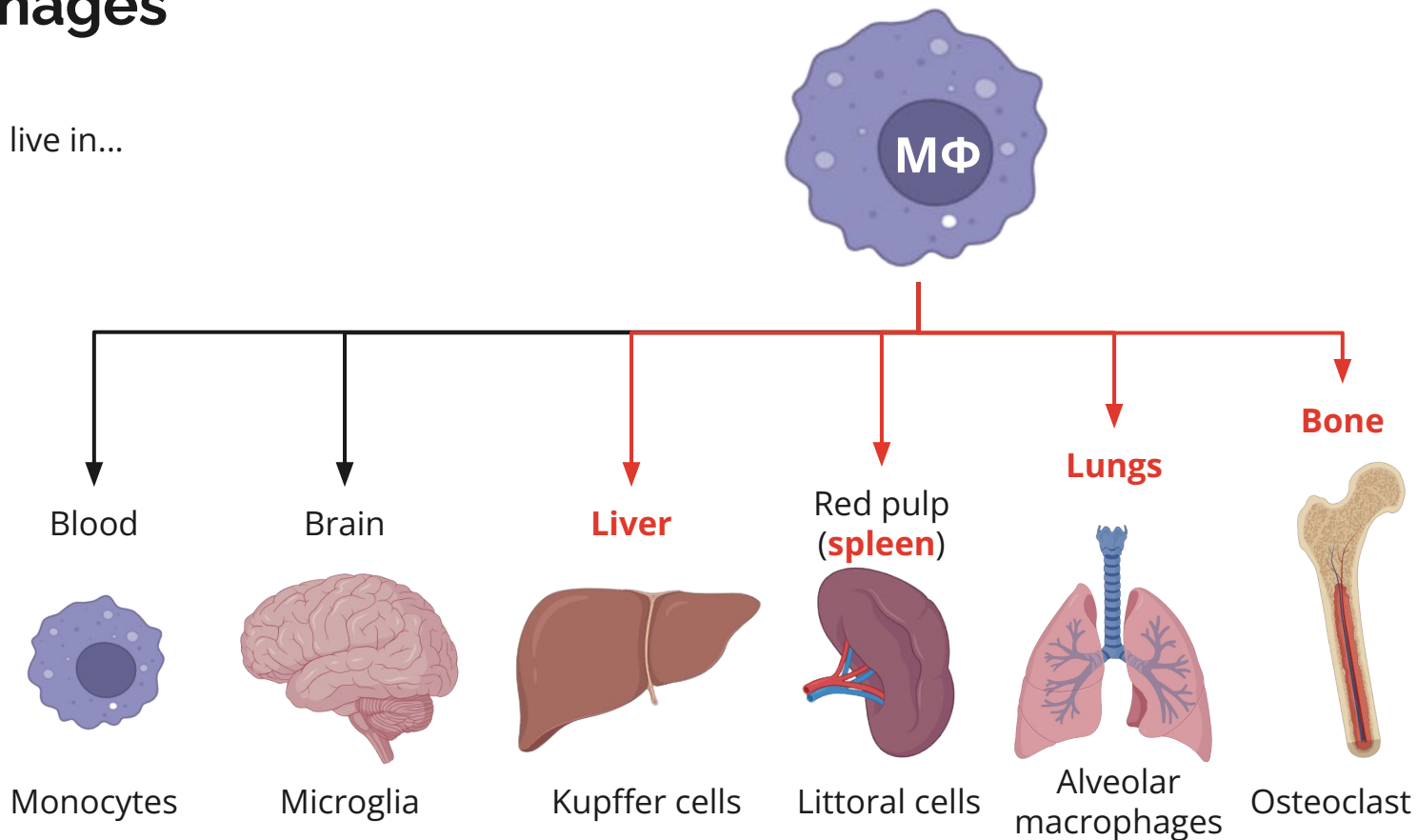
HLH triggers

MΦ & ferritin

Clinical manifestations

# Macrophages

Macrophages live in...



Normal Th1 response

Positive loops

HLH triggers

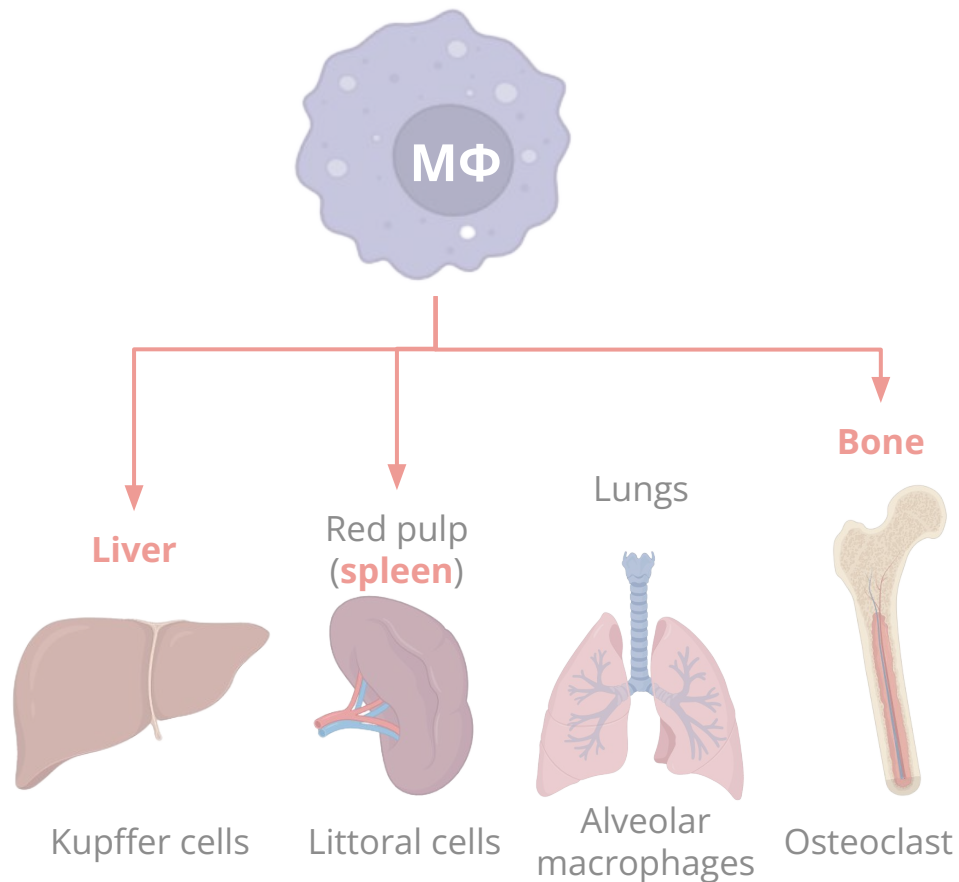
MΦ & ferritin

Clinical manifestations

# Macrophages

Macrophages live in...

- **Liver** (Kupffer cells)
  - Red pulp of the **spleen**
  - **Bone marrow**
  - Lungs
- } Part of the Hscore



Normal Th1 response

Positive loops

HLH triggers

MΦ &amp; ferritin

Clinical manifestations

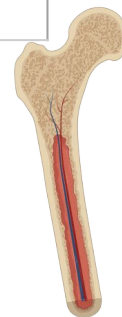
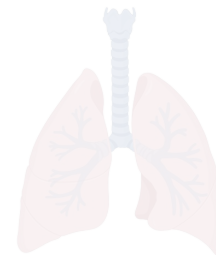
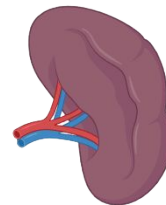
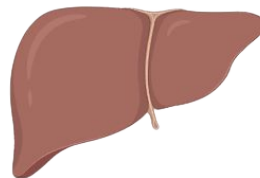
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} Part of the Hscore

HScore for HLH		+224
immunosuppression	No	
Temperature, °F	>102.9	+49
<b>Hepato/spleno-megaly</b>	<b>Both</b>	+38
<b>Number of cytopenias</b>	<b>2 lines</b>	+24
<b>Ferritin</b>	<b>&gt;6,000</b>	+50
Triglycerides	132 - 354	+44
Fibrinogen	>250	
<b>AST</b>	<b>≥30</b>	+19
Bone marrow Bx	TBD	



Normal Th1 response

Positive loops

HLH triggers

MΦ & ferritin

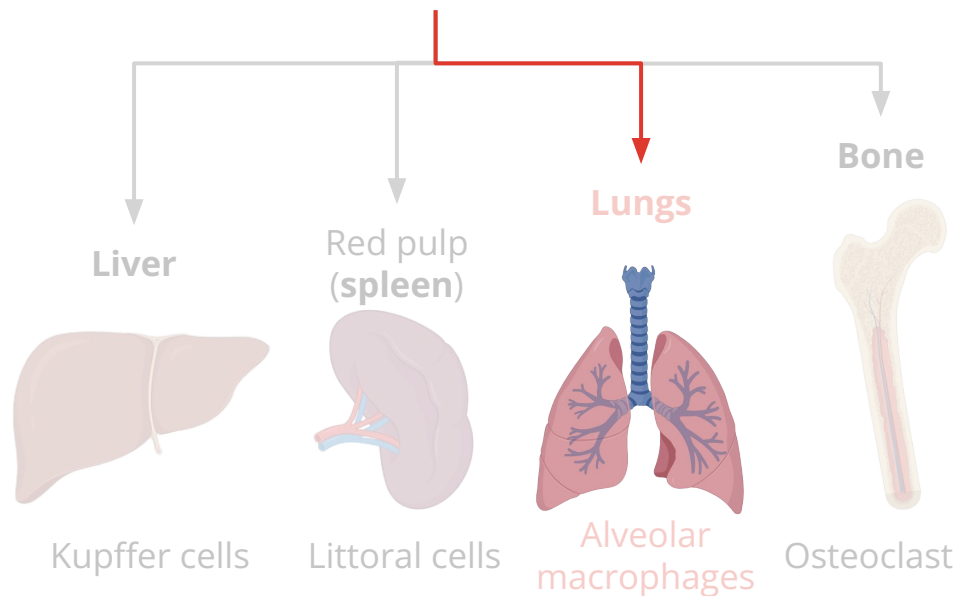
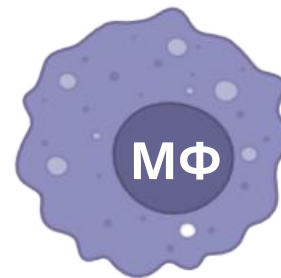
Clinical manifestations

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Macrophages live in...

- **Liver** (Kupffer cells)
  - Red pulp of the **spleen**
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- } Part of the Hscore

- ❖ Influenza (HLH trigger)
- ❖ COVID-19 (↑↑ ferritin)



Normal Th1 response

Positive loops

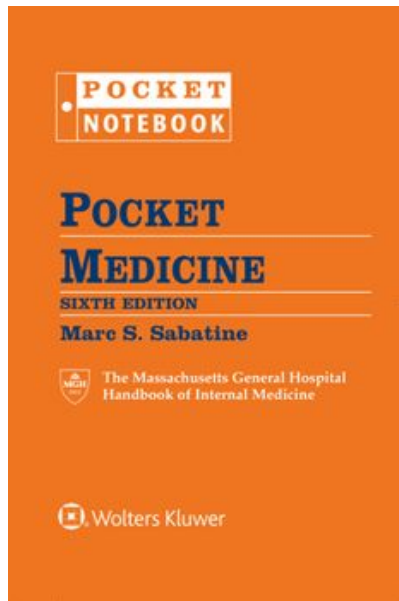
HLH triggers

MΦ & ferritin

Clinical manifestations

# HyperFerritinemia

IFN- $\gamma$   $\rightarrow$  M $\Phi$   $\rightarrow$  Ferritin axis



**Clinical pearl** (from MS3)

Causes of **ferritin >10,000**

# HyperFerritinemia

Revisiting the causes of HLH (and related syndromes)

**Autoimmune:** Macrophages

**Malignancy:** Persistent antigens

**CAR-T:** T-cell activation

**Infections:** Intracellular pathogens that target immune cells drive a strong T cell response (including viruses)

## Clinical pearl (from MS3)

### Causes of **ferritin >10,000**

- Rickettsial infection
- Histoplasmosis

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- Lymphoma

# HyperFerritinemia

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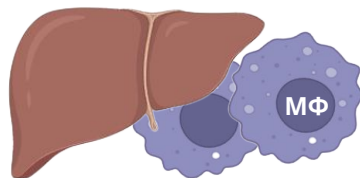
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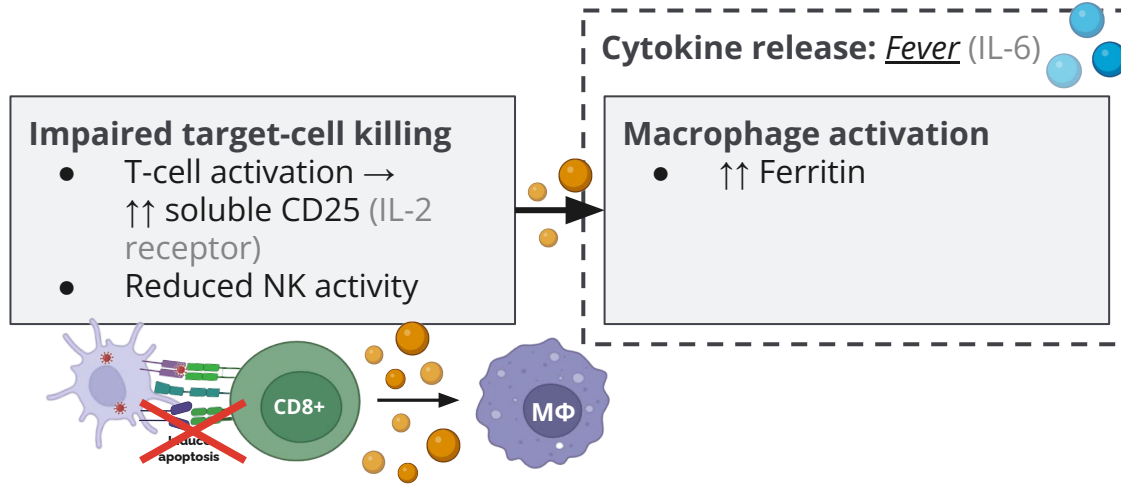
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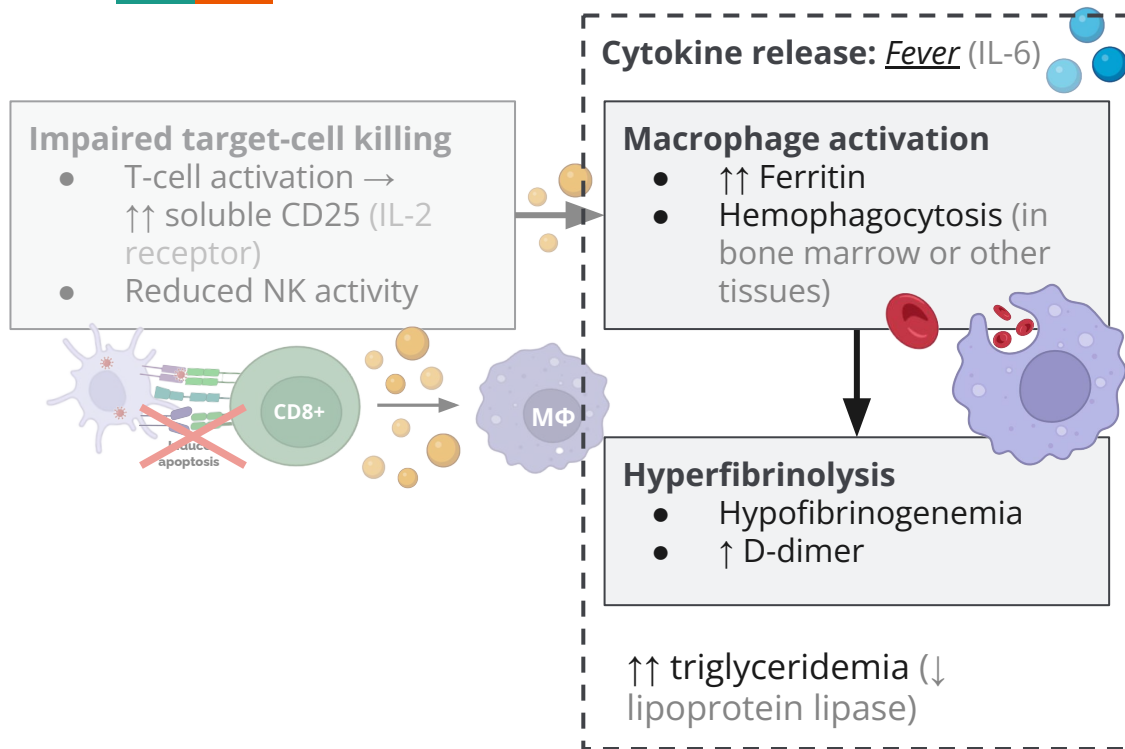
- Rickettsial infection
- Histoplasmosis
- Adult onset Still's disease
- Lymphoma
- Hepatitis causing *liver failure* (viral)
- Severe viral infections (HSV, CMV, EBV)



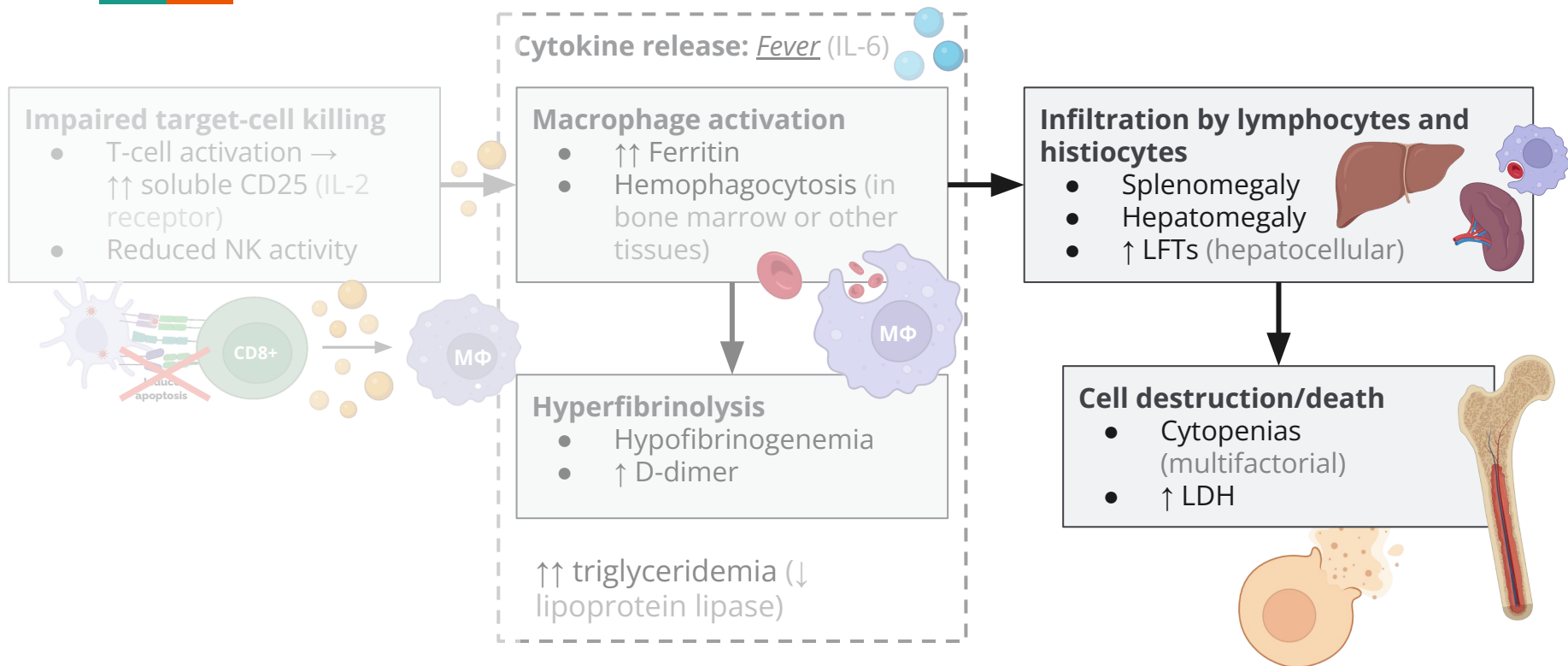
## Conceptual overview



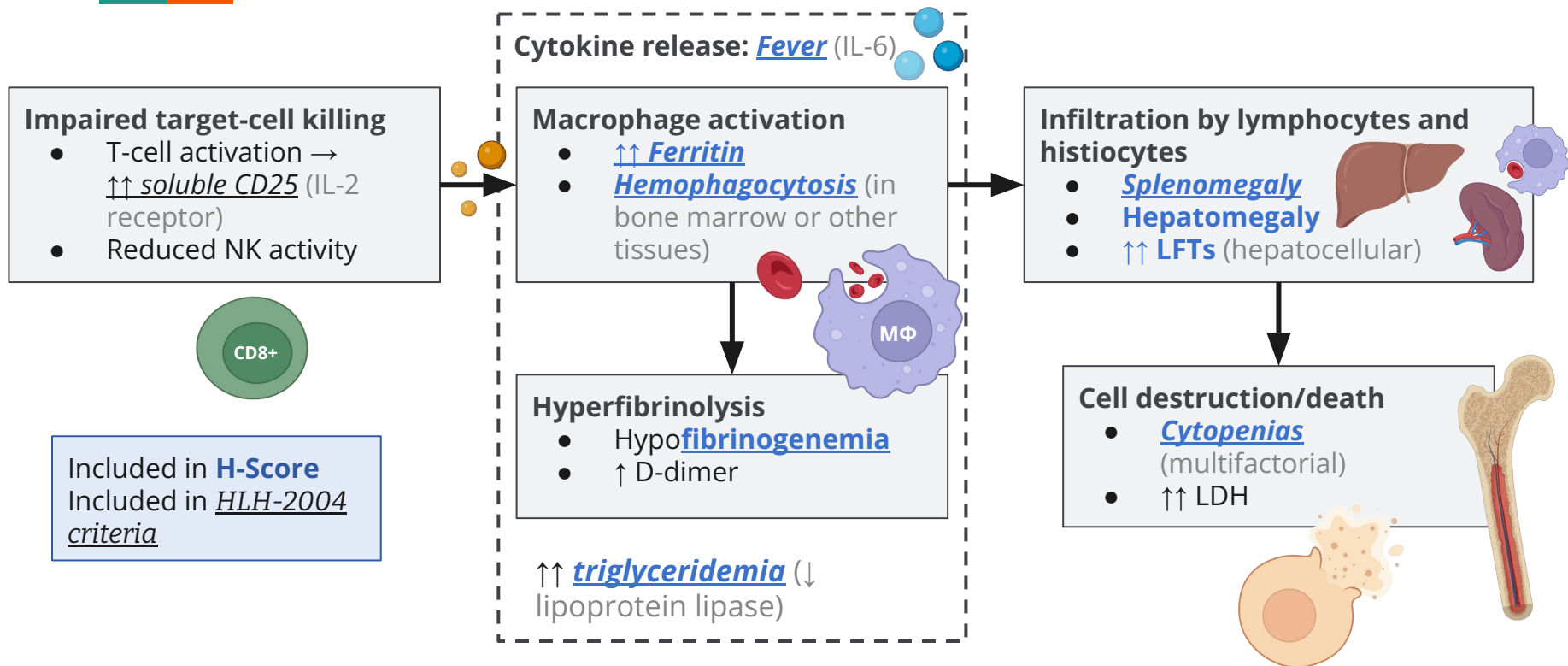
## Conceptual overview



# Conceptual overview



# Conceptual overview



Normal Th1 response

Positive loops

HLH triggers

MΦ & ferritin

Clinical manifestations

## Conceptual overview

Cytokine release: *Fever* (IL-6)

Admit labs	Our patient	Case report
WBC	3.0	3.3
Hgb	17.0	13.9
Platelets	72	16
Creat	1.7	3.96
AST	335	330
ALT	104	183
Ferritin	8,830 (29 x ULN)	>33,511 (>110 x ULN)
LDH	1,501	1,337

Often, we **only look at these** numbers

But what about these?

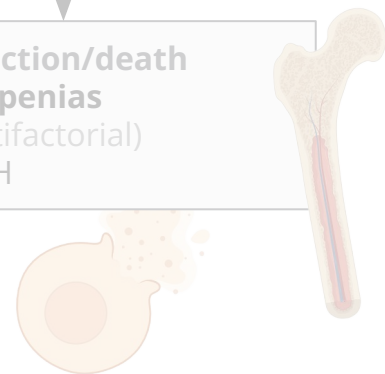
Infiltration by lymphocytes and histiocytes

- Splenomegaly
- Hepatomegaly
- ↑ LFTs (hepatocellular)



Cell destruction/death

- **Cytopenias** (multifactorial)
- ↑ LDH





# Do tick-borne diseases cause HLH?

- Anaplasmosis → HLH **reported in the literature**
- Infectious pathogens that **trigger HLH are intracellular** (most obligate intracellular)
  - DNA viruses > other viruses
  - TB, Rickettsia, Histo, Leishmania
- **“Tick appearing labs”** look similar to HLH labs
  - Cytopenias + LFTs
  - Typhoidal syndrome clinically

Serologies	IgM	IgG
Lyme	Pos	Neg
Ehrlichia	?	?
Anaplasma	?	?
RMSF	?	?

# Cytokine levels in anaplasmosis induced HLH [6]



An older study evaluated 29 patients:

- With laboratory confirmed anaplasmosis
- Versus controls
  - Suspected to have anaplasmosis
  - But all lab testing indicated otherwise (negative serologies, PCR, smear)

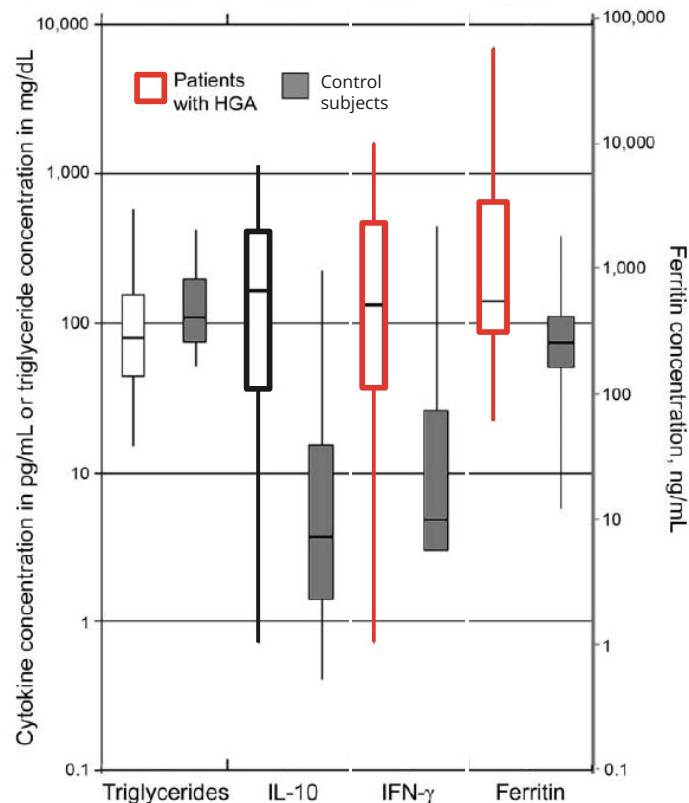
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Patients with anaplasmosis had some cytokines elevated higher than would be expected

- Higher levels of **IL-10, IL-12, IFN- $\gamma$**



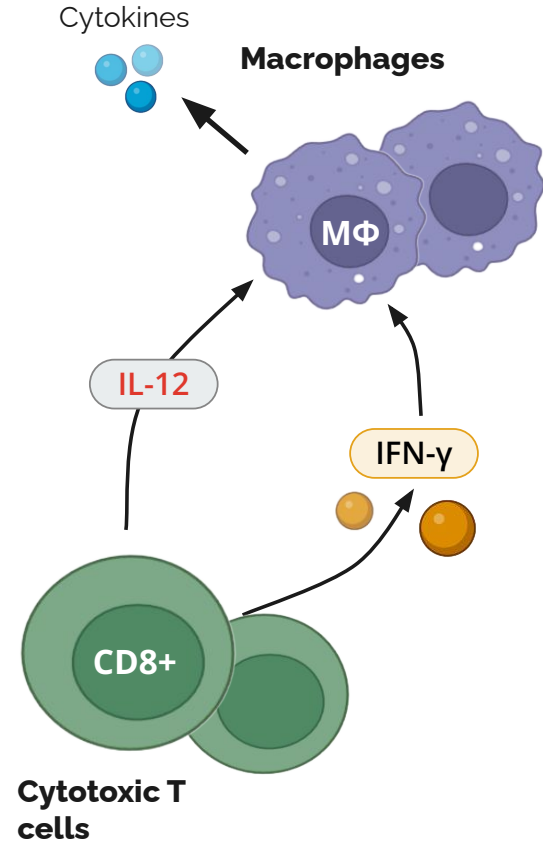
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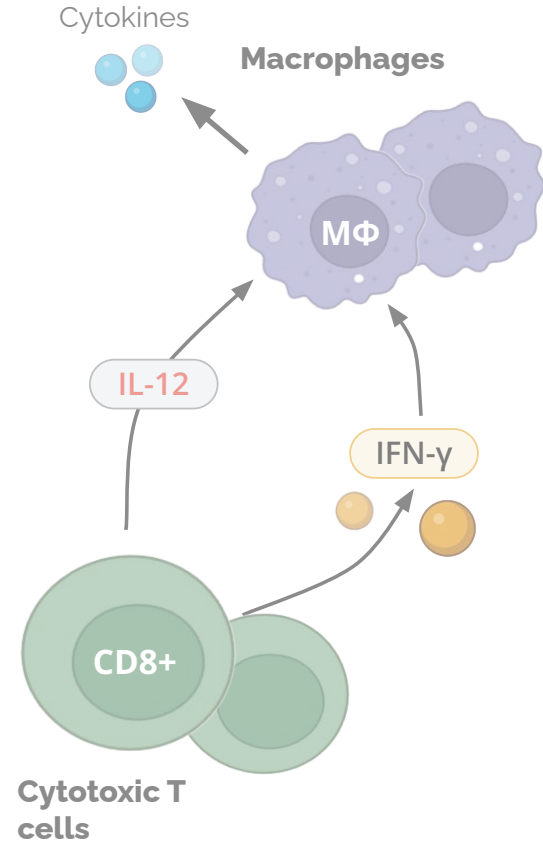
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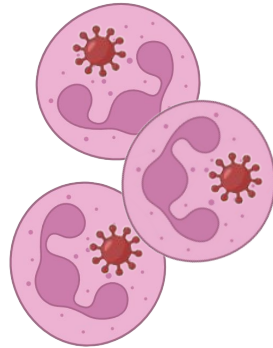
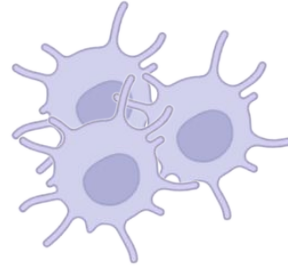
- Higher levels of **IL-10, IL-12, IFN- $\gamma$**
- But **others were not** (TNF- $\alpha$  was normal) implying a *slightly different mechanism* than Ehrlichia



# But...

Anaplasmosis does not infect APCs, **neutrophils are infected**

Normal APCs

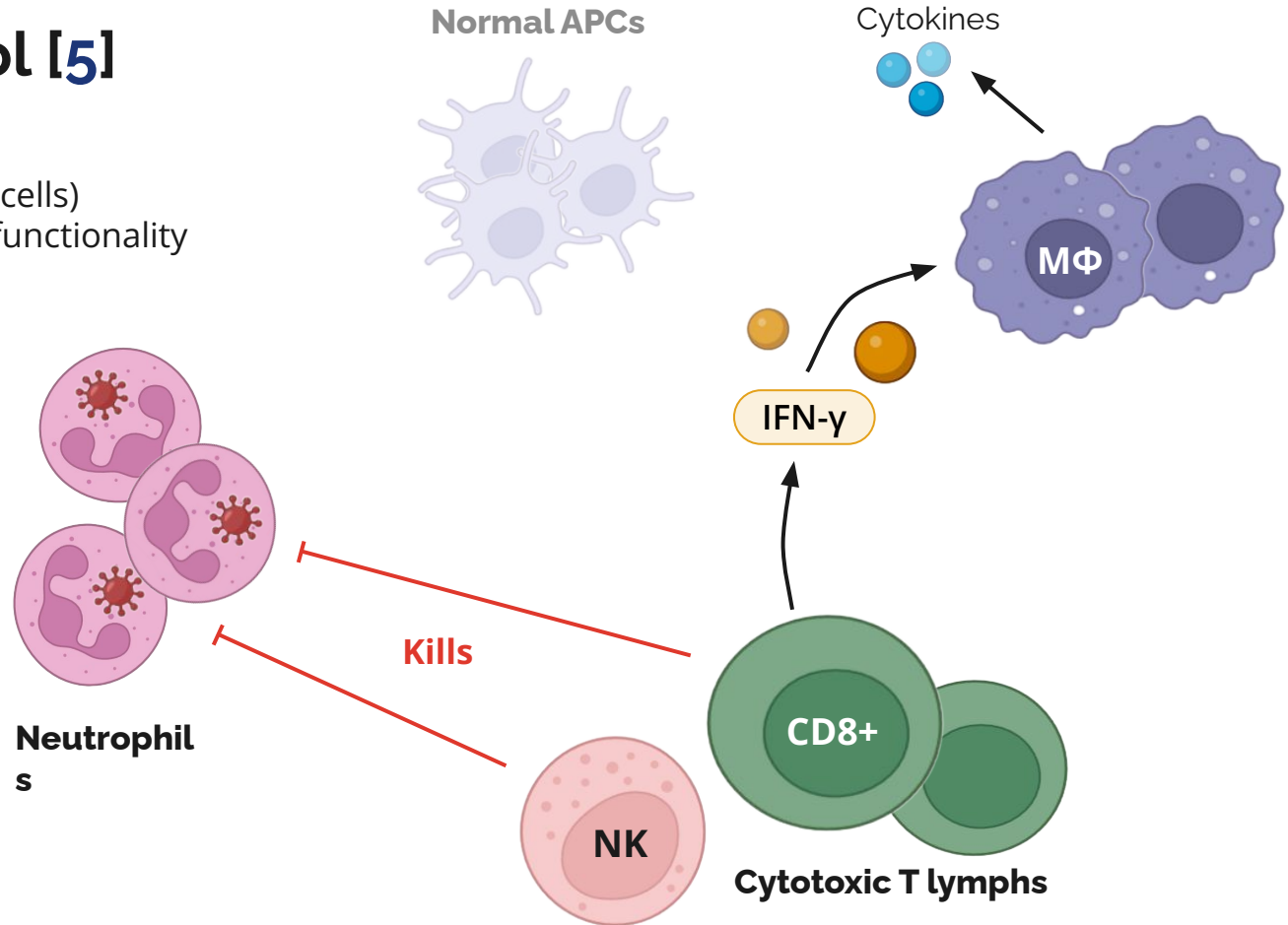


**Neutrophils**

# Front Immunol [5]

Animal model (of human cells)

- Looking at cellular functionality

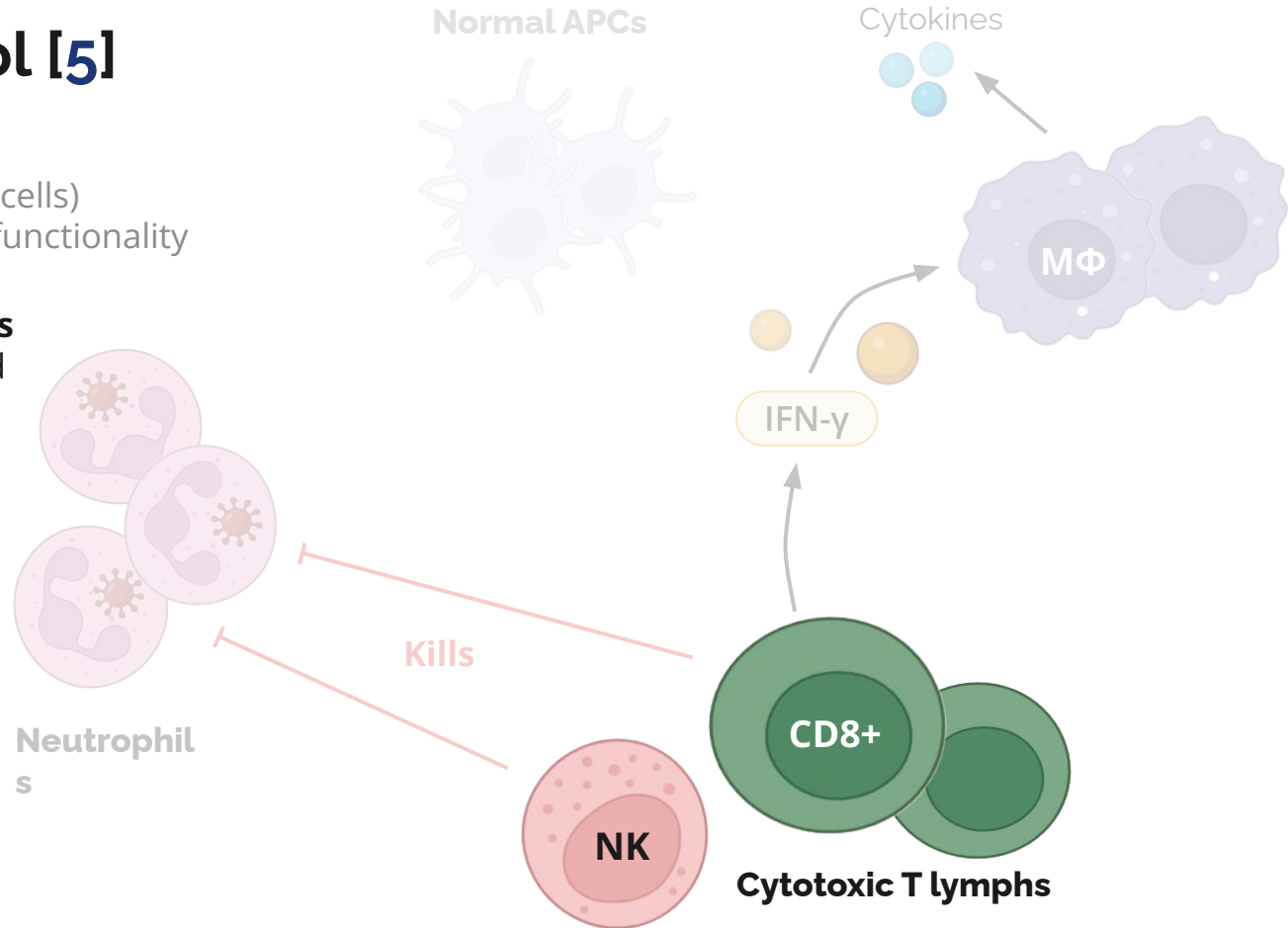


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**Cytotoxic T lymphocytes**  
don't work when exposed  
to anaplasmosis



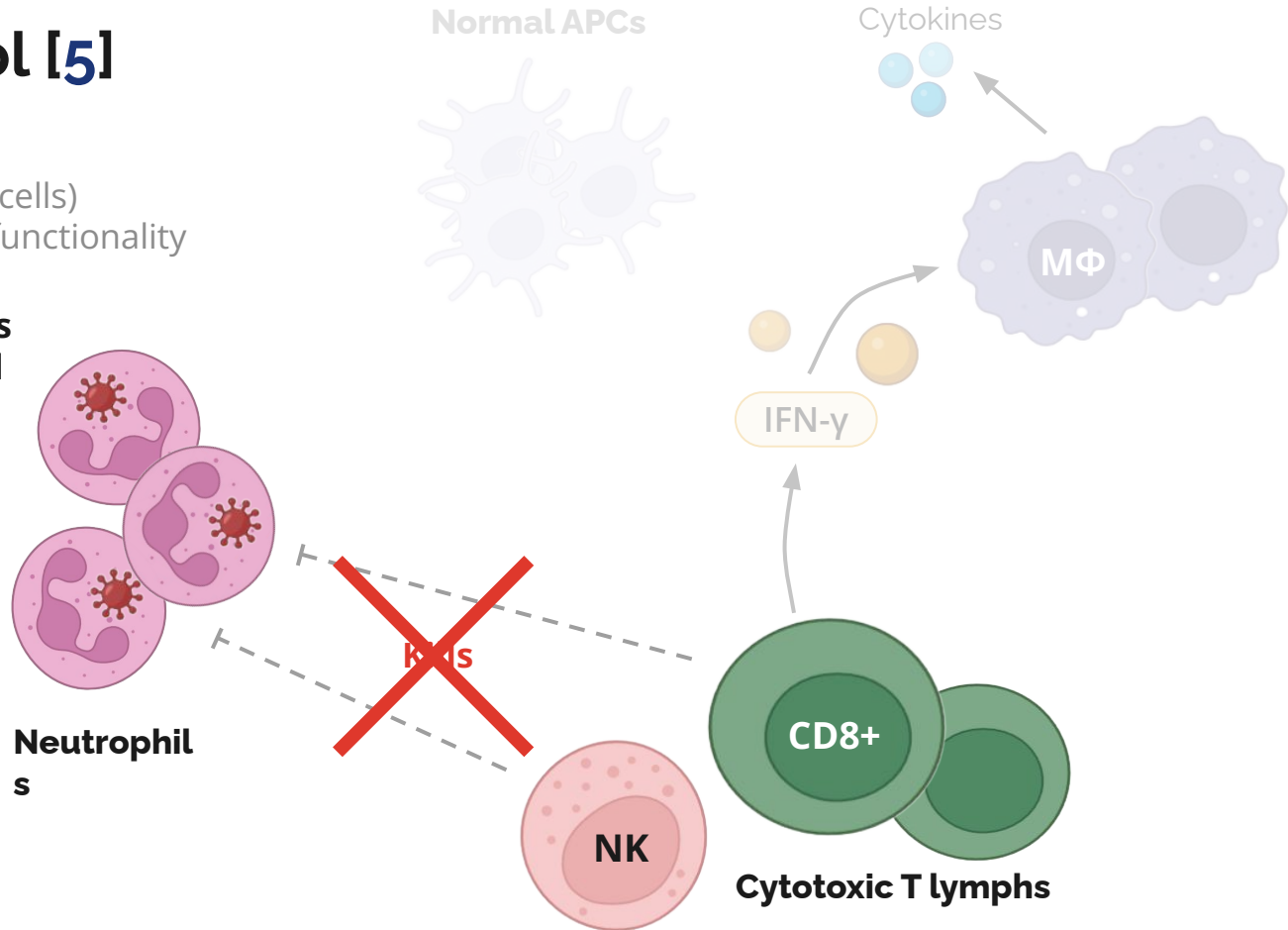
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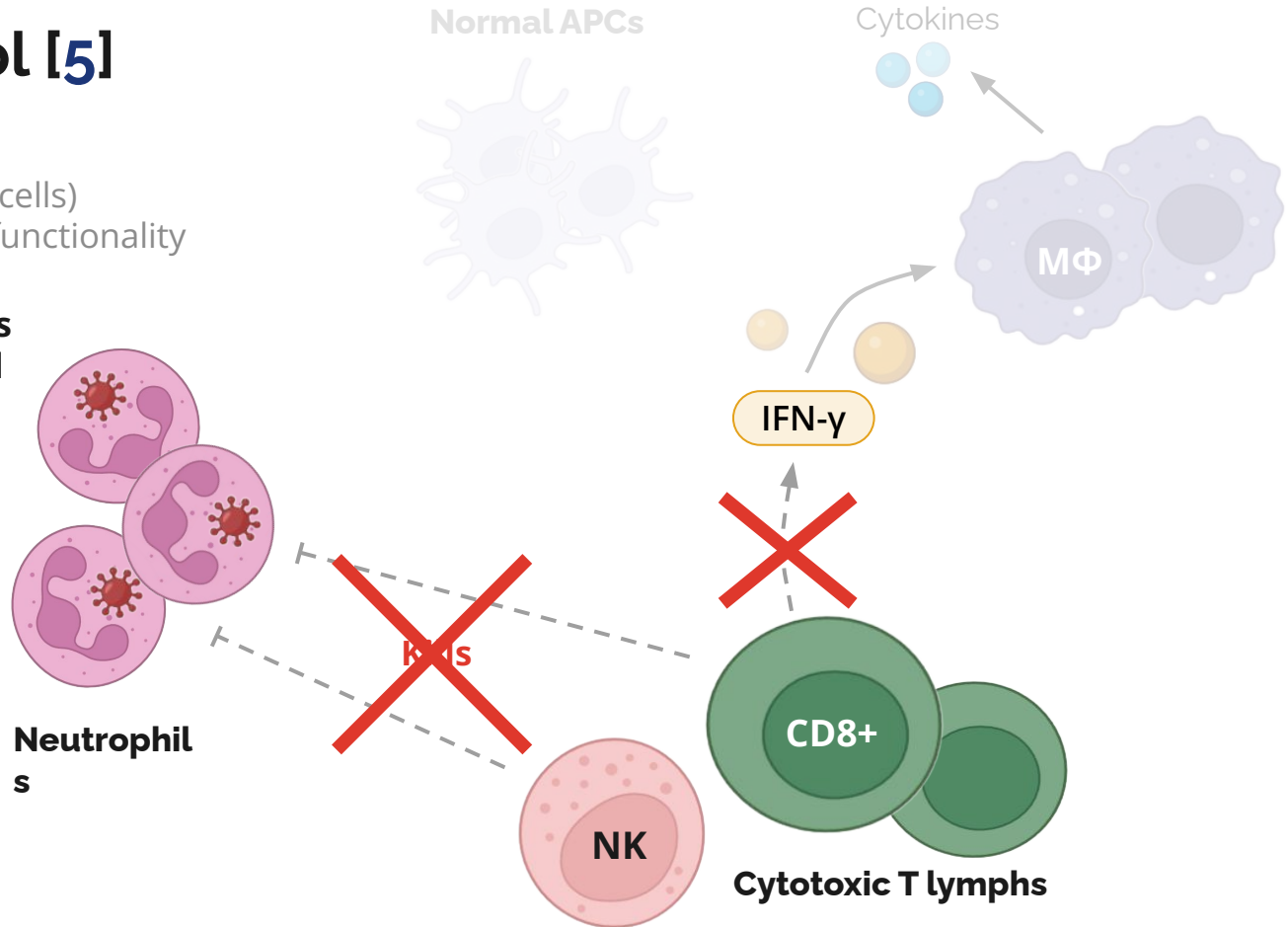
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- Also don't secrete IFN- $\gamma$



# Front Immunol [5]

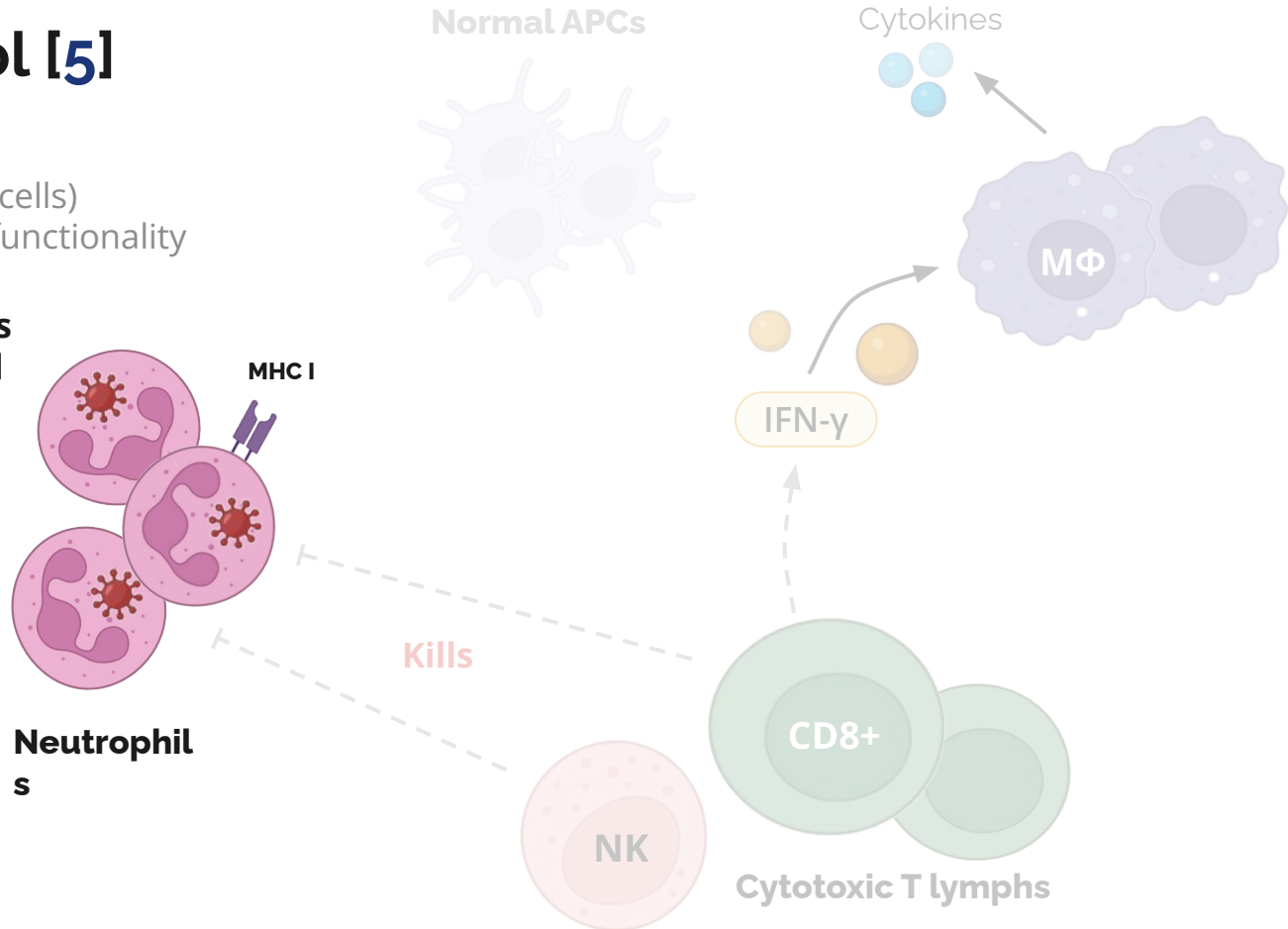
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- Also don't secrete IFN- $\gamma$

Possibly due to **poor presentation** by **MHC I**  
infected cells



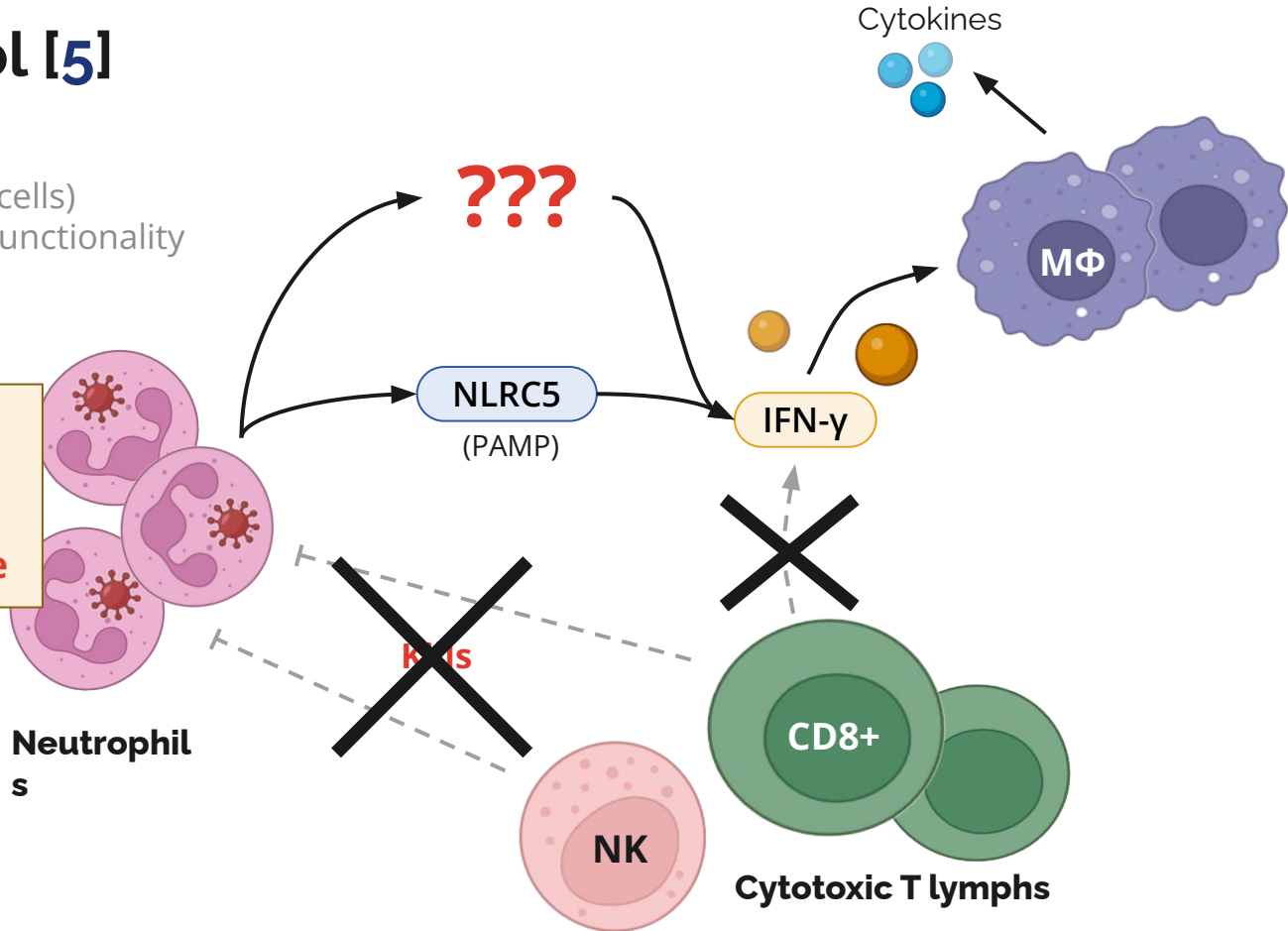
# Front Immunol [5]

Animal model (of human cells)

- Looking at cellular functionality

## Implication

**Something else** in the immune system may be driving the IFN- $\gamma$  release



## Case 1: Hospital course

Serologies	IgM	IgG
Lyme	Pos	Neg
Ehrlichia	?	?
Anaplasma	???	???
RMSF	?	?

Other	Result
Parasite smear	Neg
Monospot	Neg

Serum PCR	Copies
Anaplasmosis	
Lyme	
Adenovirus	
HSV	
CMV	
EBV	

Bone marrow Bx	
CMV PCR	
EBV PCR	
Flow cyto	

# Case 1: Hospital course

Serologies	IgM	IgG
<b>Lyme</b>	<b>Pos</b>	Neg
Ehrlichia	<1:20	<1:64
Anaplasma	<1:20	<1:64
RMSF	Neg	Neg

Other	Result
Parasite smear	Neg
Monospot	Neg

Serum PCR	Copies
Anaplasmosis	?
Lyme	?
Adenovirus	?
HSV	?
CMV	?
EBV	?

Bone marrow Bx	
CMV PCR	?
EBV PCR	?
Flow cyto	?

# Case 1: Hospital course



(Lyme OR "Lyme Disease"[Mesh]) AND (HLH OR "Lymphohistiocytosis, Hemo



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4 results

RMSF	Neg	Neg
------	-----	-----

Other	Result
Parasite smear	Neg
Monospot	Neg

HSV	?
CMV	?
EBV	?



Well, then does Lyme cause HLH?



# Hemophagocytic Lymphohistiocytosis (HLH) in Patients with Tick-Borne Illness: A Scoping Review of 98 Cases [9]

Systematic Review

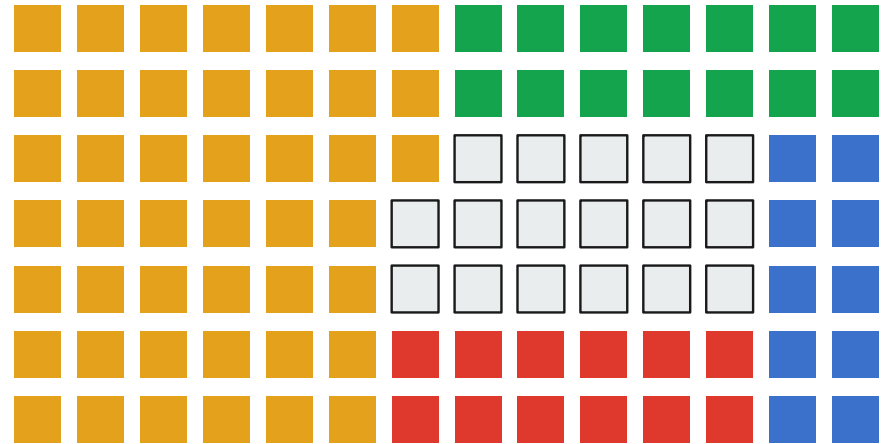


20 February 2024

Of their 98 cases identified

- Ehrlichia spp (n=45)
- Anaplasma spp (n=12)
- Rickettsia spp (n=14)
- Babesia spp (n=10)

**Ehrlichia** spp (n=45)    **Rickettsia** spp (n=14)



**Anaplasma**  
spp (n=12)

**Babesia**  
spp (n=10)

# Hemophagocytic Lymphohistiocytosis (HLH) in Patients with Tick-Borne Illness: A Scoping Review of 98 Cases [9]

Systematic Review

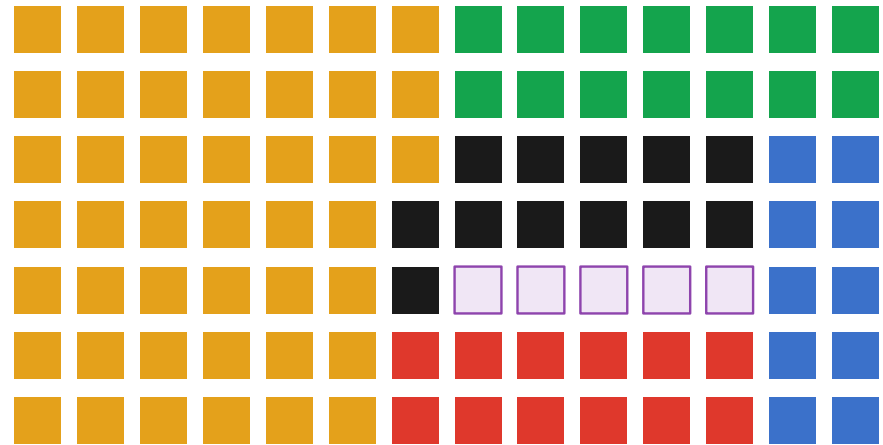


20 February 2024

Of their 98 cases identified

- Ehrlichia spp (n=45)
- Anaplasma spp (n=12)
- Rickettsia spp (n=14)
- Babesia spp (n=10)
- Orientia spp (n=8)
- Coxiella spp (n=5)
- Heartland virus (n=3)
- Bunyavirus spp (n=1)

**Ehrlichia** spp (n=45)    **Rickettsia** spp (n=14)



**Anaplasma**  
spp (n=12)

**Babesia**  
spp (n=10)

**But no Lyme!**

## Case 1: Hospital course

Serologies	IgM	IgG
<b>Lyme</b>	<b>Pos</b>	Neg
Ehrlichia	<1:20	<1:64
Anaplasma	<1:20	<1:64
RMSF	Neg	Neg

Other	Result
Parasite smear	Neg
Monospot	Neg

Serum PCR	Copies
Anaplasmosis	?
Lyme	?
Adenovirus	?
HSV	?
CMV	?
EBV	?

Bone marrow Bx	
CMV PCR	?
EBV PCR	?
Flow cyto	?



Well, then does  
Lyme cause HLH?  
**Nope!**

## Case 1: Hospital course

Serologies	IgM	IgG
<b>Lyme</b>	<b>Pos</b>	Neg
Ehrlichia	<1:20	<1:64
Anaplasma	<1:20	<1:64
RMSF	Neg	Neg

Other	Result
Parasite smear	Neg
Monospot	Neg

Serum PCR	Copies
Anaplasmosis	0
Lyme	0
Adenovirus	???
HSV	0
CMV	0
EBV	???

Bone marrow Bx	
CMV PCR	Neg
<b>EBV</b> PCR	<b>Pos</b>
Flow cyto	Normal

## Case 1: Hospital course

Serologies	IgM	IgG
<b>Lyme</b>	<b>Pos</b>	Neg
Ehrlichia	<1:20	<1:64
Anaplasma	<1:20	<1:64
RMSF	Neg	Neg

Other	Result
Parasite smear	Neg
Monospot	Neg

Serum PCR	Copies
Anaplasmosis	0
Lyme	0
<b>Adenovirus</b>	<b>23,648</b>
HSV	0
CMV	0
EBV	IgG+

Didn't send PCR :(



Bone marrow Bx	
CMV PCR	Neg
<b>EBV PCR</b>	<b>Pos</b>
Flow cyto	Normal

Discharged on **21 days of doxy** (while waiting on these tests)

# Learning points & take aways

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# Learning points & take aways

- **HLH** is a hyperinflammatory syndrome that can mimic severe infection or sepsis
  - Clues: persistent fever, cytopenias, splenomegaly, hepatitis/transaminitis, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and elevated soluble IL-2 receptor
  - Driven by **macrophages** / IFN- $\gamma$  / **Th1 response**
- Infectious triggers are common, almost always **intracellular pathogens** (**viral infections**, especially **EBV**; bacterial, fungal, and parasitic infections also possible)
  - Can be tick-borne (ehrlichiosis, anaplasmosis, babesiosis), but uncommon to be from lyme
  - That said, viral is still by far the most common
- Delays in diagnosis and treatment can be fatal → consider HLH (or at minimum **ordering a ferritin**)
- May or **may not need immunosuppression**, but for non-EBV often okay to just treat the infection +/- steroids

