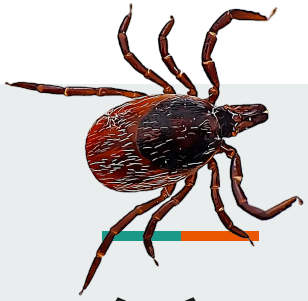
(s)TICK season

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

Takeaway slide

Key discussion slides

- **Main Topic** | subtopic | subtopic
- **Main Topic** | subtopic | subtopic
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Season of the Ticks

Case #1

Case 1: HPI

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

Geographic & Travel	• Lives 15 minutes NW of **Uniontown, PA** with female partner of many years • No travel outside of country or recent domestic travel
Occupational	• Works as EMT
Substance & needles	• **Former heavy EtOH** a few years ago, rare EtOH now that on GLP-1 • Never smoker, no drugs
Animals	• Indoor **cats** • Had **construction** in his home a few months ago and **his cats find mice** (but no exposure to rodent urine/feces)
Exposures	When not working, **loves to spend time outdoors**, including hiking, freshwater activities, and caves

Case 1: Social history, exposures, & risk factors

Geographic & Travel	Lives northwest of **Uniontown** with female partner. Never international, no recent travel
Occupational	Works as EMT
Substances	**Remote heavy EtOH**, rare EtOH now that on GLP-1. Never smoker, no drugs
Animals	Indoor cats. Recent **construction**. **Cats will find mice**, but no exposure to urine/feces
Exposures	• Hiking: Does not regularly use bug spray when hiking, but can not recall finding any embedded ticks (but has seen ticks that were not embedded) • Water: kayaking and canoeing - in freshwater • Caves: A month ago, went to commercialized cave, might have been bats there

Case 1: Physical exam

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

Case 1: Labs

CBC	Result
WBC	3.0
Hgb	17.0
Platelets	72
Neut %	80%
Lymph %	15%
Eos %	0%

Chem7	Result
Na	125
K	3.5
HCO3	17
BUN	20
Cr	1.7

LFTs	Result
AST	335
ALT	104
Alk Phos	55
Bili	1.1
Albumin	3.5

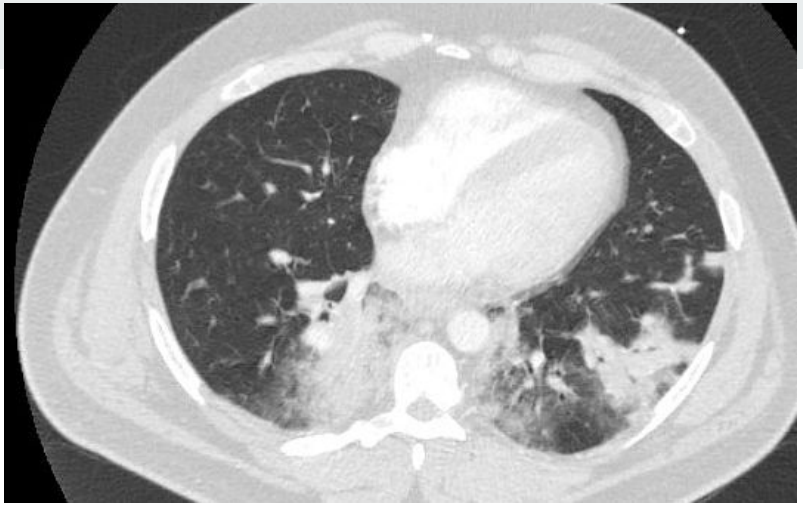
Other	Result
CRP	215
Procal	30.7

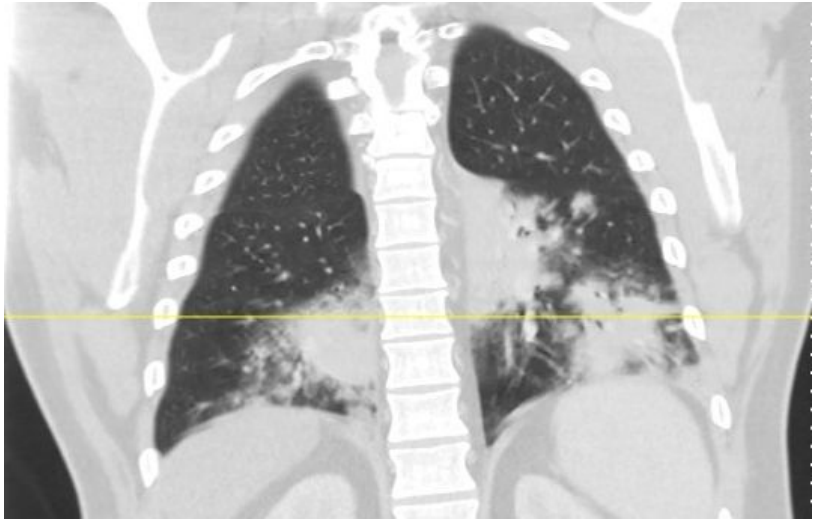
Other	Result
CK	16,100

Urine	Result
Heme	**Pos**
LeukEst	Neg
Protein	**>1000**
RBC	0-2
WBC	3-5

Case 1: Imaging

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

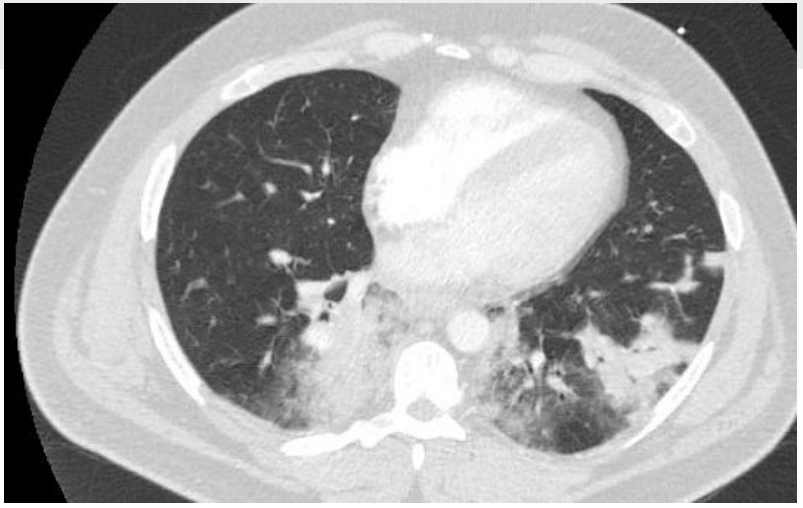


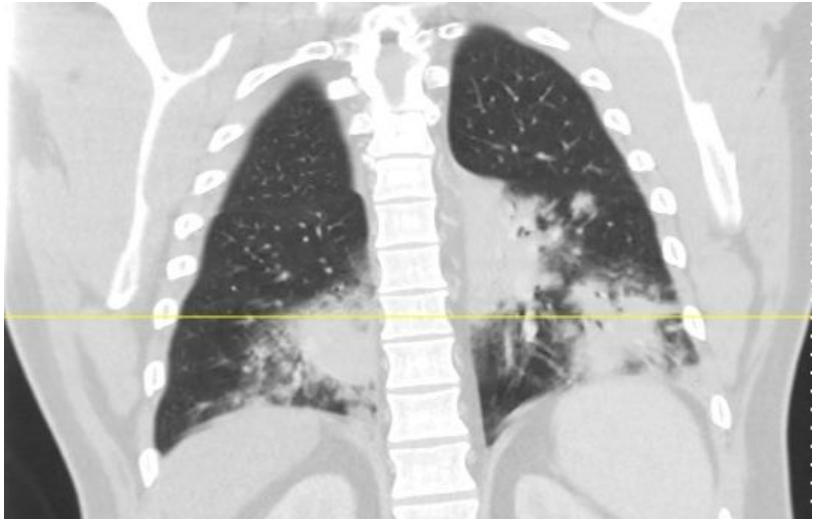


Case 1: Imaging

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

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



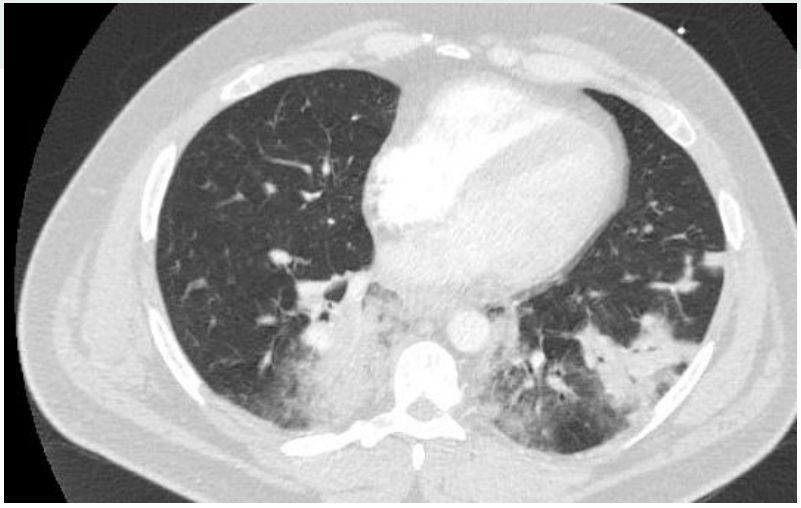


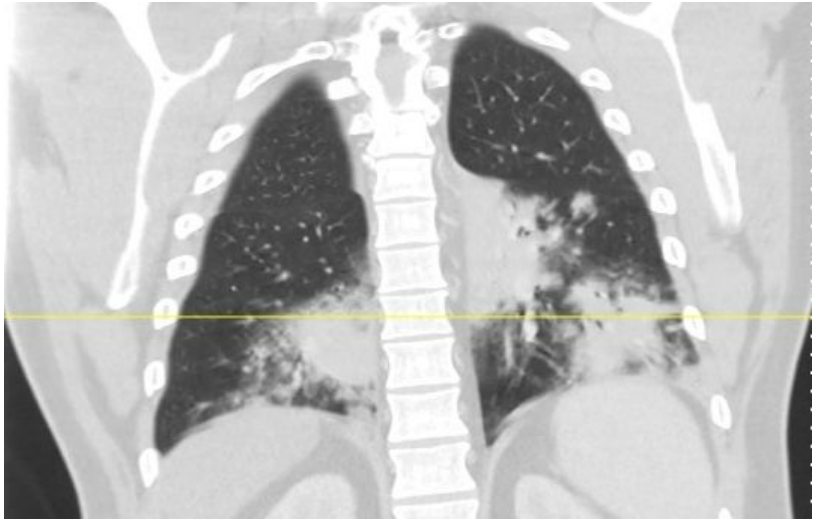
Case 1: Imaging

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

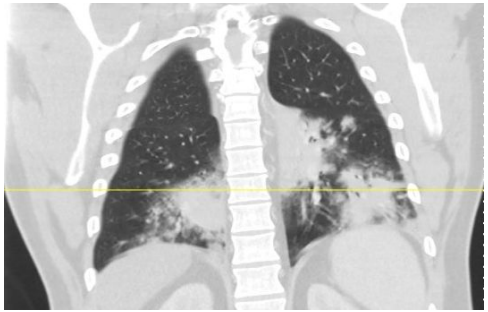
Work=EMT, but play is...

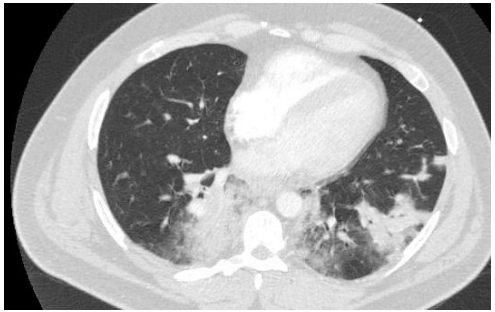
- **Hiking** (no bug spray), ?ticks
- **Freshwater** (kayaking)
- **Caves** (1 month ago), ?bats
- **Cats** (mice?)

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

Chem7	Result
Na	125
K	3.5
HCO3	17
BUN	20
Cr	1.7
CK	16k

LFTs	Result
AST	335
ALT	104
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	**Adenovirus**
C diff	Neg

Case 1: Outside ED course

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**

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- 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	**3.0**			
Hgb	17			
Platelets	**72**			
# Lymph	0.45			
CRP	215			
Procal	**30.7**			
CK	**16k**			

CMP	ED	#2	#3	#4
Na	**125**			
K	3.5			
HCO3	**17**			
BUN	20			
Cr	**1.7**			
AST	**335**			
ALT	**104**			
ALkP	55			
Bili	1.1			

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CBC/Inflm	ED	#2	#3	#4
WBC	**3.0**	4.1		
Hgb	17	15.4		
Platelets	**72**	75		
# Lymph	0.45	0.41		
CRP	215	---		
Procal	**30.7**	---		
CK	**16k**	18k		

CMP	ED	#2	#3	#4
Na	**125**			
K	3.5			
HCO3	**17**			
BUN	20			
Cr	**1.7**			
AST	**335**			
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CBC/Inflm	ED	#2	#3	#4
WBC	**3.0**	4.1	**2.5**	
Hgb	17	15.4	14.3	
Platelets	**72**	75	**46**	
# Lymph	0.45	0.41	0.73	
CRP	215	---	215	
Procal	**30.7**	---	---	
CK	**16k**	18k	**21k**	

CMP	ED	#2	#3	#4
Na	**125**			
K	3.5			
HCO3	**17**			
BUN	20			
Cr	**1.7**			
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CBC/Inflm	ED	#2	#3	#4
WBC	**3.0**	4.1	**2.5**	3.4
Hgb	17	15.4	14.3	12.5
Platelets	**72**	75	**46**	**42**
# Lymph	0.45	0.41	0.73	0.65
CRP	215	---	215	345
Procal	**30.7**	---	---	**59.9**
CK	**16k**	18k	**21k**	19k

CMP	ED	#2	#3	#4
Na	**125**			
K	3.5			
HCO3	**17**			
BUN	20			
Cr	**1.7**			
AST	**335**			
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ALkP	55			
Bili	1.1			

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

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CK	**16k**	18k	**21k**	19k

CMP	ED	#2	#3	#4
Na	**125**	132	135	
K	3.5	3.4	4.4	
HCO3	**17**	14	16	
BUN	20	18	23	
Cr	**1.7**	1.4	1.27	
AST	**335**	**334**	**481**	
ALT	**104**	105	**135**	
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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CK	**16k**	18k	**21k**	19k

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

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

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

	Result
Ferritin	**7,088**
Triglycerides	173
LDH	**1,501**

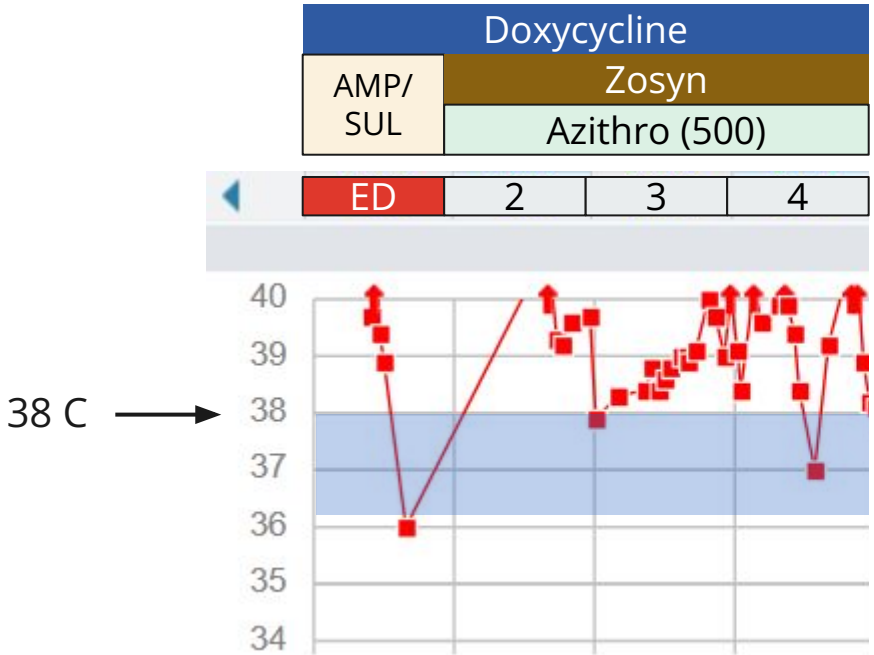
CMP	ED	#2	#3	#4
Na	125	132	135	133
K	3.5	3.4	4.4	3.4
HCO3	17	14	16	17
BUN	20	18	23	25
Cr	1.7	1.4	1.27	0.98
AST	335	334	481	538
ALT	104	105	135	125
ALkP	55	49	41	37
Bili	1.1	0.7	1.1	1.2

Case 1: Outside hospital course

Continues to fever despite:

- Unasyn → Zosyn
- Doxycycline
- Azithro

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



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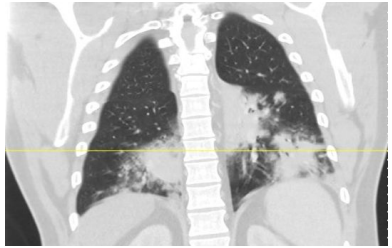
Continues to fever, worsening O2

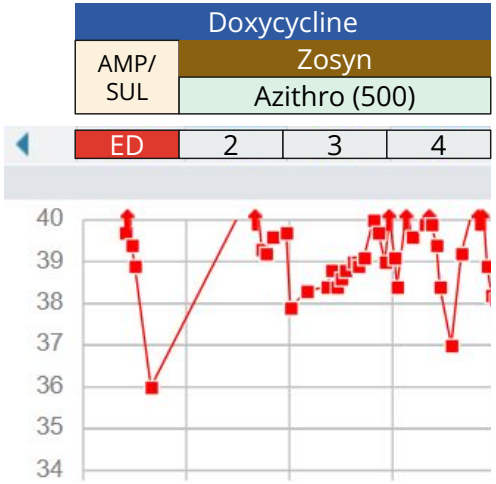
CMP	
Na	**125** ± 132
K	3's
HCO3	**17** ± 2
BUN	20s
Cr	**1.7** → **1.0**
AST	**335** → **538**
ALT	**104** → **125**
ALkP	40-50s
Bili	1.0 ± 0.2

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

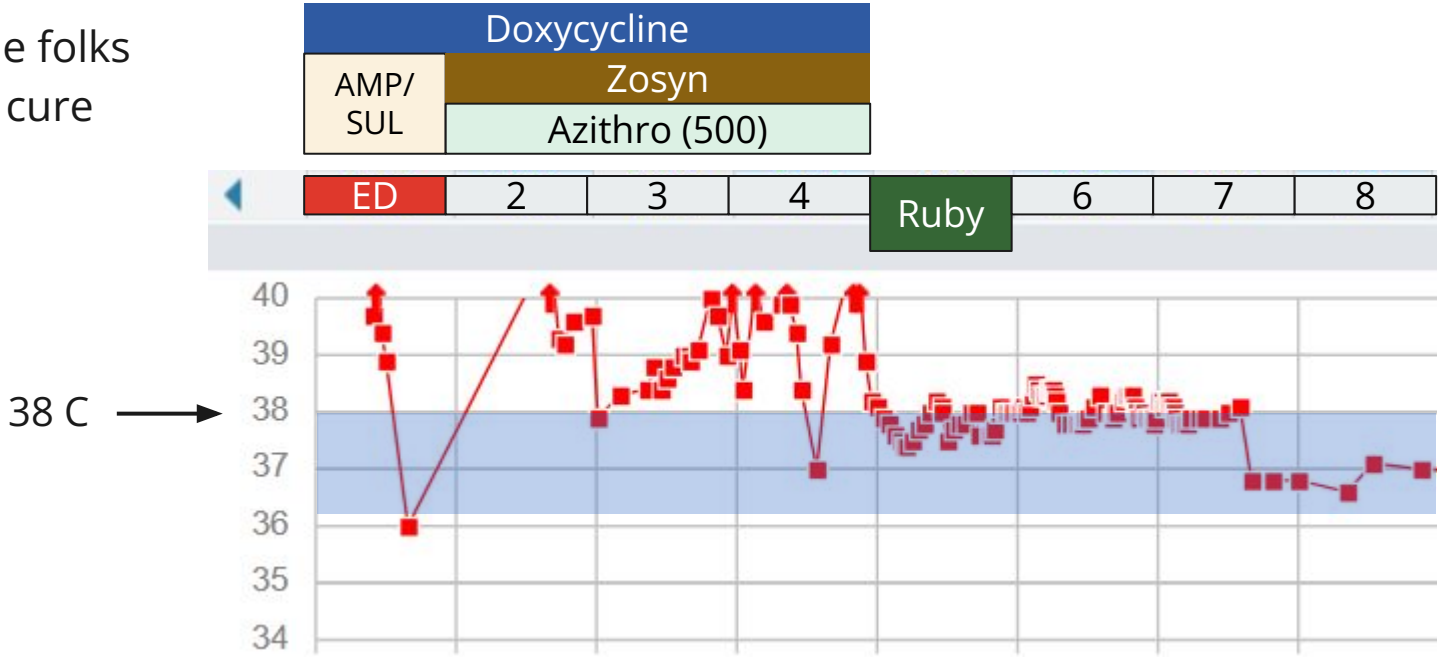
Ferritin	**7,088**
LDH	**1,501**





Case 1: Outside hospital course → Ruby MICU

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



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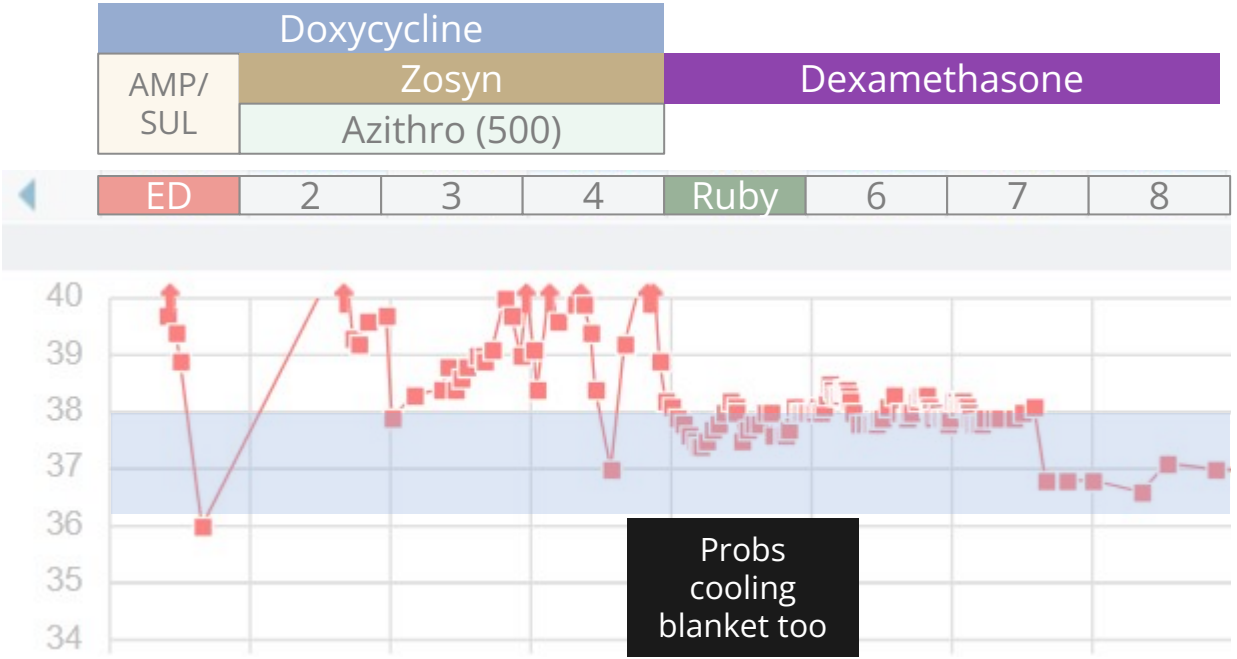
Guess what the folks at Ruby did to cure the fever?

Antipyretics!!

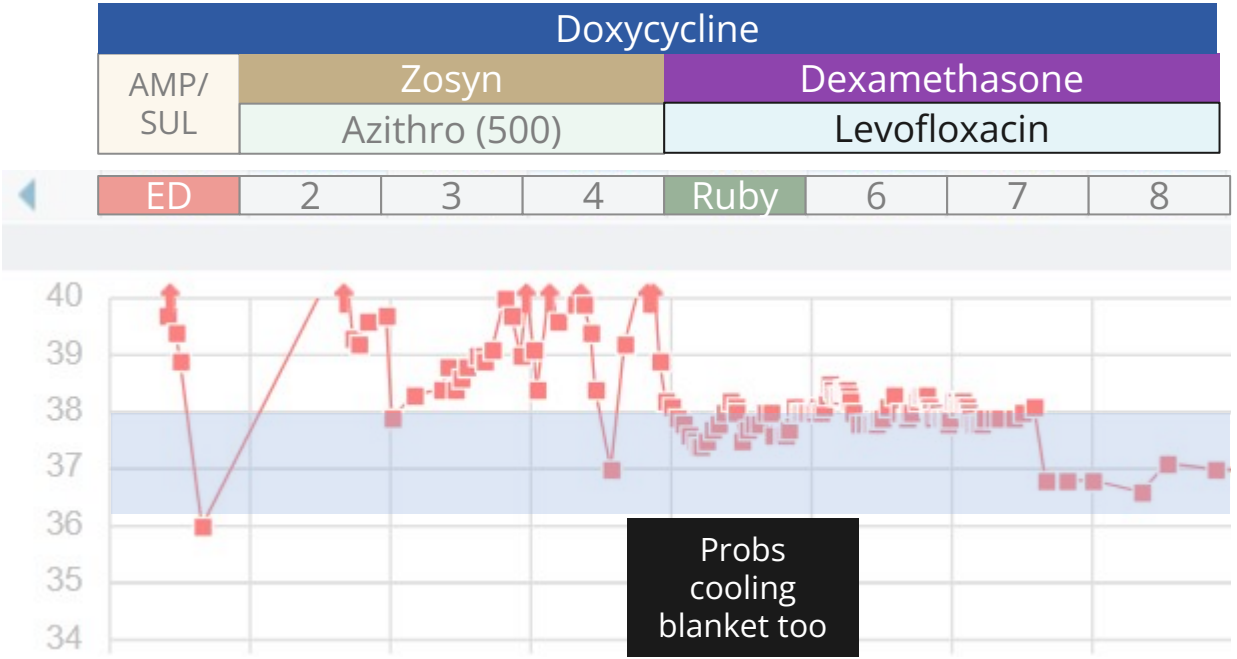


Case 1: Outside hospital course → Ruby MICU

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

Antipyretics!!

(and levaquin)



Case 1: Ruby MICU

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

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- 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	???	

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- 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	
Temperature, °F	**>102.9**	+49
Hepato/spleno-megaly	Neither	
Number of cytopenias	2 lines	+24
Ferritin	**>6,000**	+50
Triglycerides	132 - 354	+44
Fibrinogen	>250	
AST	**≥30**	+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

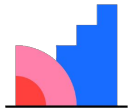
- H-score is high
  - **70-80%** chance of HLH
- They order some sendout labs

MICU **starts on steroids**

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

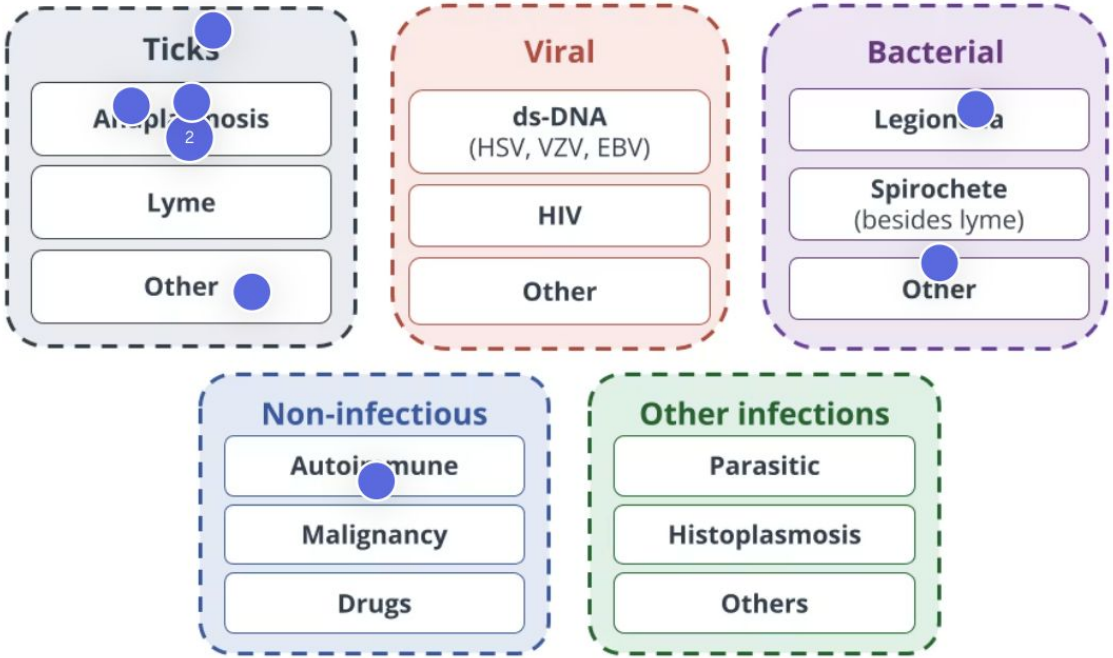
HScore for HLH		+186
Known underlying immunosuppression	No	
Temperature, °F	**>102.9**	+49
Hepato/spleno-megaly	Neither	
Number of cytopenias	2 lines	+24
Ferritin	**>6,000**	+50
Triglycerides	132 - 354	+44
Fibrinogen	>250	
AST	**≥30**	+19
Bone marrow Bx	TBD	

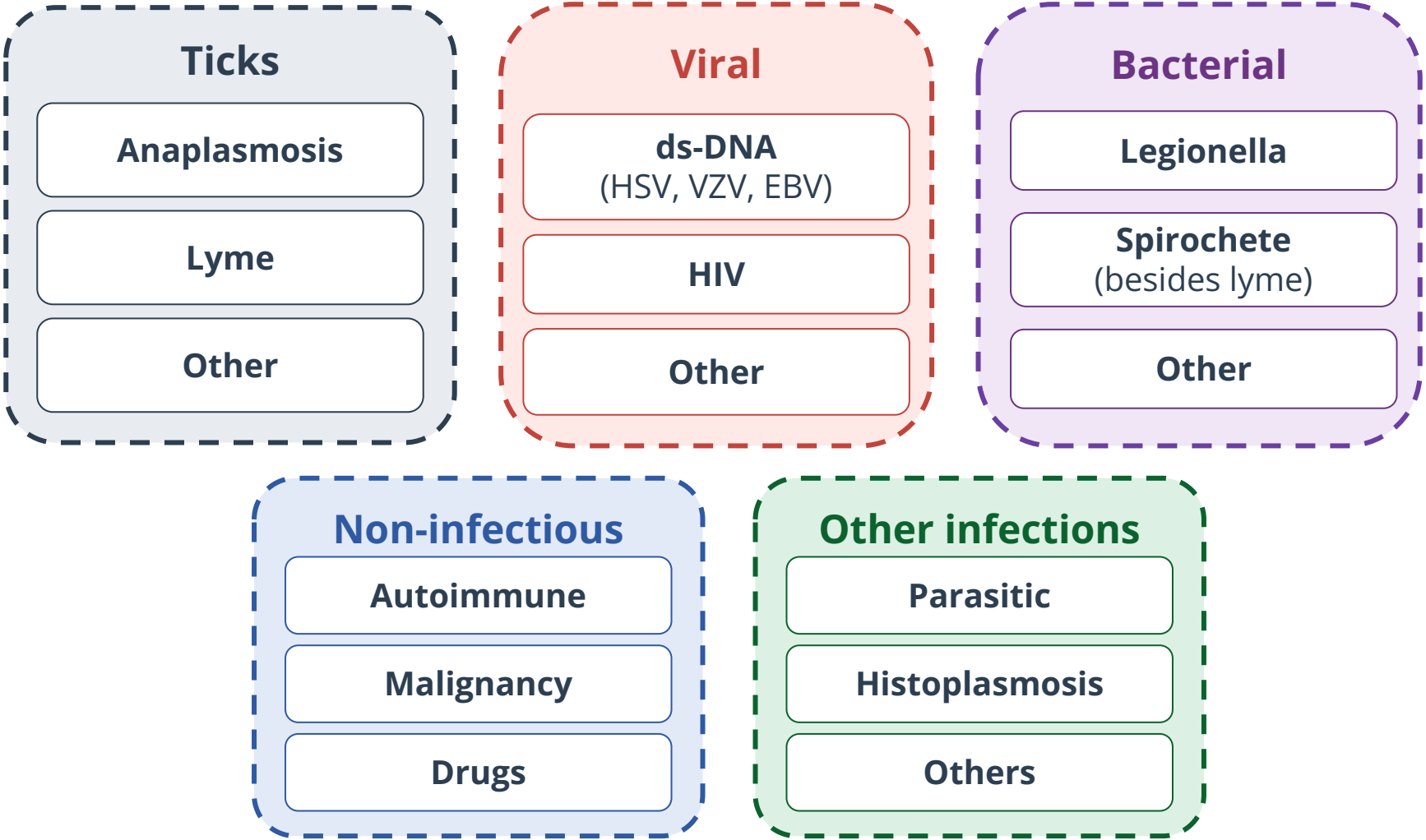
What's going on?



Mentimeter

Drop a pin where...




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

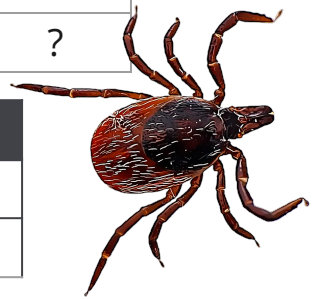
CBC/inflammatory	
WBC	**3.0** ± 1
Hgb	17 → **12**
PLT	**72** → **42**
CRP	215 → 345
PCT	**30.7** → **59.9**
CK	**21k** (peak)

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

Case 1: Further workup

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

Other	
Parasite smear	
Monospot	



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

Other	Result
Parasite smear	Neg
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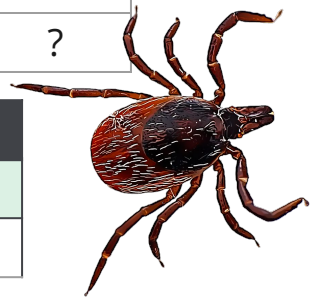

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Do ticks cause HLH?

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,[1] Benita Wu,[2] Andre Lamyaithong,[2] Victor Arcega,[1] and Daphne-Dominique Villanueva[1]

[1]Department of Medicine Section of Infectious Diseases, West Virginia University, Morgantown, West Virginia, USA, and [2]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

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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
Platelets	72	16
Creat	1.7	3.96
AST	335	330
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Comparing with the case report [1]

ID TEACHING CASES

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AST	335	330
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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]

ID TEACHING CASES

Admit labs	Our patient	Case report
WBC	3.0	3.3
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Triglycerides	173	448	**<150**	↑
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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
Platelets	72	16
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AST	335	330
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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	---	448	**<150**	↑
Fibrinogen	297	256	**200** - 400	↓
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]

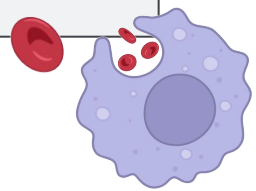
Med student explanation

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

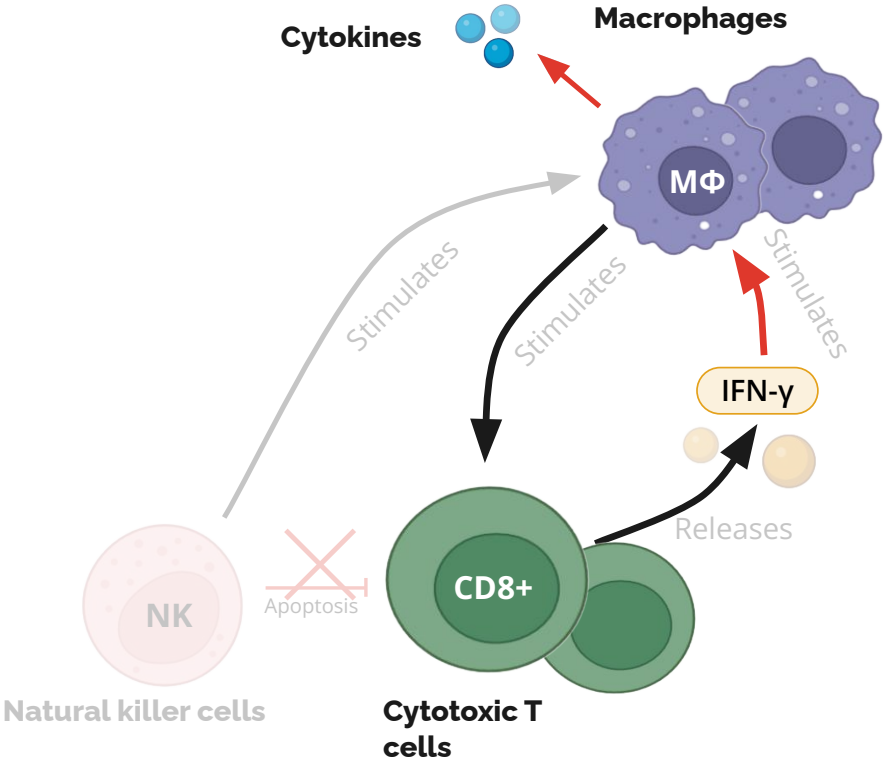
What is HLH? [2]

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



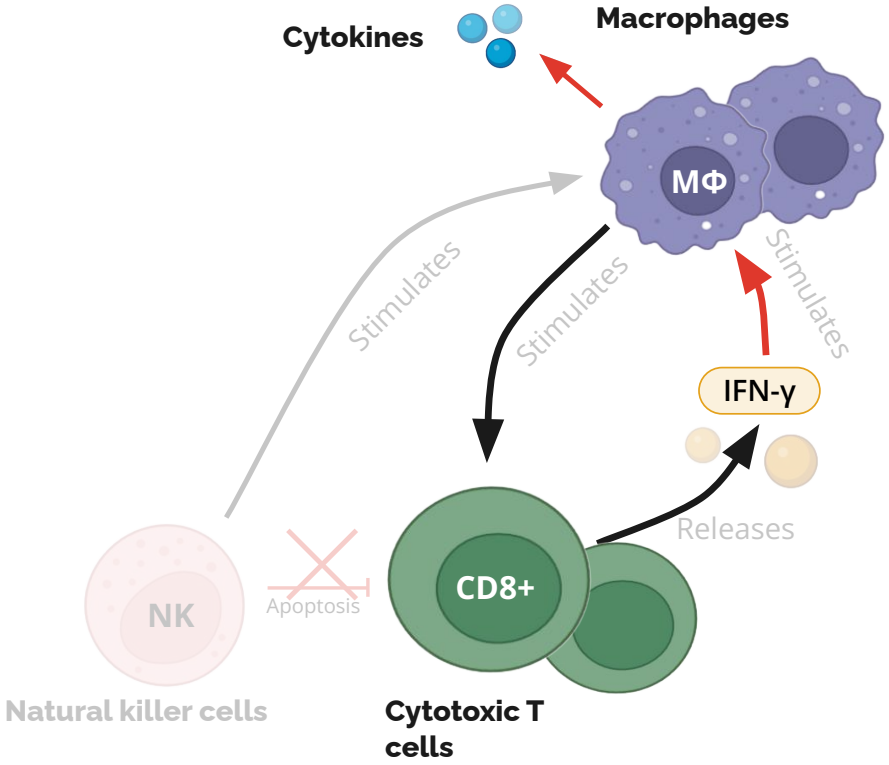
What is HLH? [2]



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 ≥5)

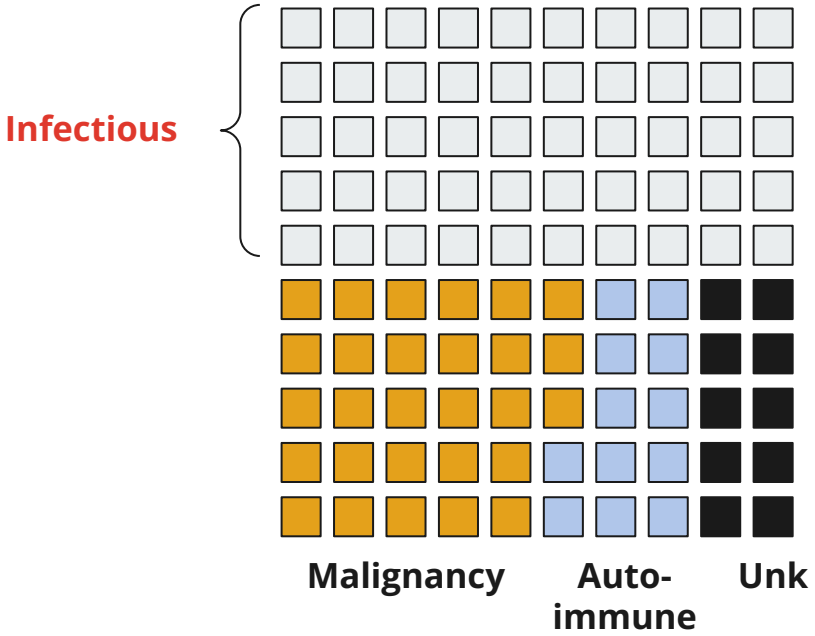
1. Fever
2. Splenomegaly
3. Cytopenias (≥2 lineages)
4. Either (or both)
   a. ↑ triglycerides
   b. ↓ fibrinogen
5. Hemophagocytosis (BMBx, spleen, LN)
6. ↓ NK cell activity
7. ↑ Ferritin (≥500)
8. ↑ Soluble IL-2 receptor

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

What triggers HLH? [7]

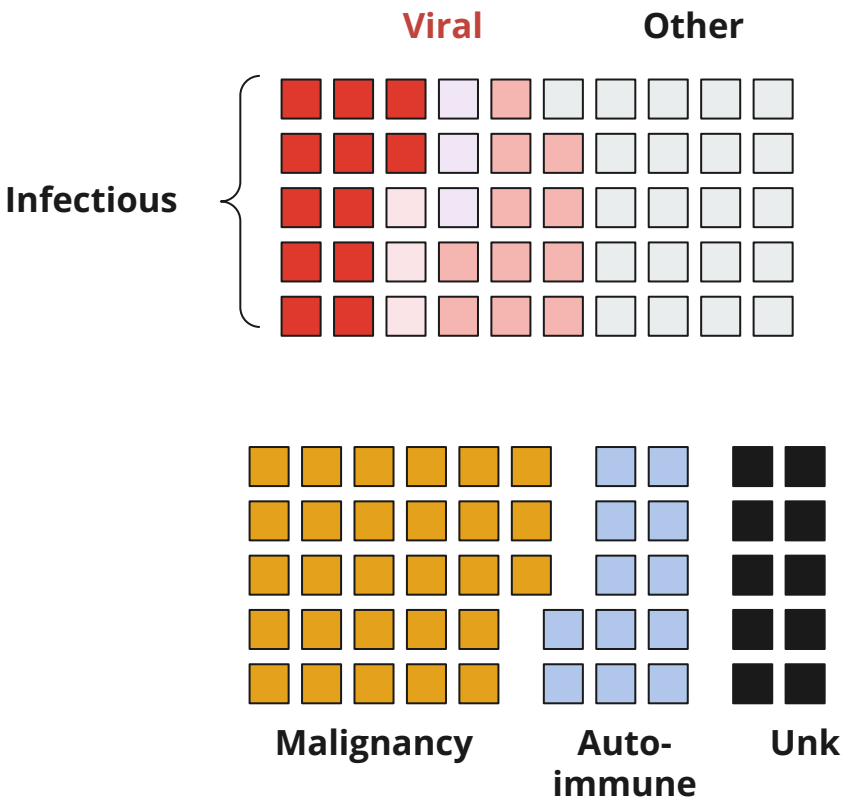
In pooled systematic review of critically ill patients:

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



What triggers HLH? [7]

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



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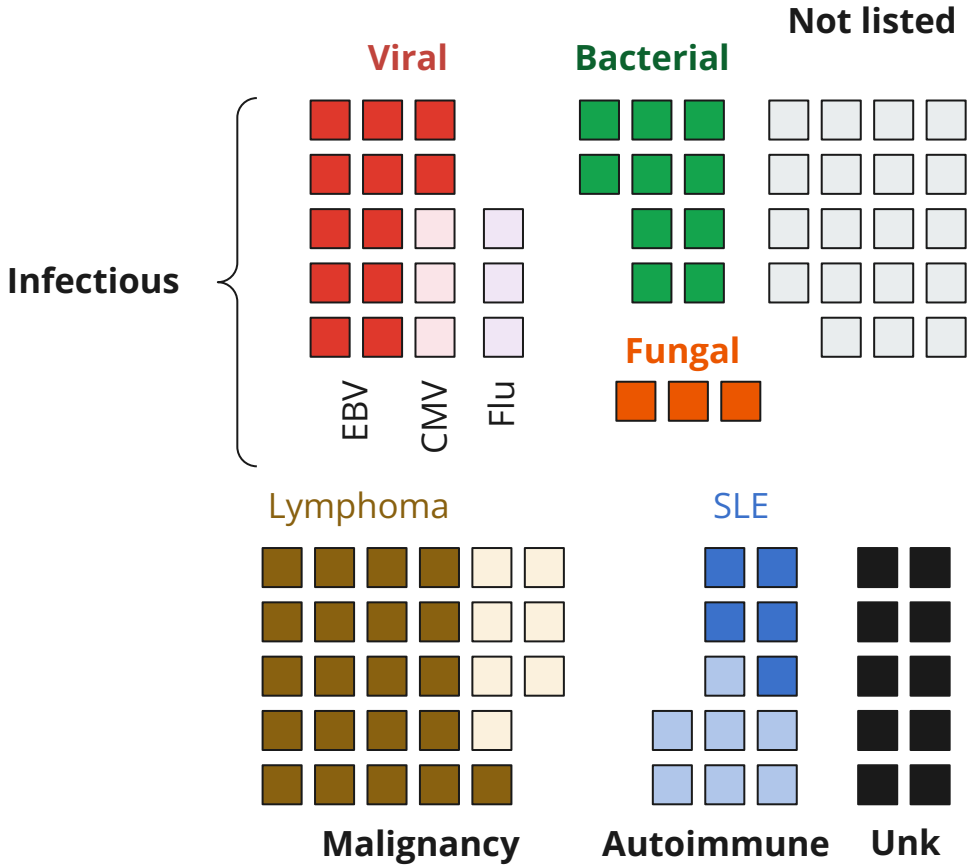
- **Bacterial** (10.1%)
  - **Lymphoma** is twice as common (21%)
- **Fungal** (2.9%)
  - On par with Adult-onset Still (2.6%)



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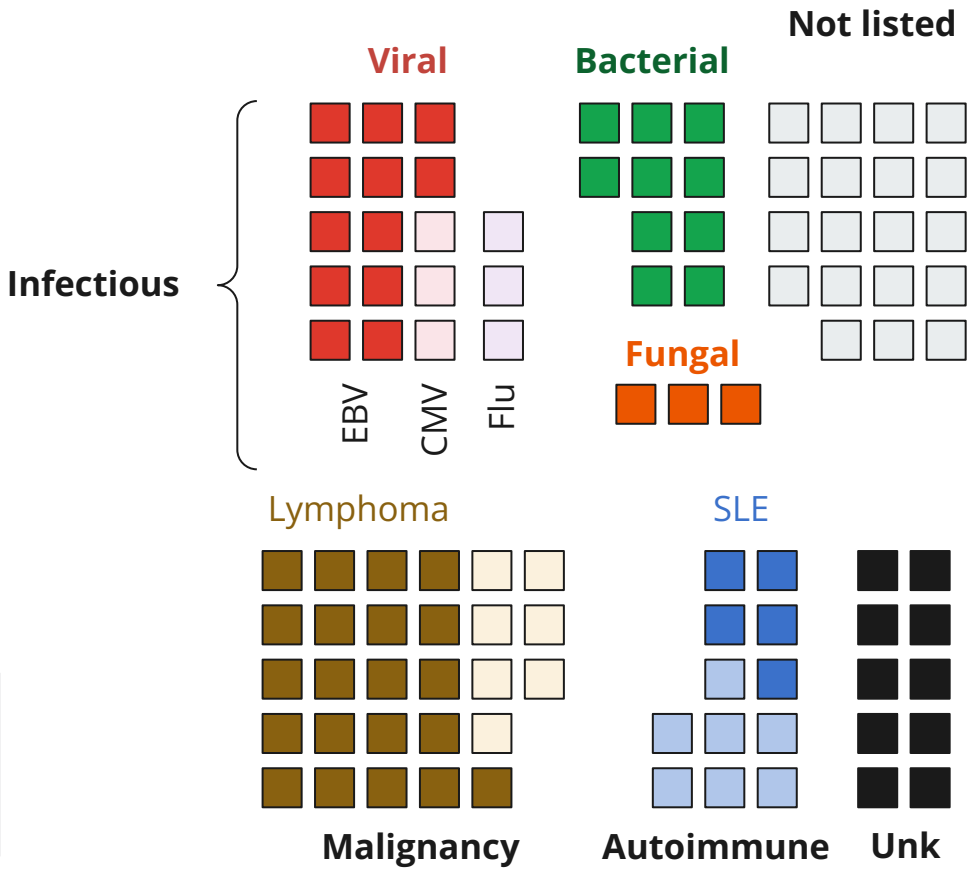
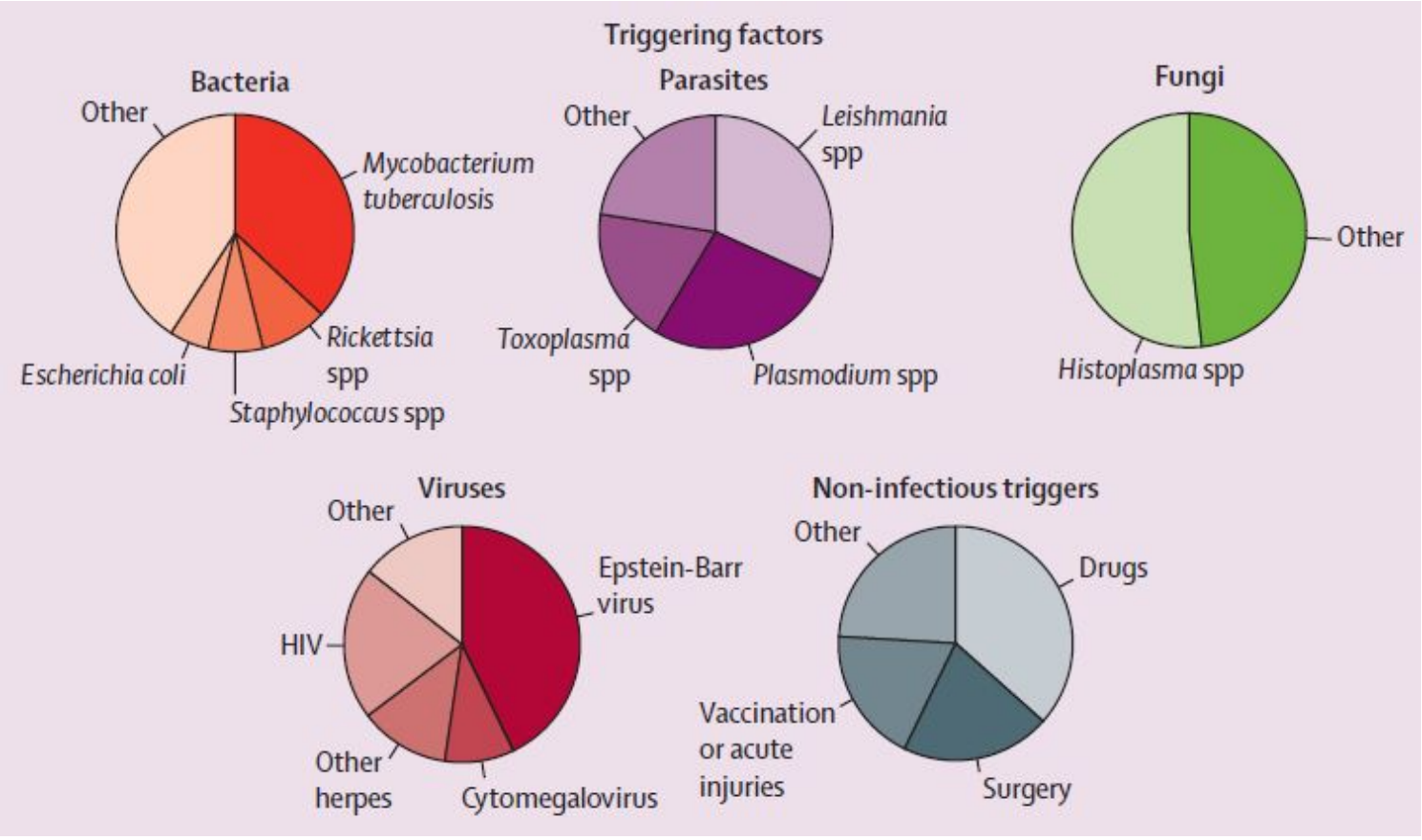
Limitation
They did not give a full breakdown of the infections

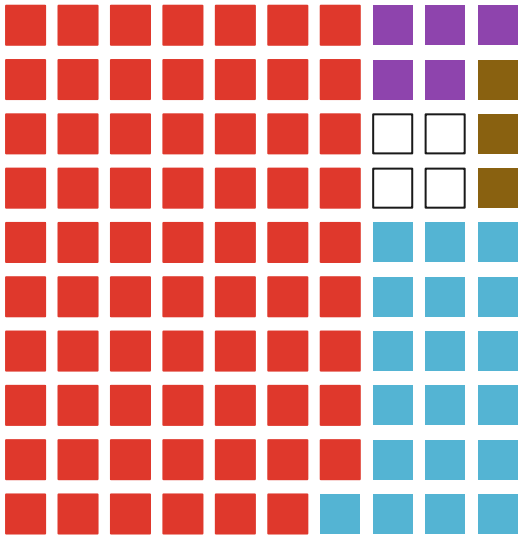


Which infections trigger HLH? [8]



Which infections trigger HLH? [8]

Infectious HLH triggers



Viral (69%)

Parasites (4.8%)

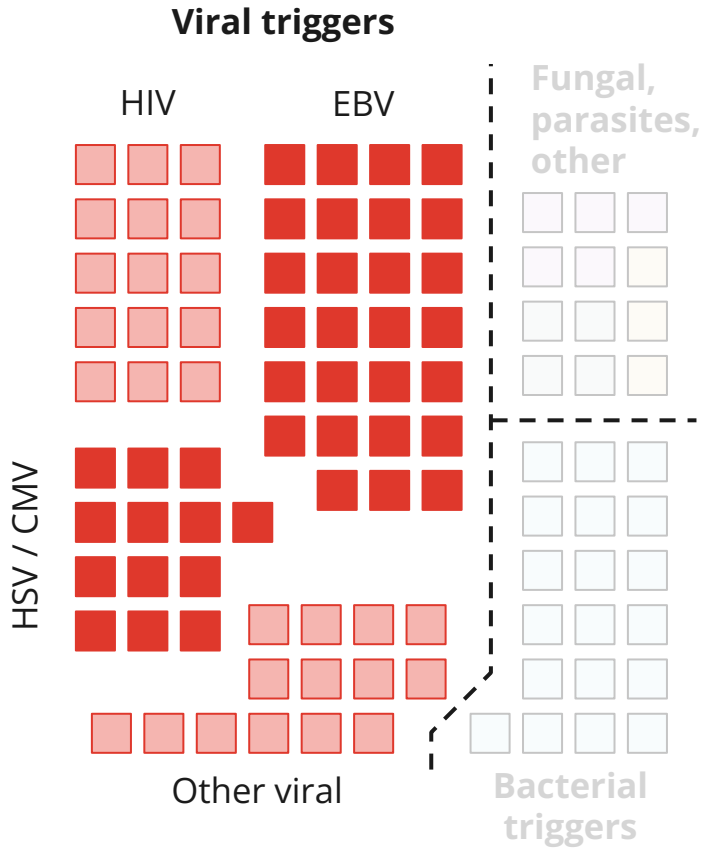
Fungal (3.3%)

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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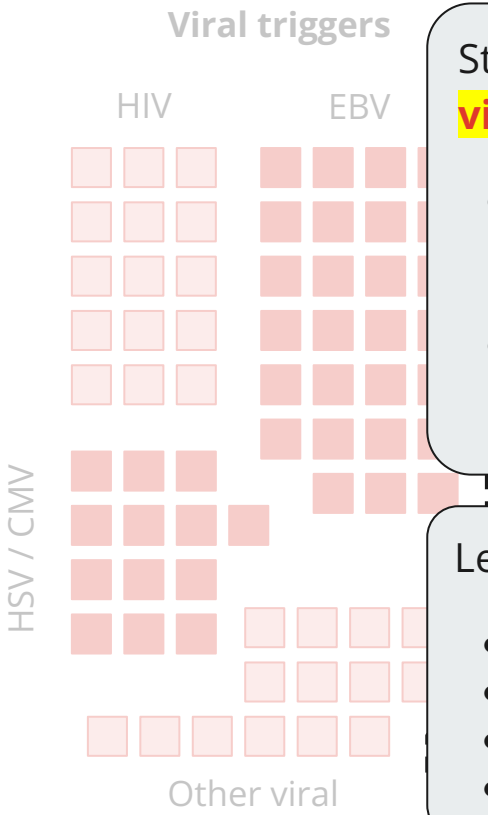

Strongest association with **DNA viruses** [3]:

- **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%)
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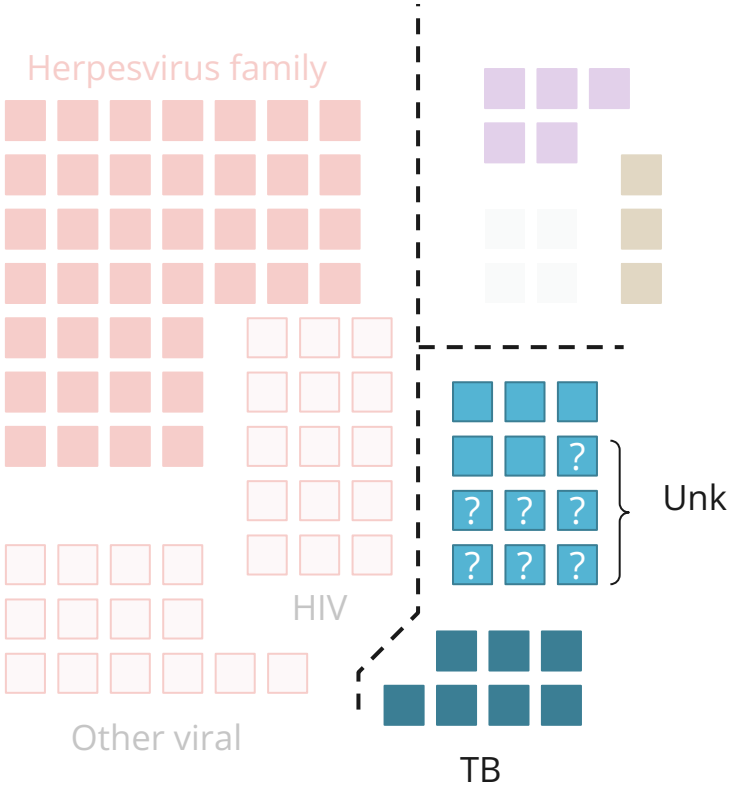

Bacterial (18.6%)

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]

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1. **EBV** (30%)
2. **HIV** (15%)
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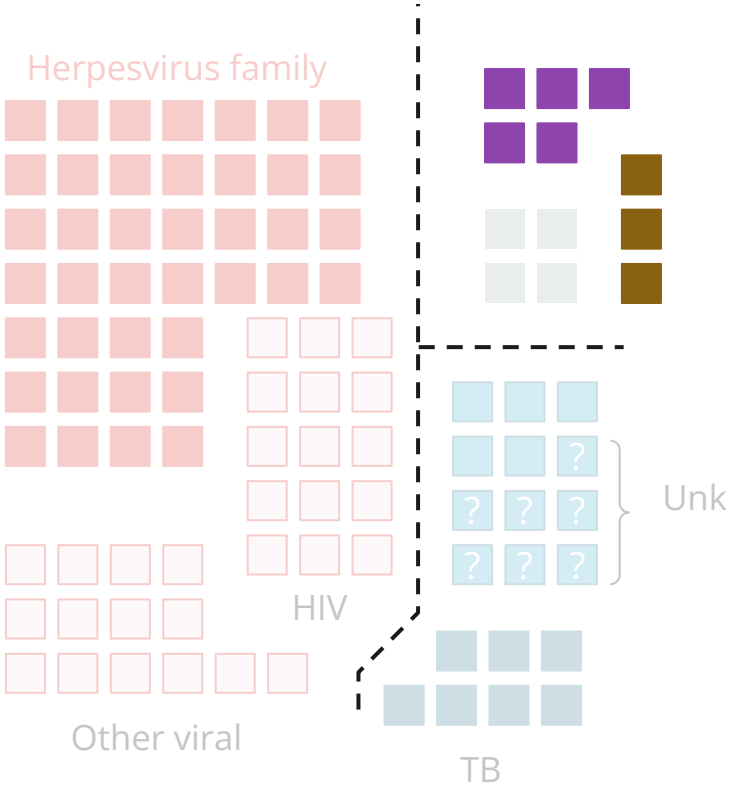

Parasites (4.8%)

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

Fungi (3.3%)

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

Bacterial (18.6%)

1. **TB** (7.0%)
2. Other / not specified (7.7%)
3. **Rickettsia** (1.5%)

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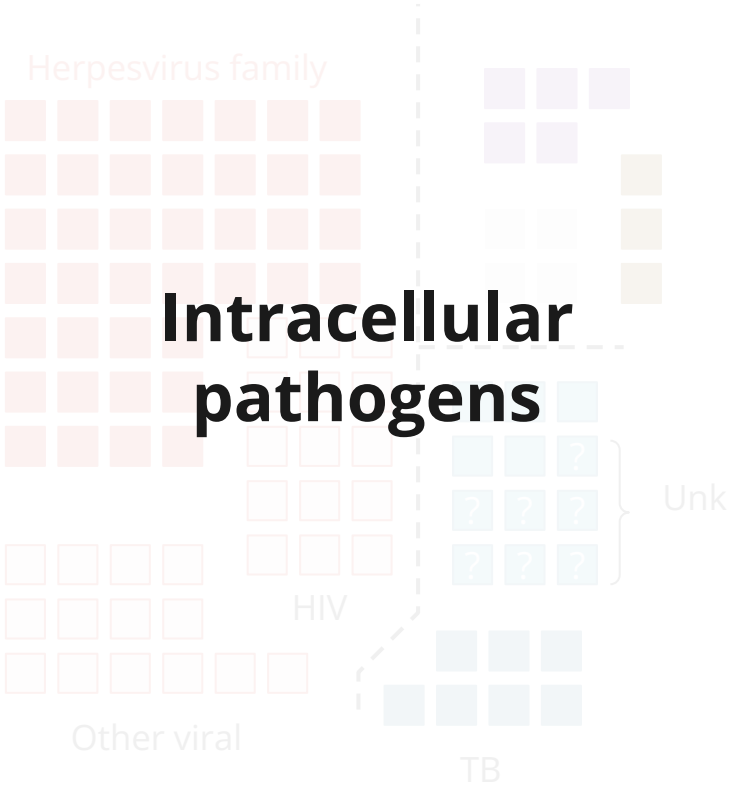

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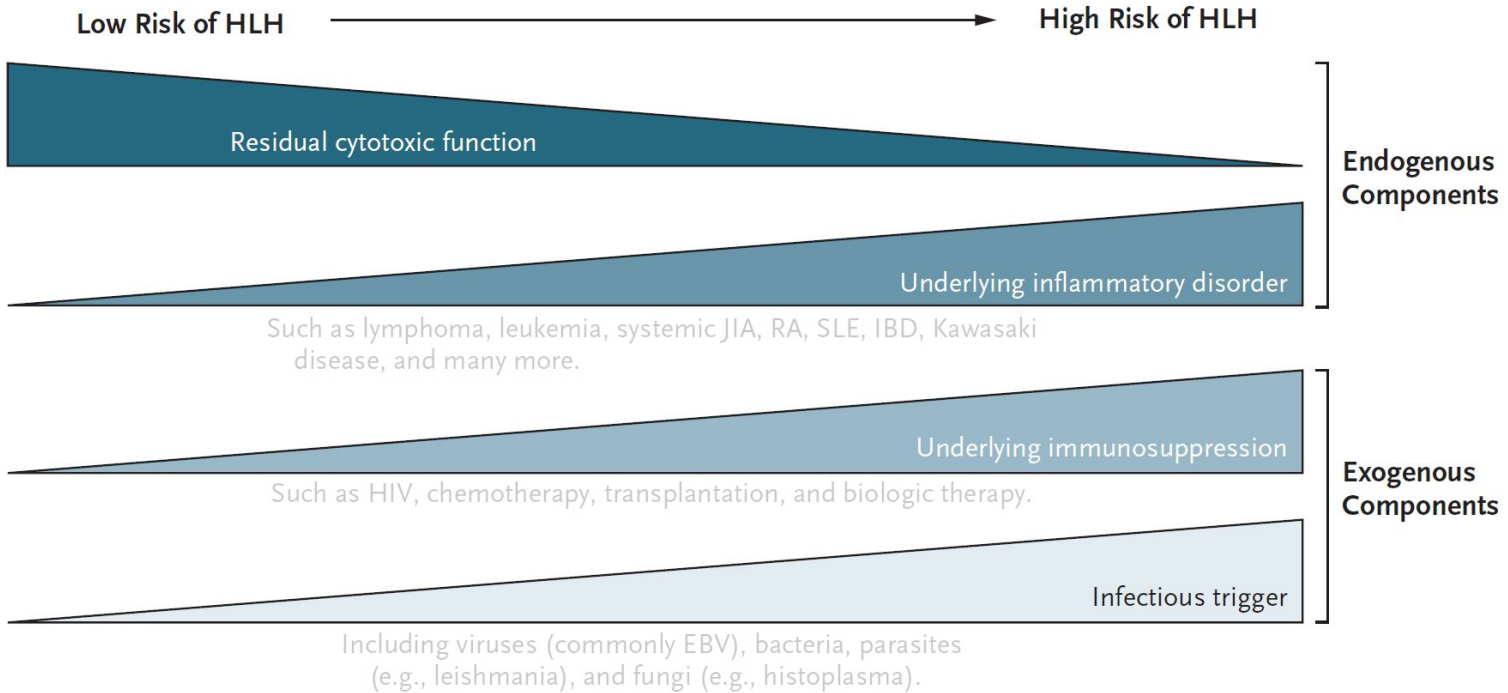


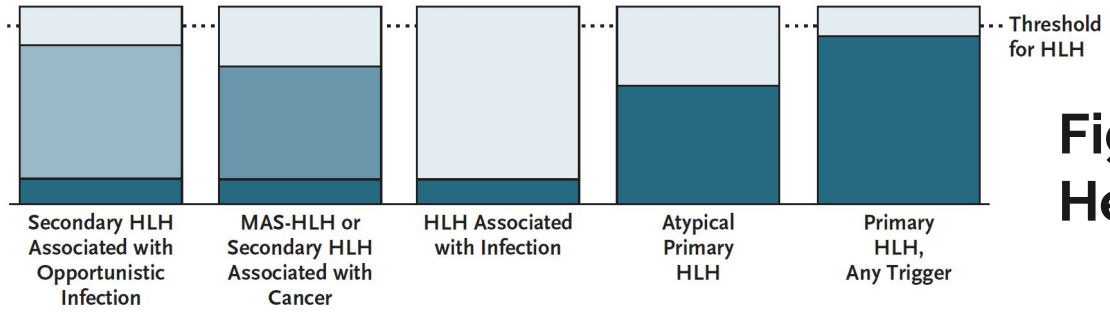
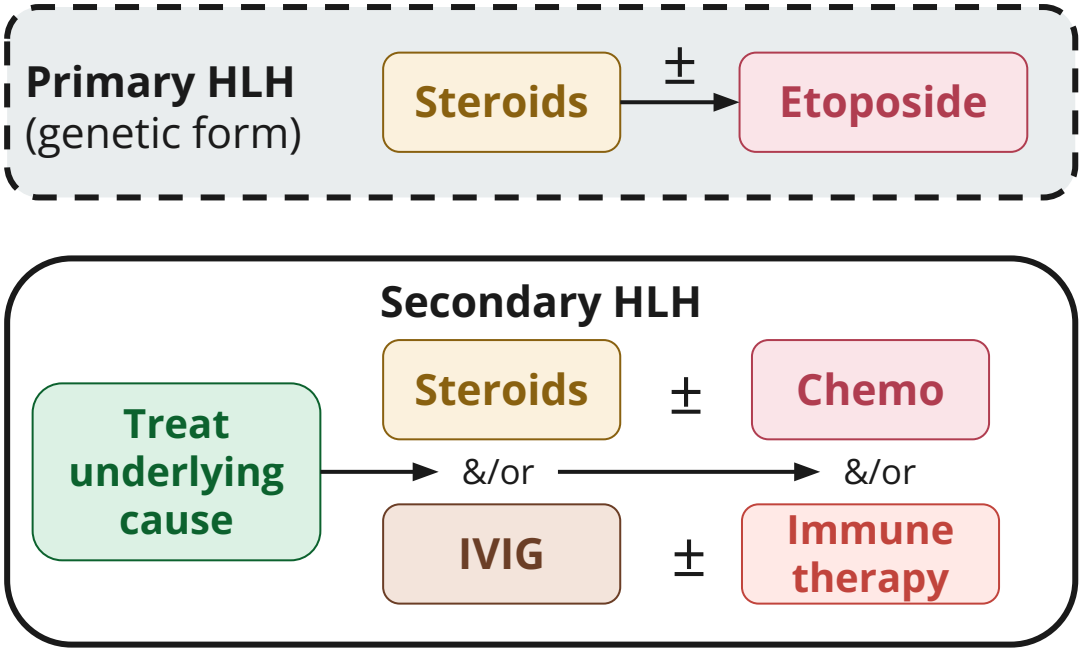


Figure 3: [2] Henter, 2025

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...

Case 1: Summary

A healthy **33 y/o M** p/w **five days** of cough + myalgias → **high fever (103.5)** + diarrhea. CT: pneumonia in **bilateral lower lobes** & **terminal ileitis**. Dx with **HLH** → **improving with steroids**

Work=EMT, but play is...

- **Hiking** (no bug spray), ticks
  - **Lyme IgM** (+), lives in PA
- **Freshwater** (kayaking)
- **Caves** (1 month ago), ?bats
- **Cats** (mice?)

CMP	
BUN	20s
Cr	1.7 → 1.0
AST	**335** → **538**
ALT	104 → **125**
ALkP	40-50s
Bili	1.0 ± 0.2

CBC/inflammatory	
WBC	**3.0** ± 1
Hgb	17 → **12**
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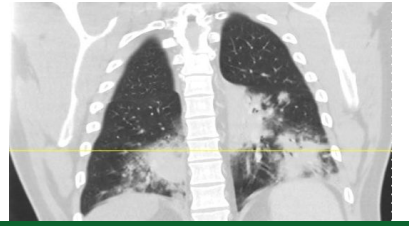
CRP	215 → 345
PCT	30.7 → 59.9

Ferritin	**7,088**
LDH	**1,501**



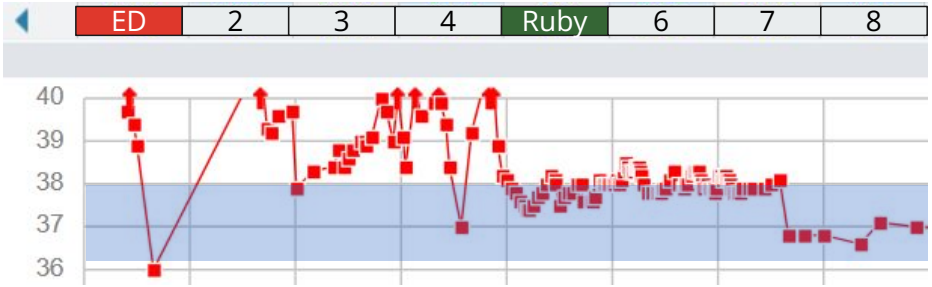
Doxycycline

AMP/SUL

Zosyn

Azithro (500)

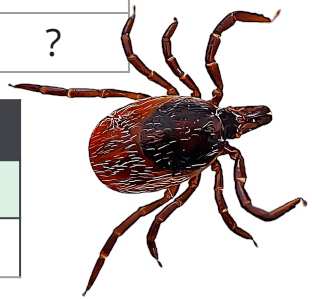
Dexamethasone



Case 1: Further workup

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

Other	Result
Parasite smear	Neg
Monospot	Neg



BMBx	
CMV PCR	?
EBV PCR	?
Flow cyto	?

Serum PCRs
Pending

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Na	**125** ± 132
K	3's
HCO3	**17** ± 2
BUN	20s
Cr	**1.7** → **1.0**
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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

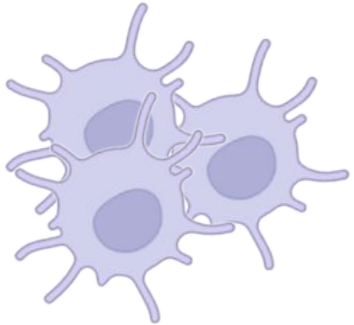
Pathophysiology of “HLH”

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

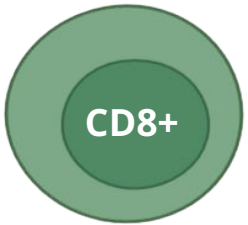
- HLH
- Macrophage activation syndrome
- Cytokine release syndrome

Normal Th1 response [2]

Antigen presenting cells



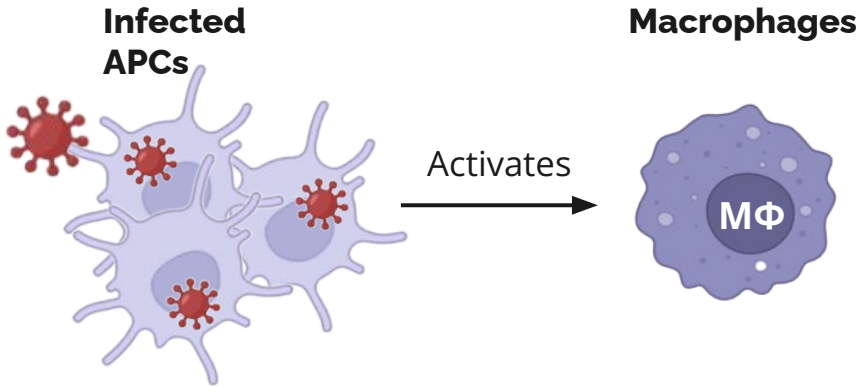
Macrophages

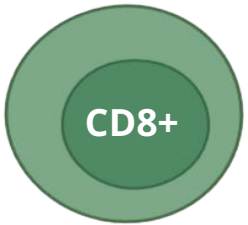


Cytotoxic T cells

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]

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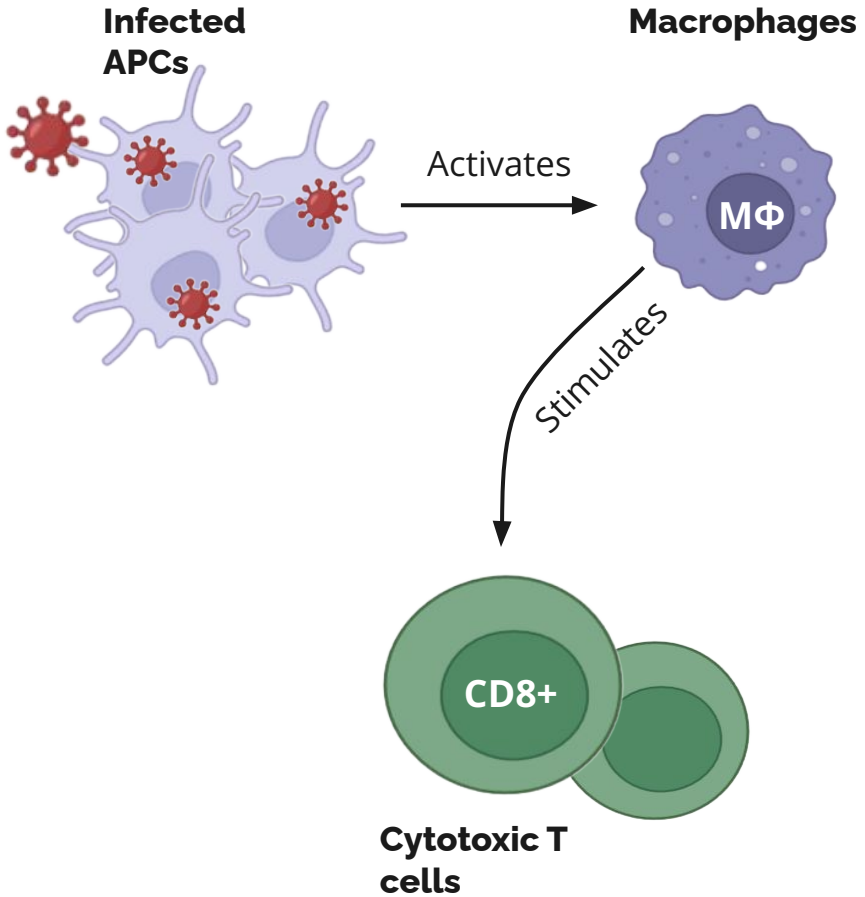
2. **Antigen-specific CD8+ T cells** are recruited and…



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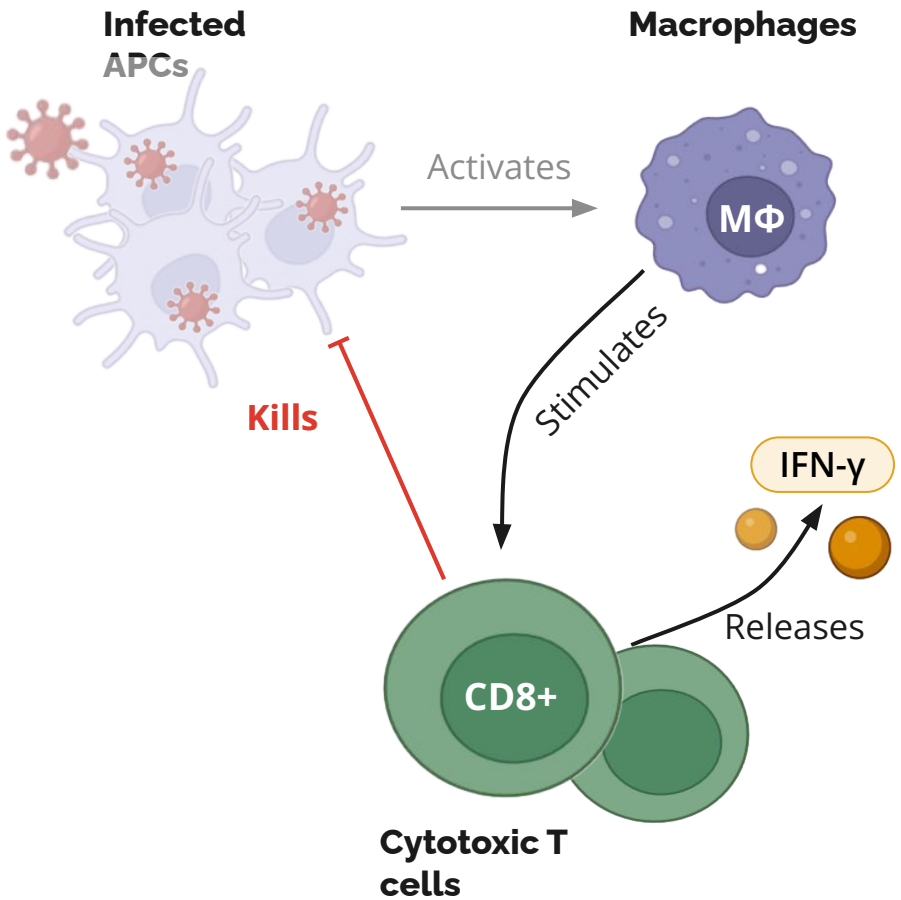
   a. **Kill infected cells** directly
   b. Secrete **interferon gamma**



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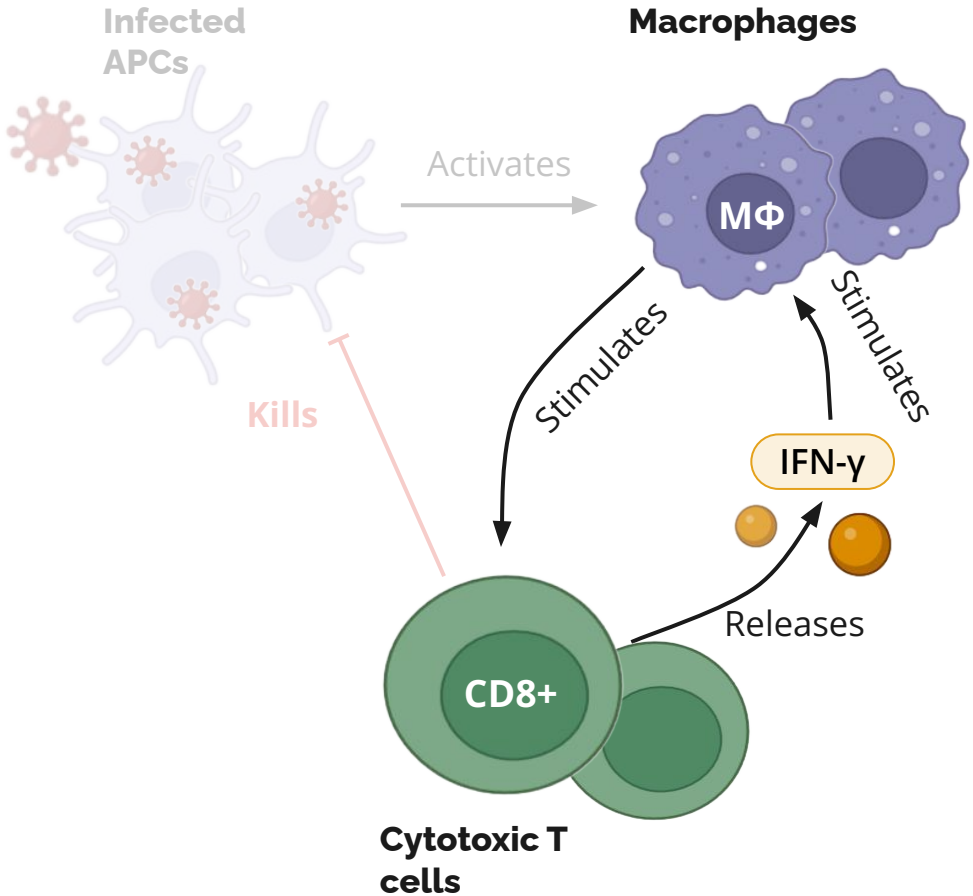
3. **IFN-γ** in turn will…
   a. Potent **activator of macrophages**



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   a. **Kill infected cells** directly
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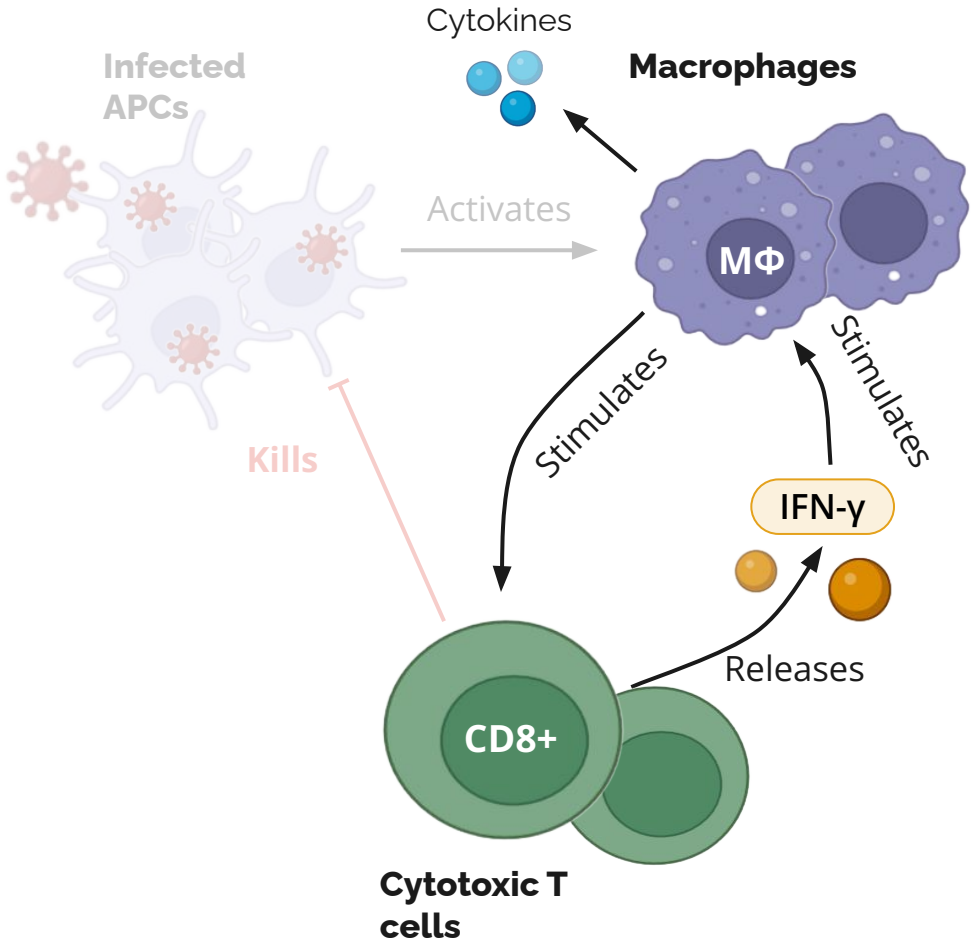
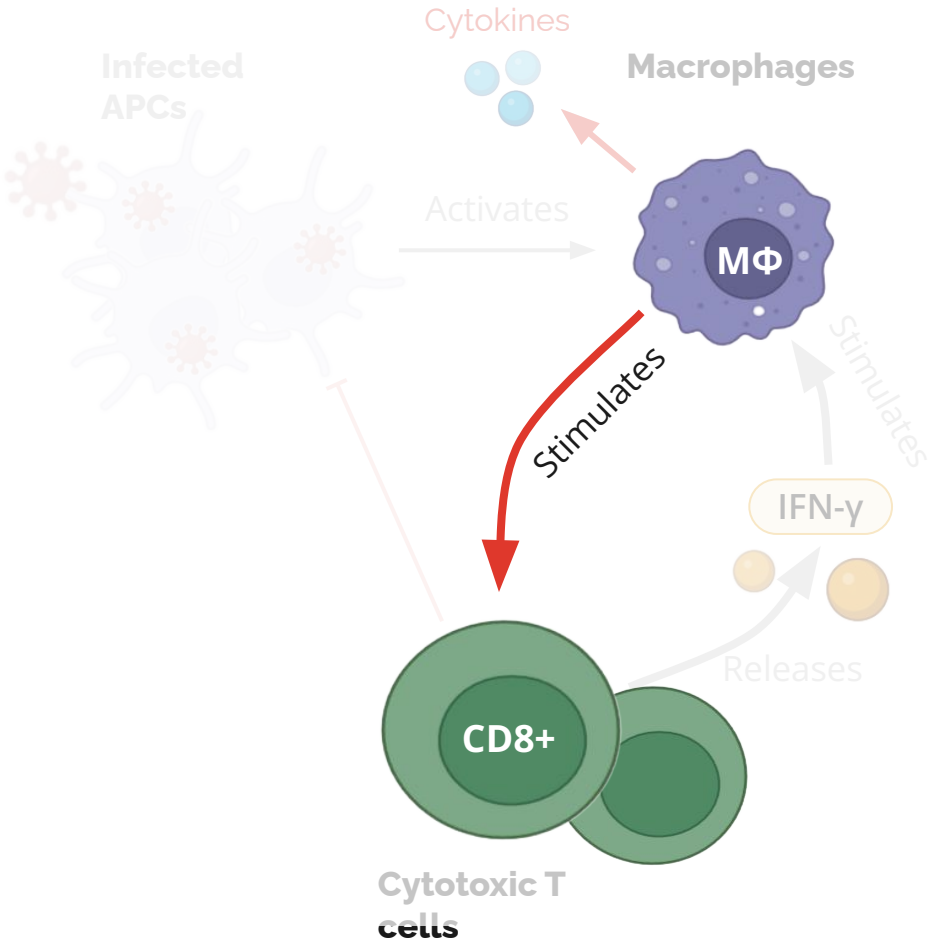
3. **IFN-γ** in turn will…
   a. Potent **activator of macrophages**
   b. Induces MΦ to **produce more cytokines**



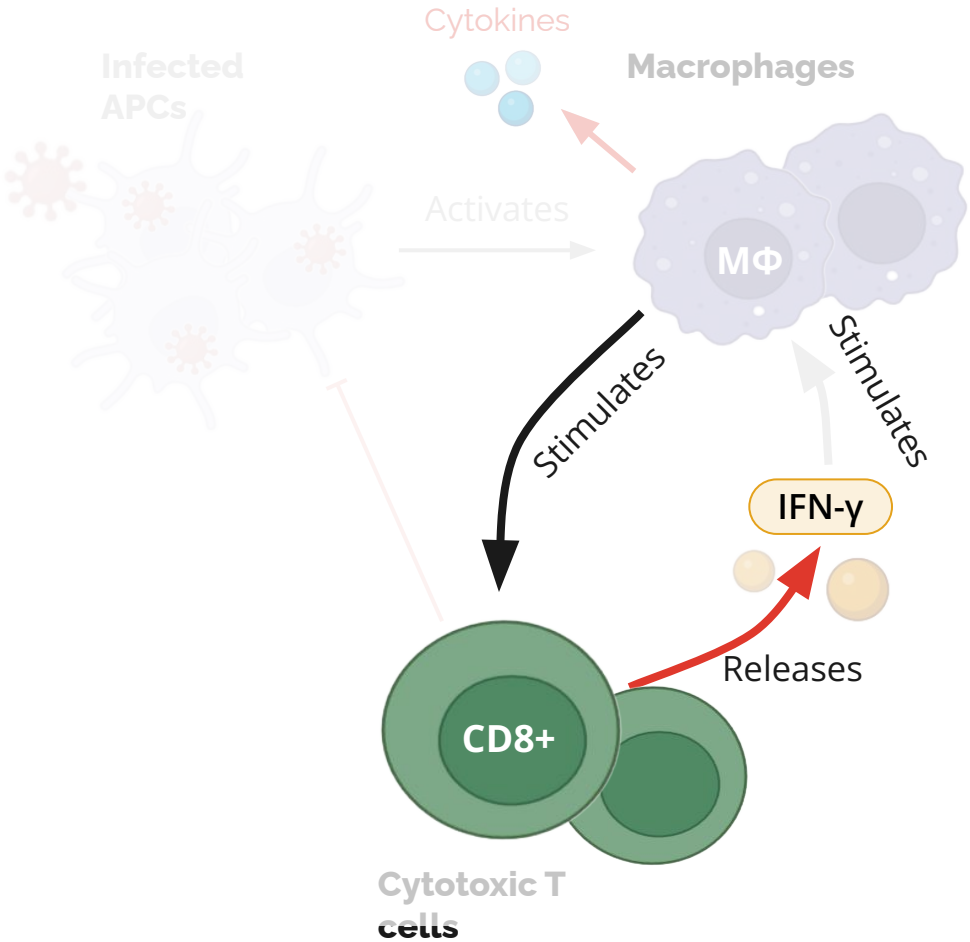
Positive feedback loop

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



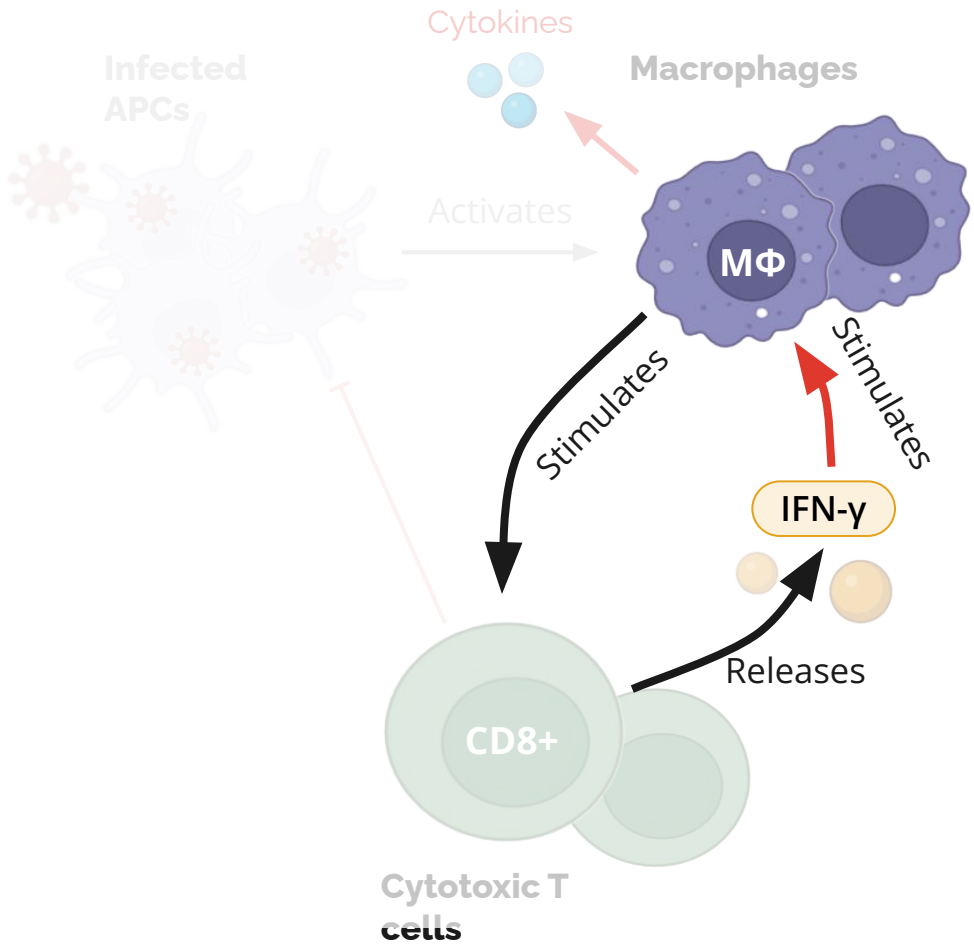
Positive feedback loop

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



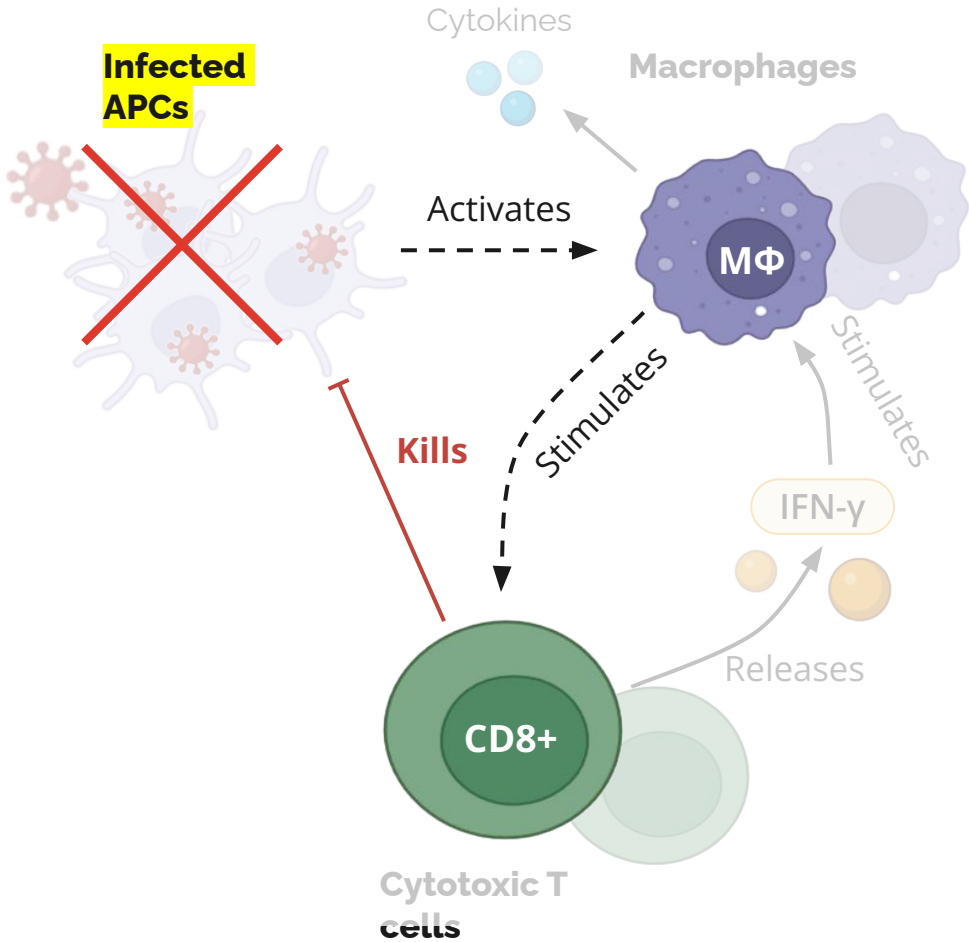
Positive feedback loop

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**
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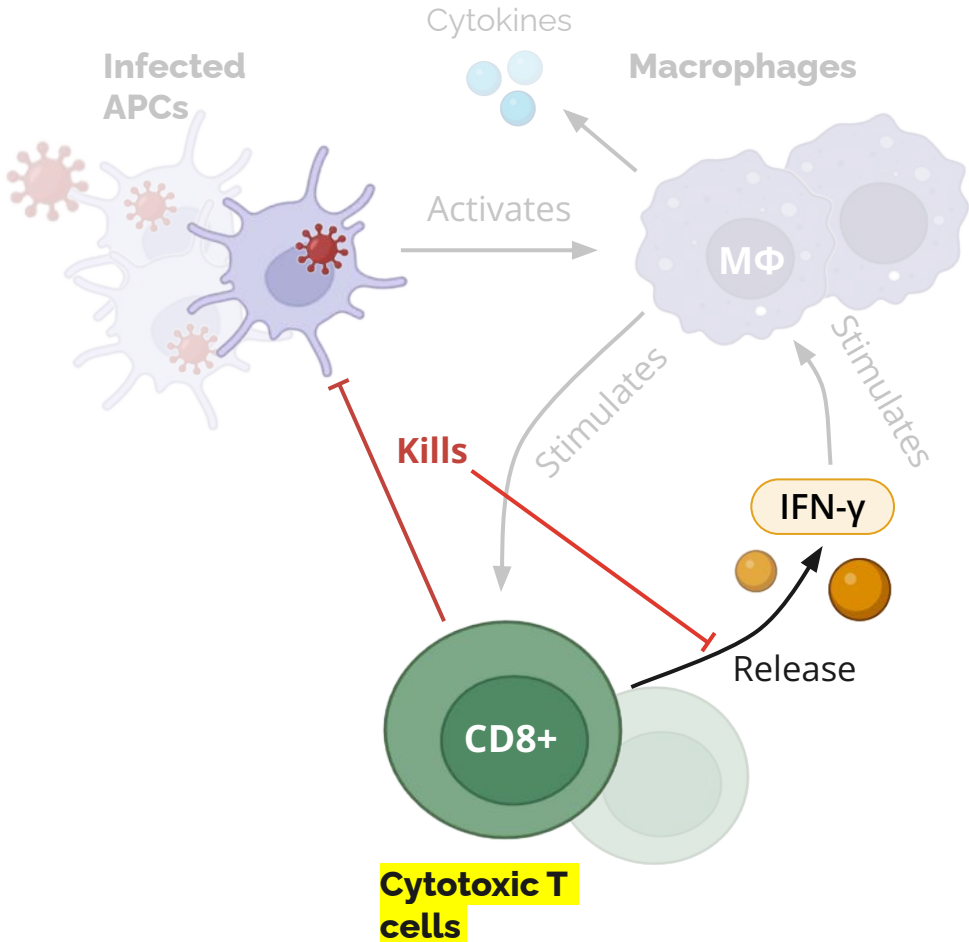
   b. When **CD8+ successfully kill** their target, they are able to **disengage from the target synapse** → can **stop releasing** cytokines



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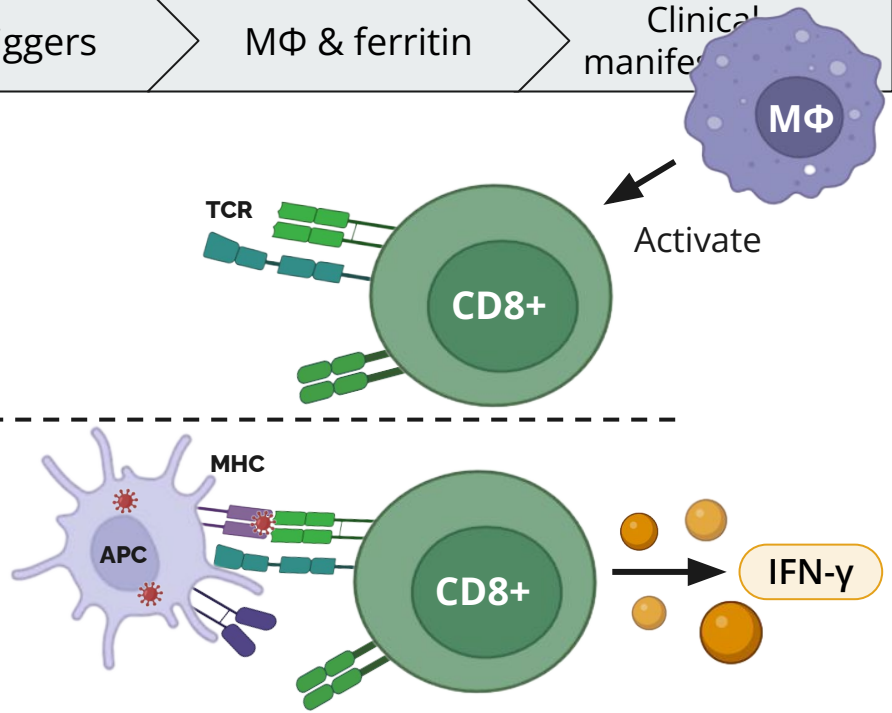

More specifically [3]

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

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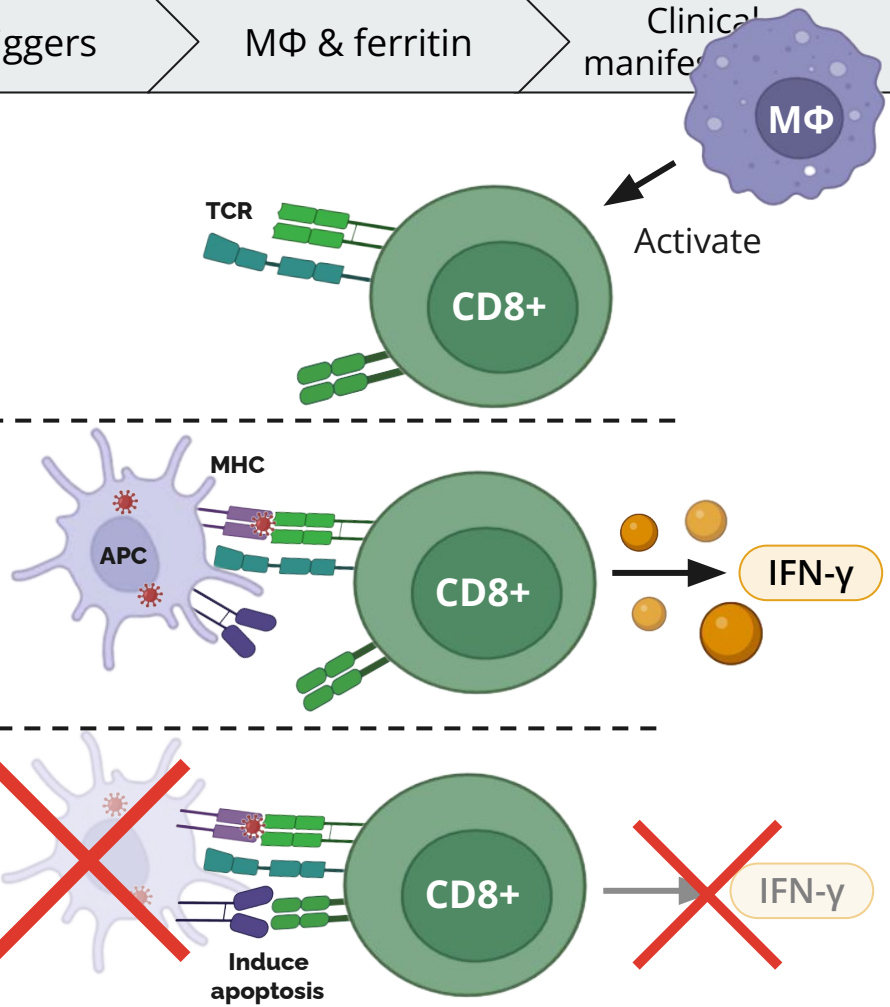


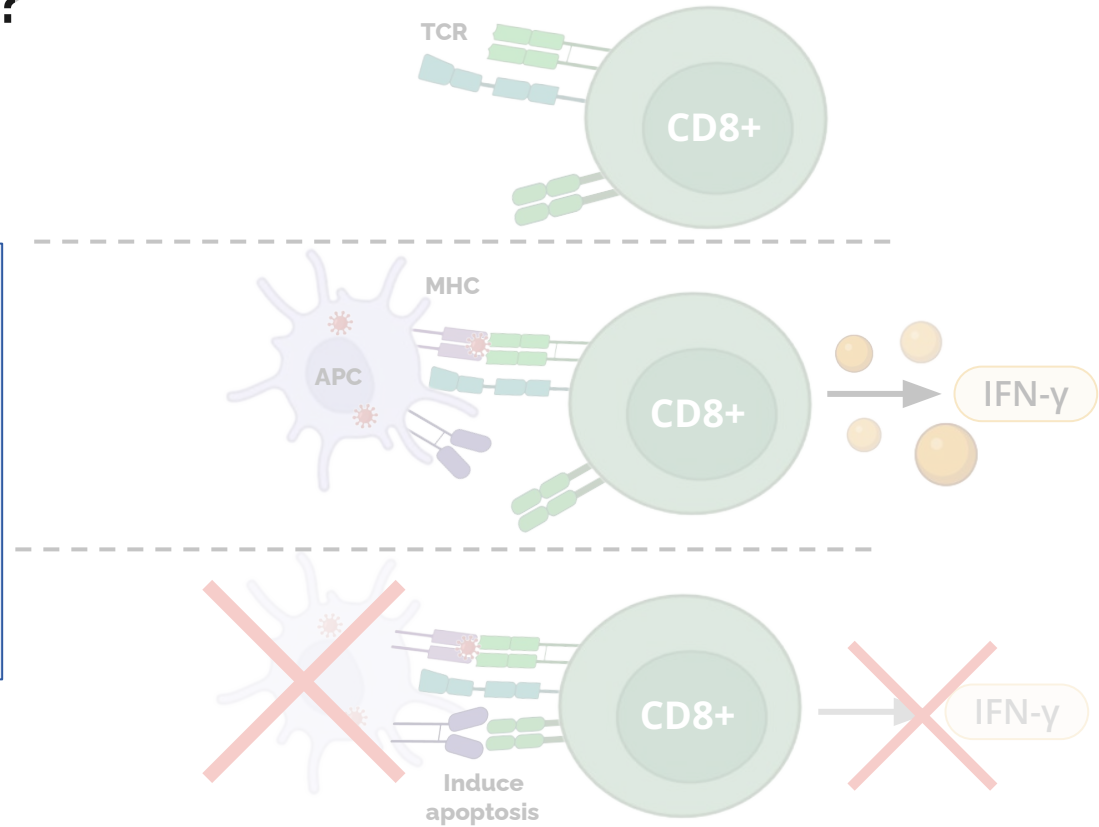
More specifically [3]

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

What stops this cycle?

Why it matters to us [3]

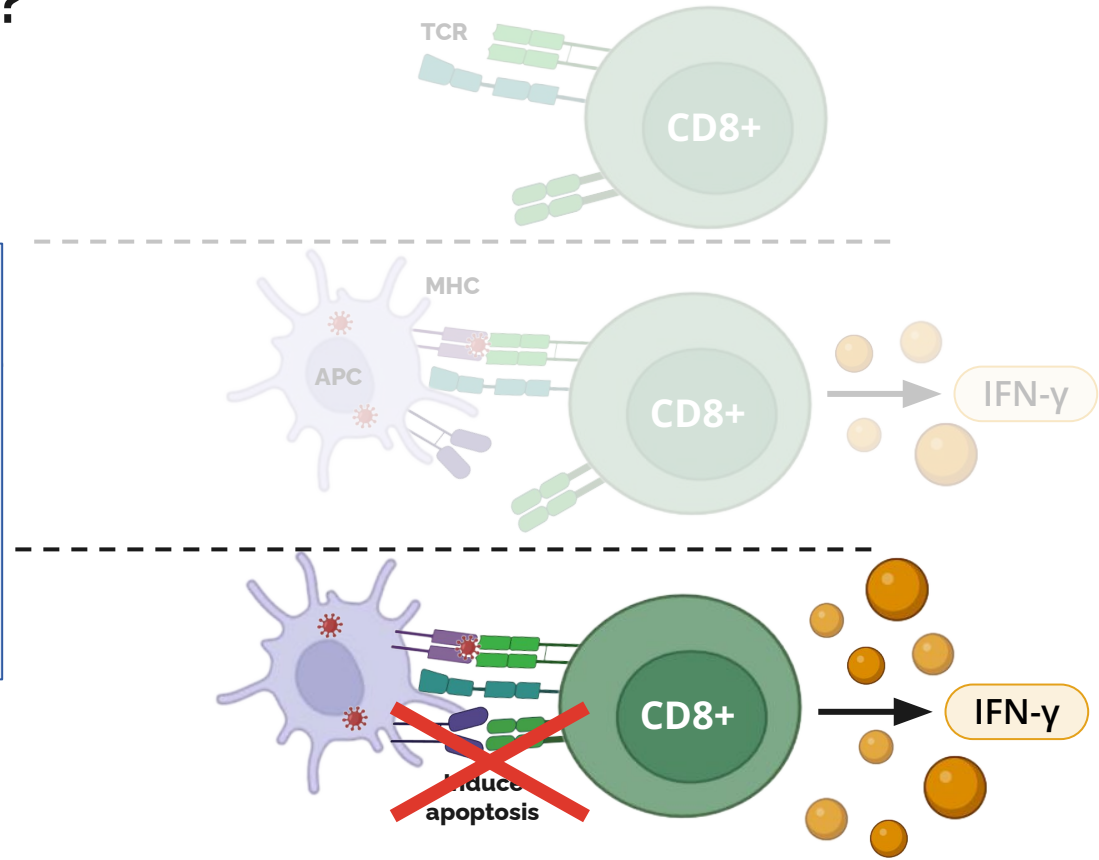
- The most common infectious **cause of HLH are viruses**, namely large DNA viruses (**herpesvirus family**)
- Over half of their genome is dedicated to **immunomodulation**



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**

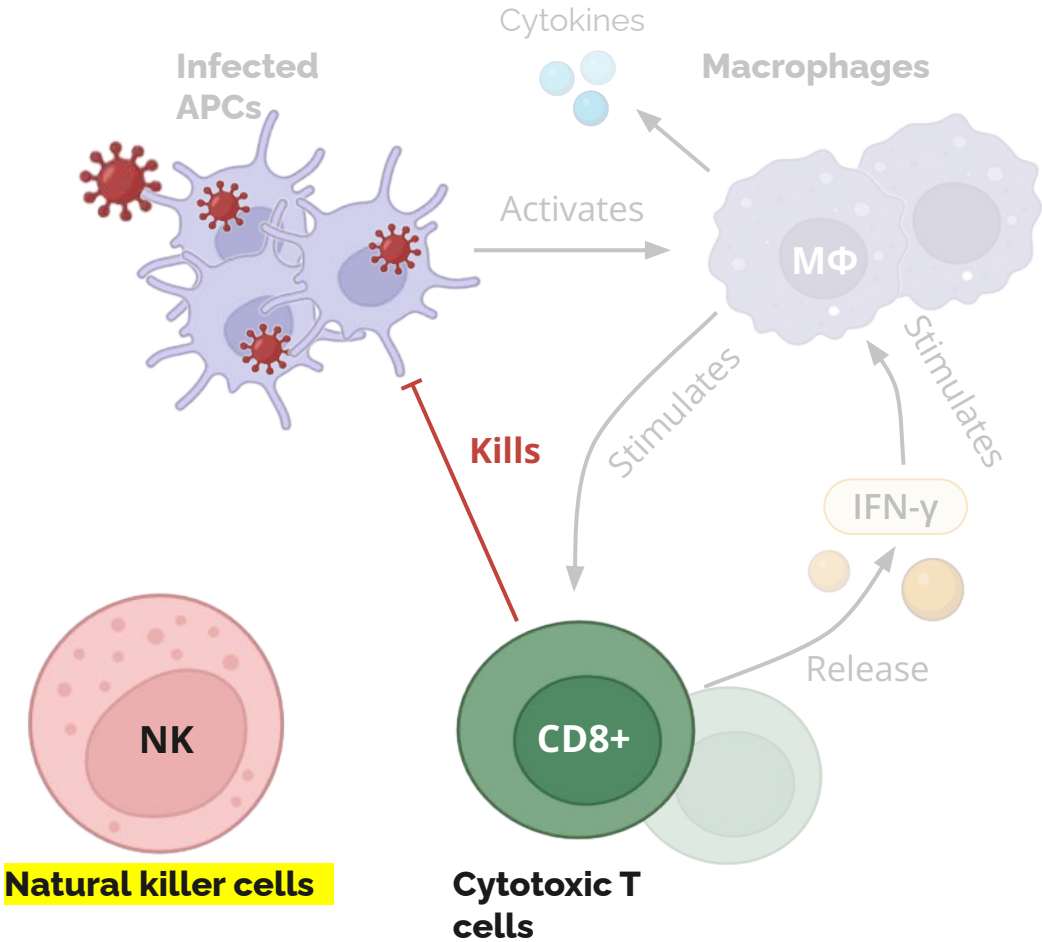


What stops this cycle?

Successfully **eliminating the infection**

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

Natural killer cells regulate CD8+



What stops this cycle?

STOP

Successfully **eliminating the infection**

1. **Macrophages** stop activating CD8+
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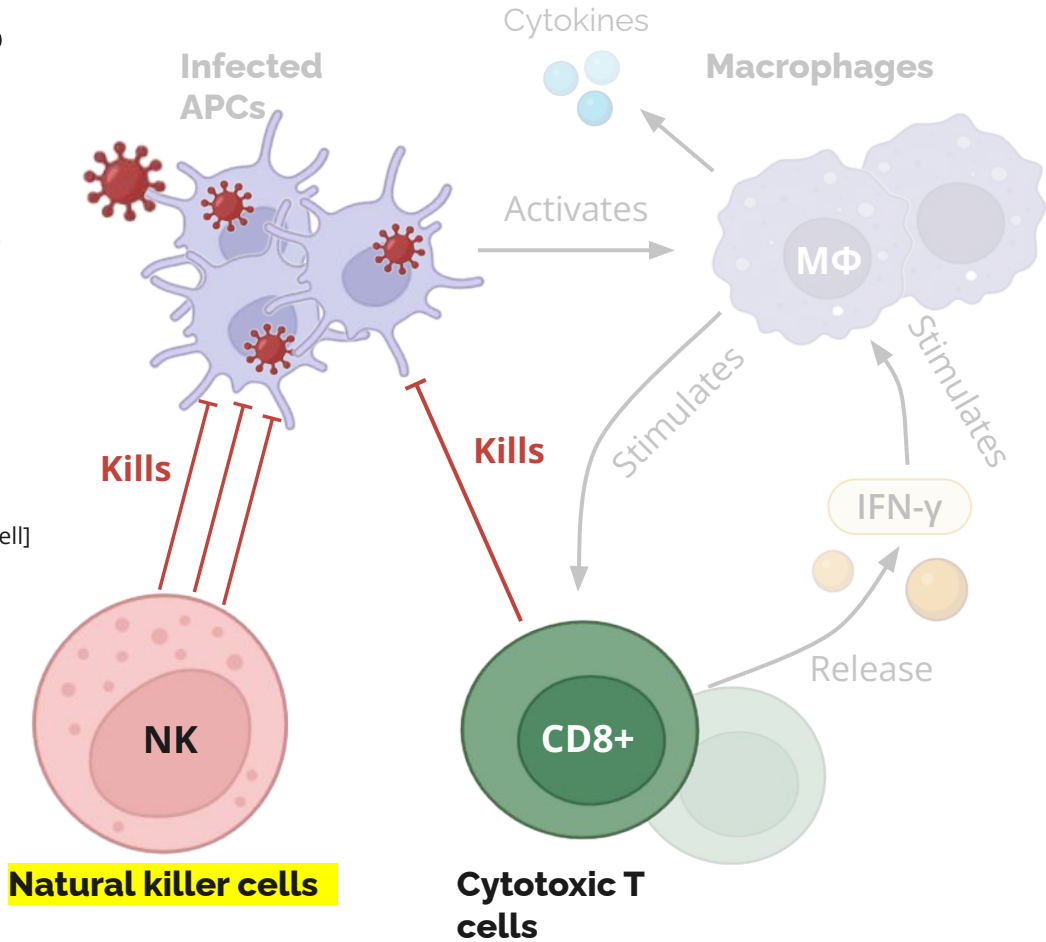
STOP

Natural killer cells regulate CD8+

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



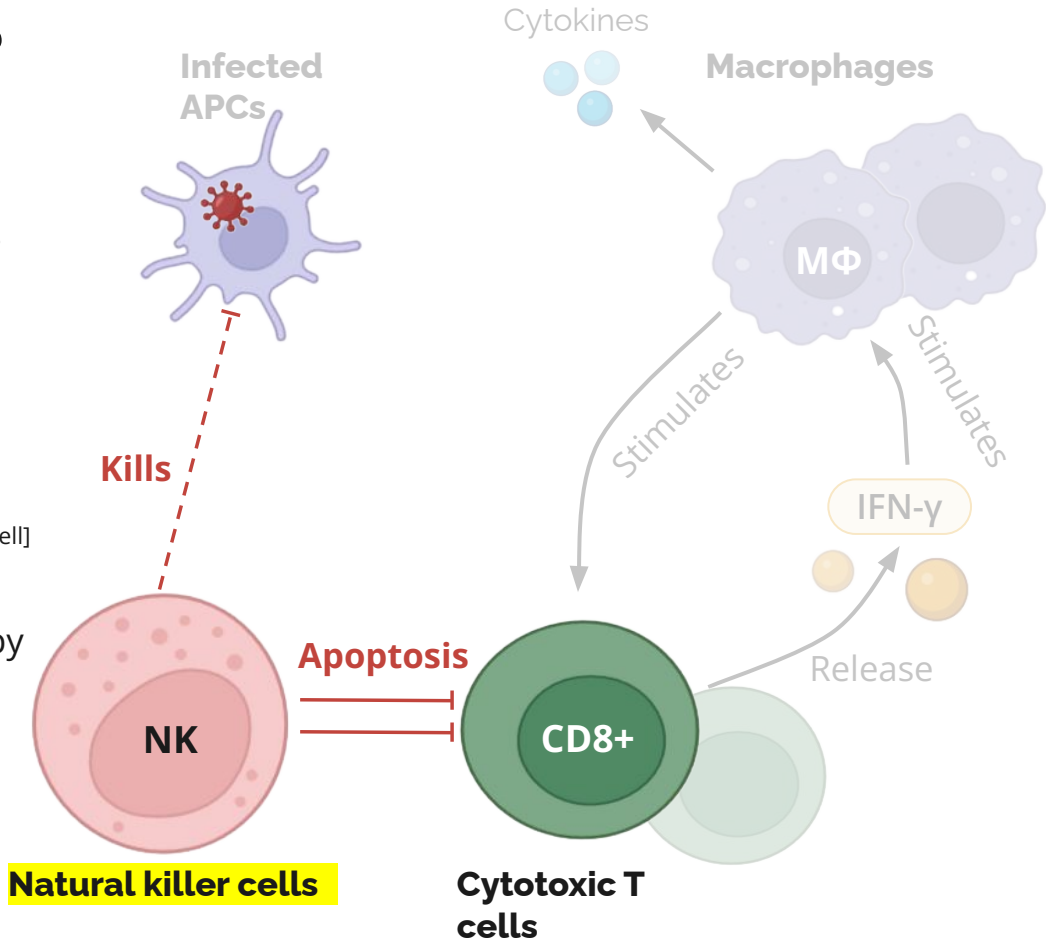
What stops this cycle?

Successfully **eliminating the infection**

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

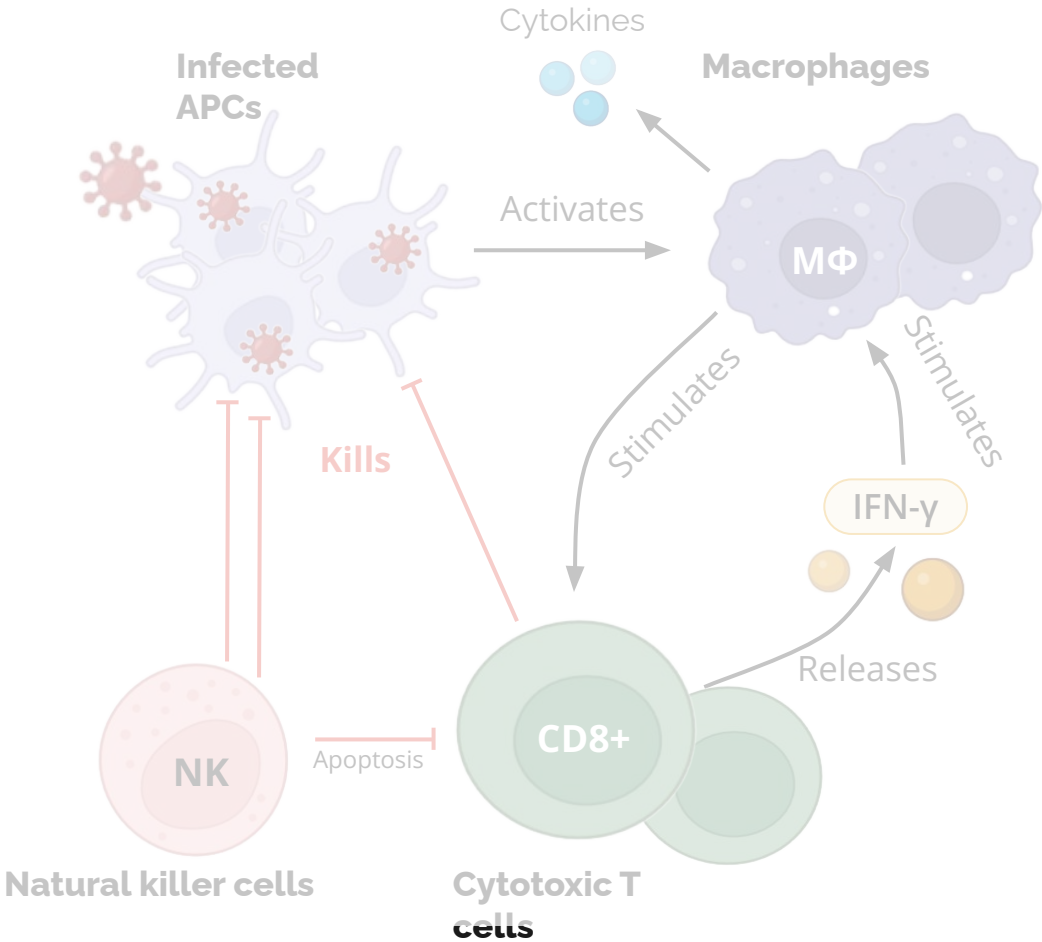
Natural killer cells regulate CD8+

- 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



Th1 hyperactivation

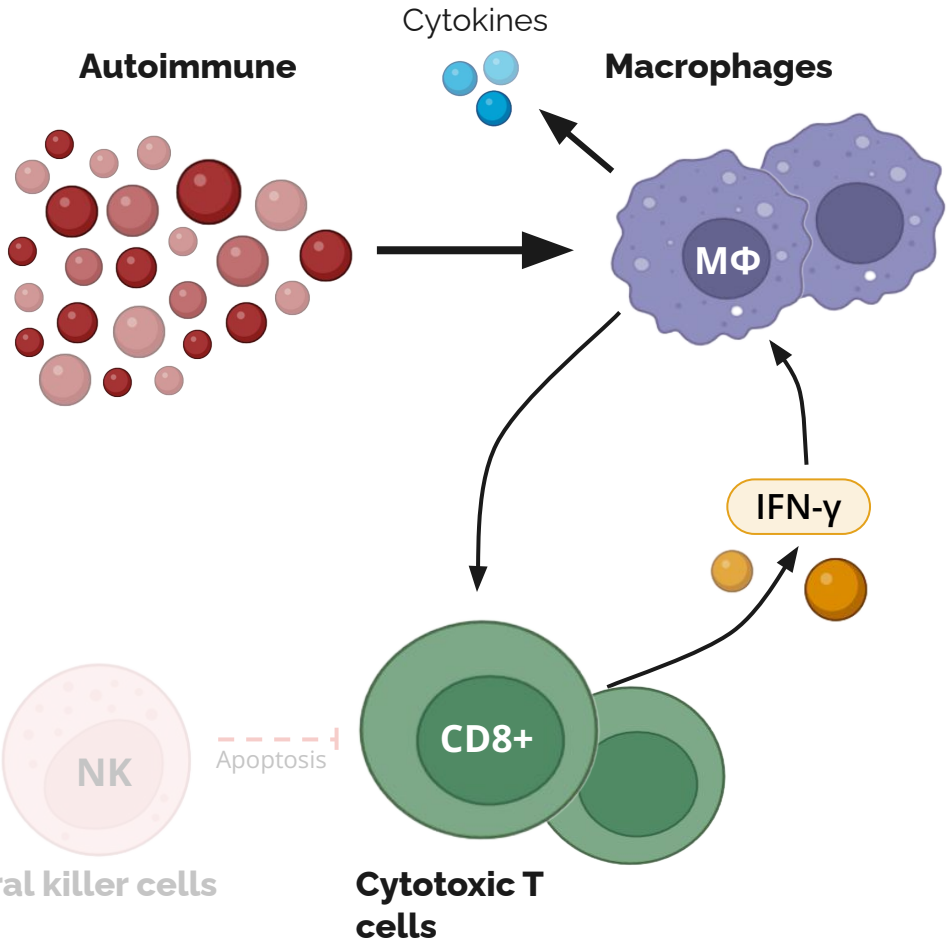
Revisiting the causes of HLH (and related syndromes)



Th1 hyperactivation

Revisiting the causes of HLH (and related syndromes)

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

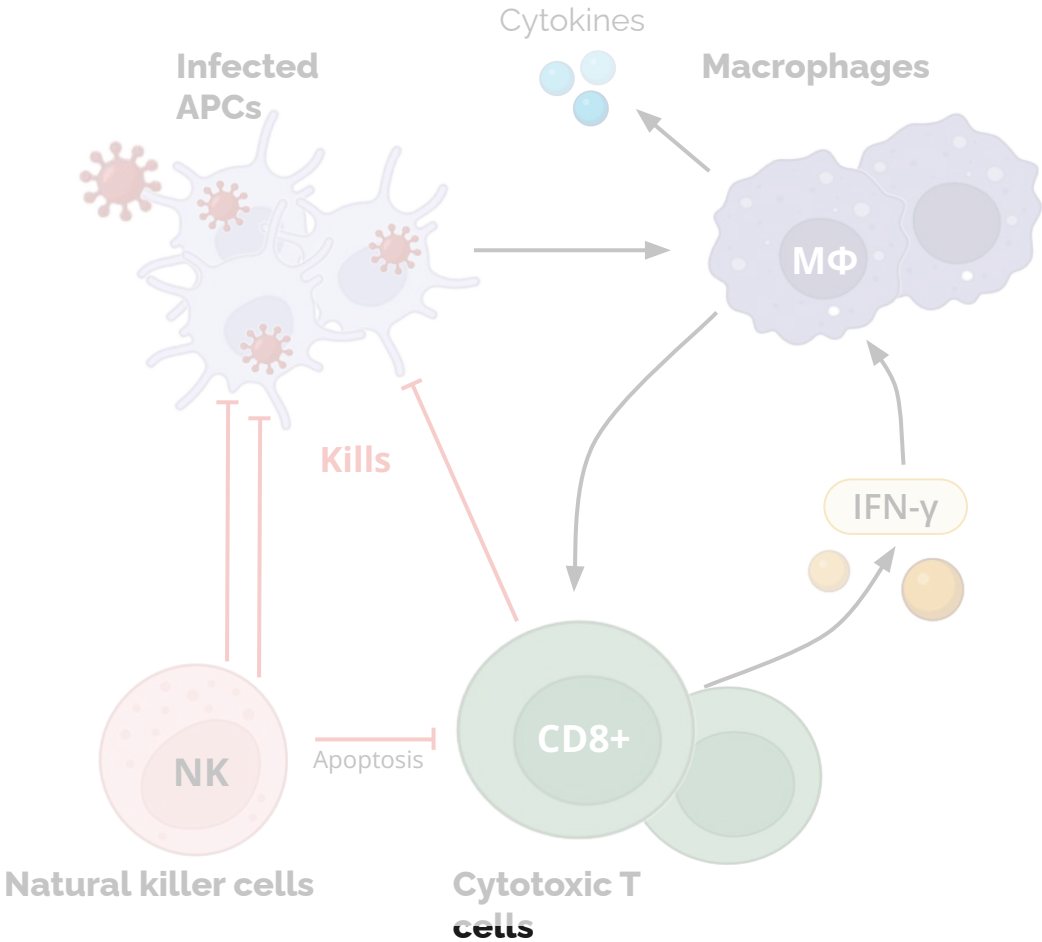


Th1 hyperactivation

Revisiting the causes of HLH (and related syndromes)

Autoimmune: Macrophages

Malignancy:

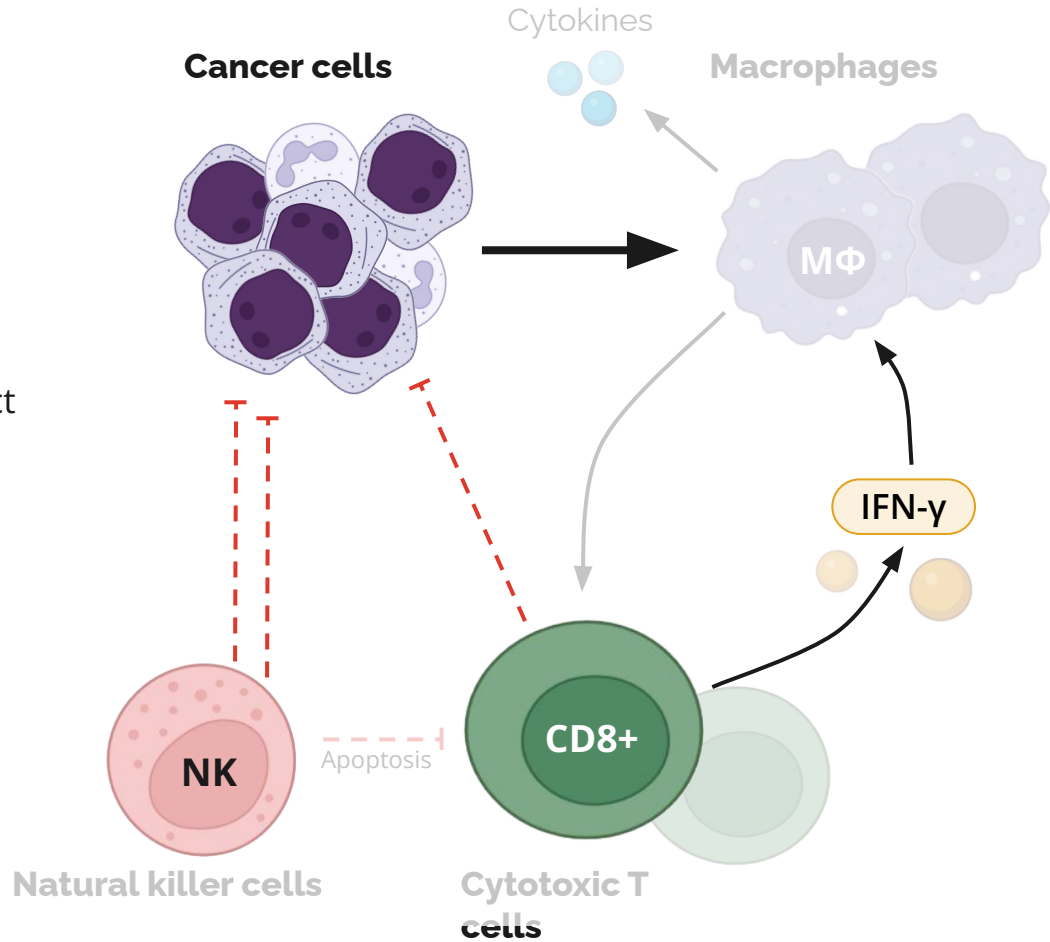


Th1 hyperactivation

Revisiting the causes of HLH (and related syndromes)

Autoimmune: Macrophages

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



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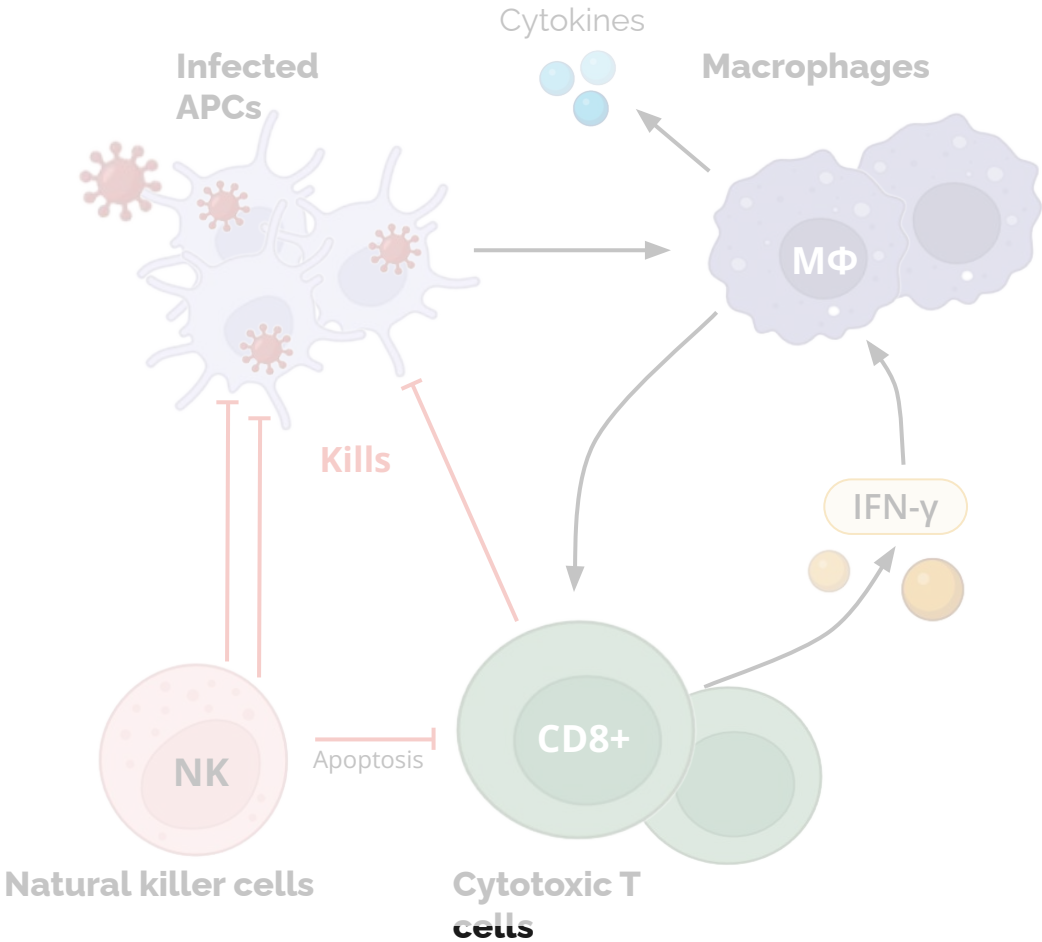
Malignancy: Persistent antigens

CAR-T:



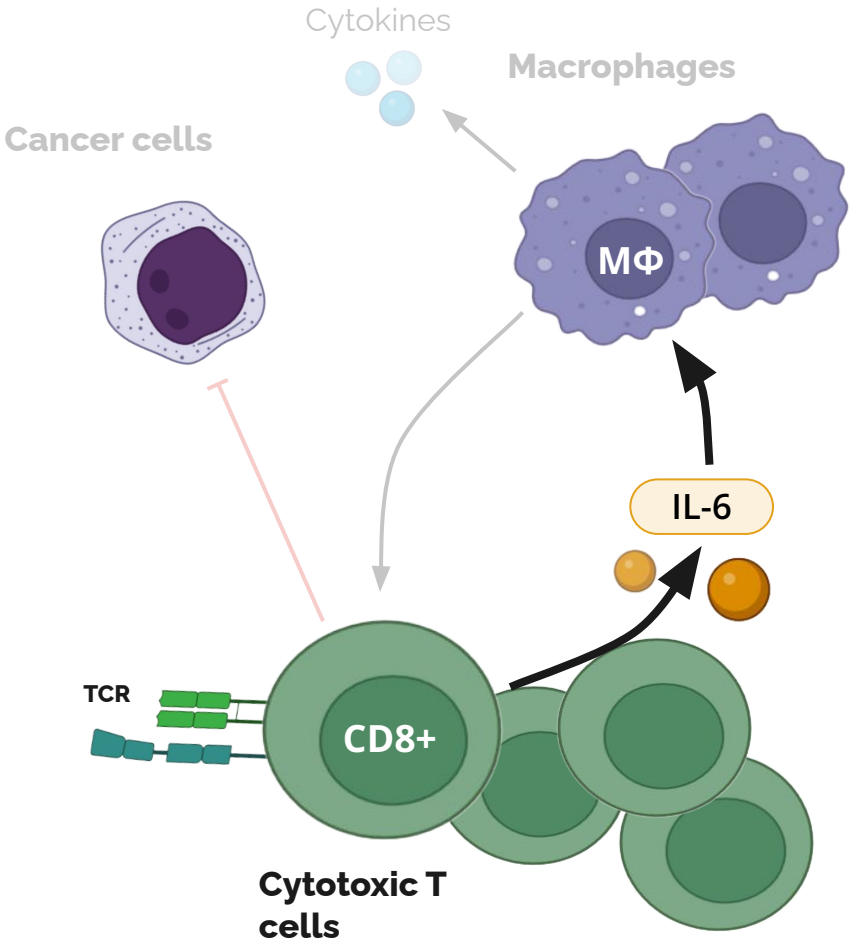
Th1 hyperactivation

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



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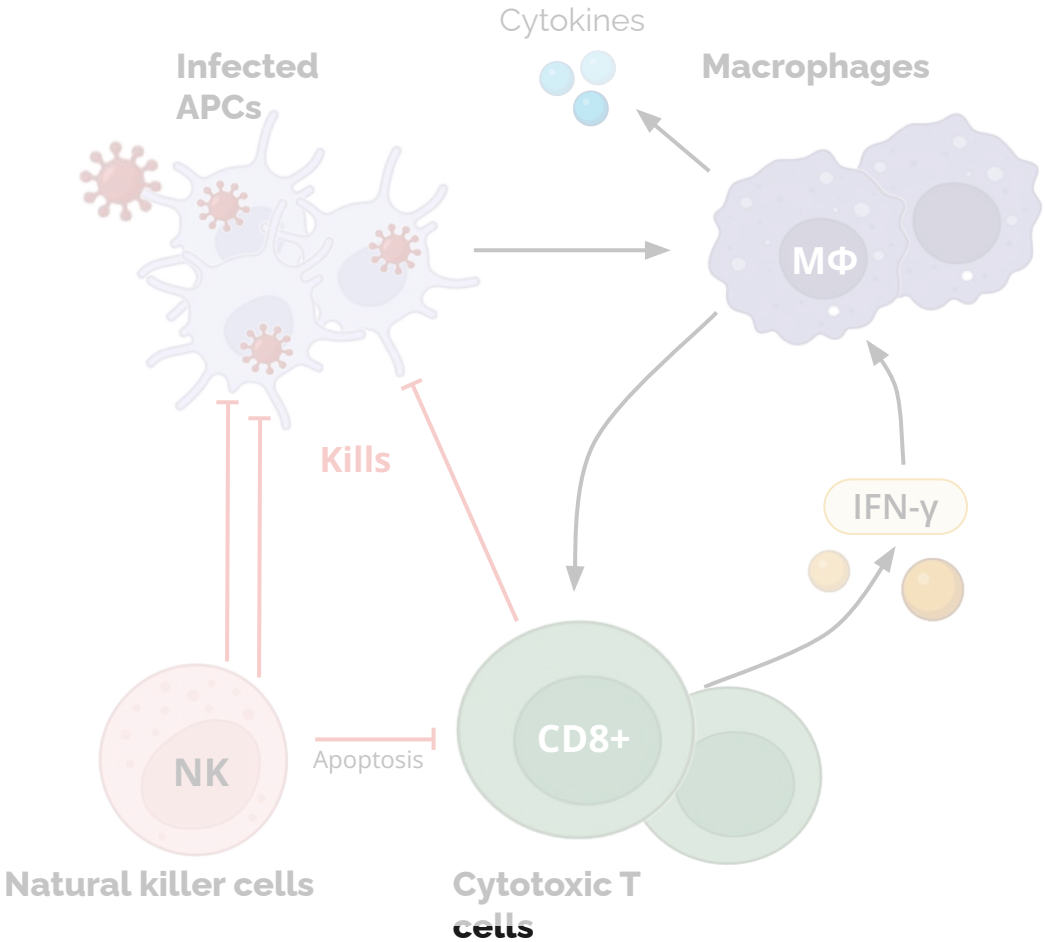
Infections:



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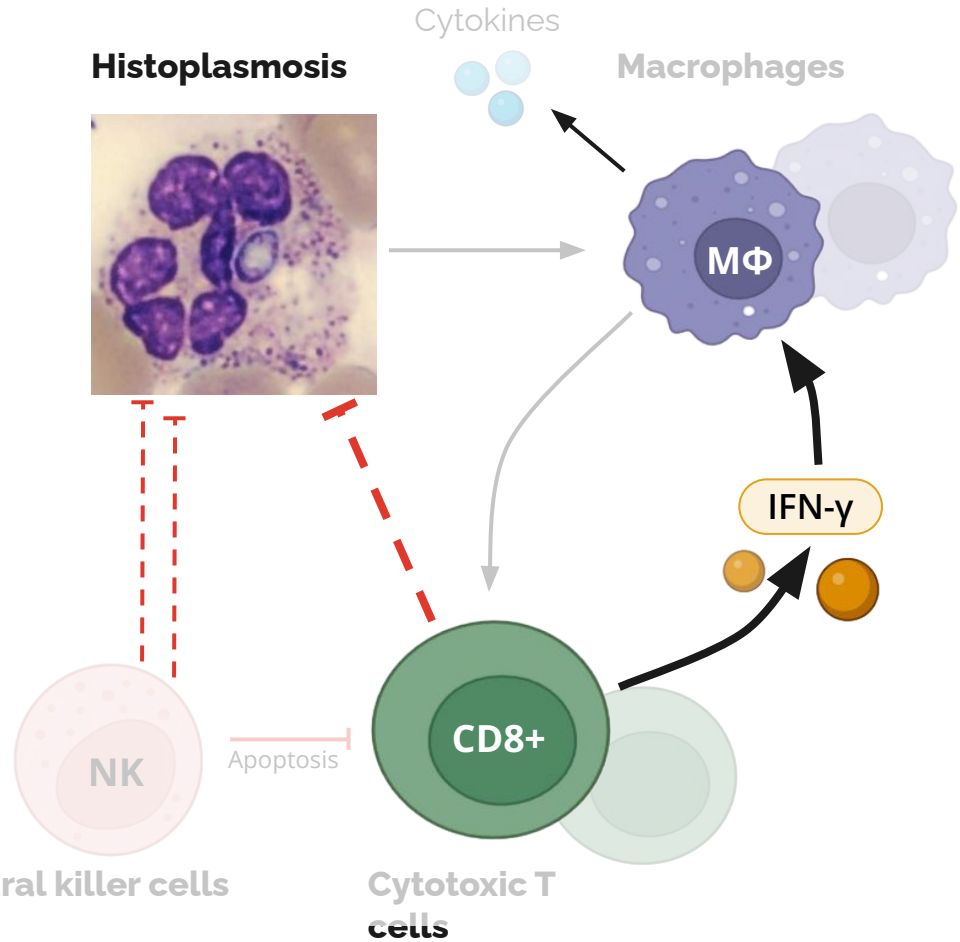
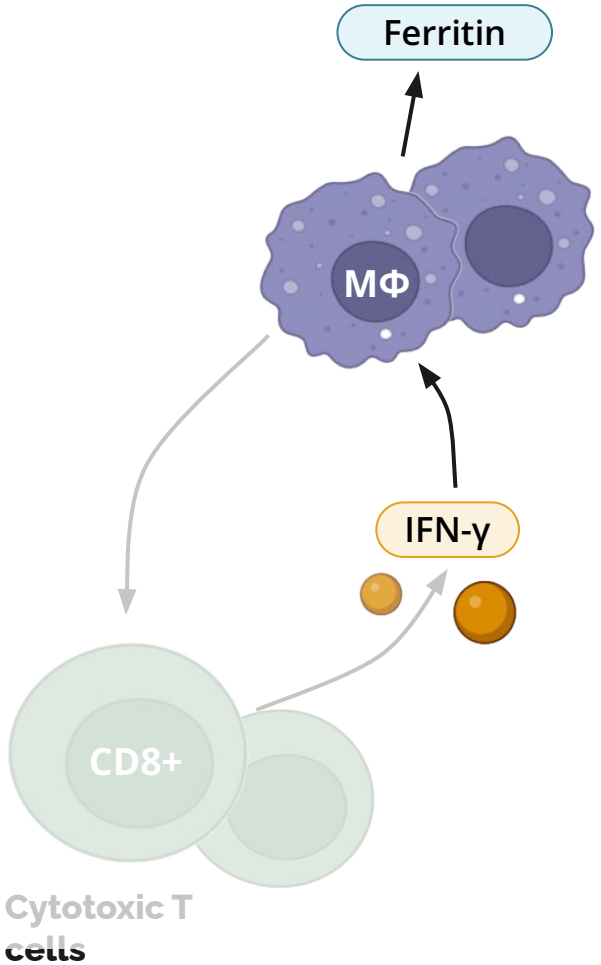


Macrophages & ferritin

IFN-γ → MΦ → Ferritin axis

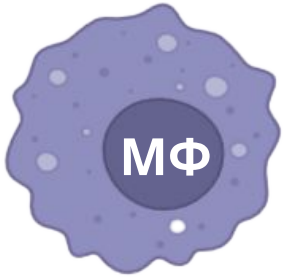
In all these conditions, the **common downstream** effector cells are **macrophages**

Although IFN-γ 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)

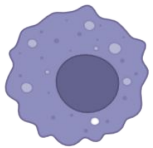


Macrophages

Macrophages live in...



Blood

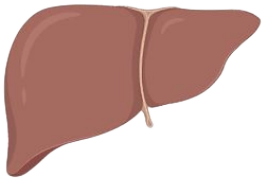


Monocytes

Brain

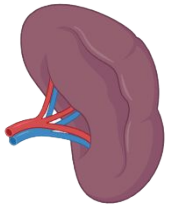
Microglia

Liver



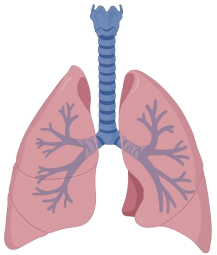
Kupffer cells

Red pulp (**spleen**)



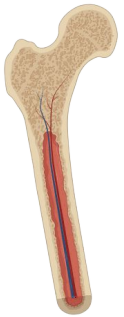
Littoral cells

Lungs



Alveolar macrophages

Bone



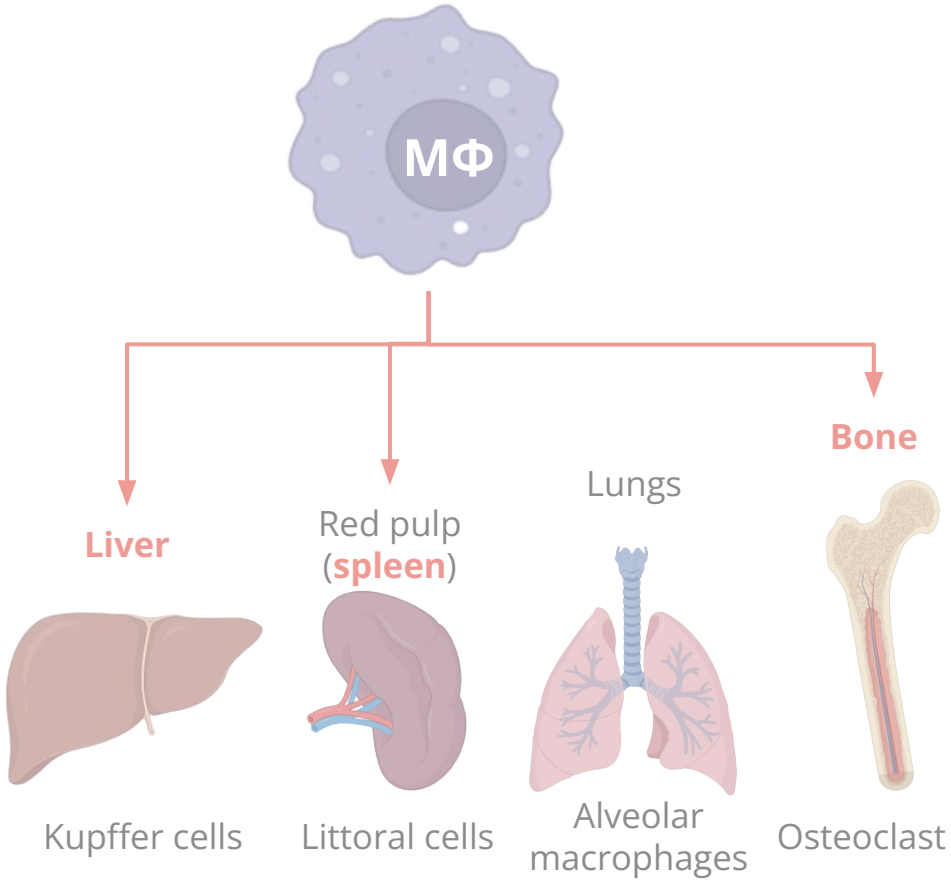
Osteoclast

Macrophages

Macrophages live in...

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

} Part of the Hscore



Macrophages

Macrophages live in...

- **Liver** (Kupffer cells)
- Red pulp of the **spleen**
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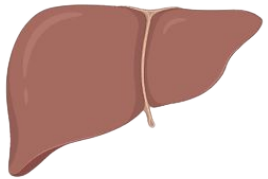
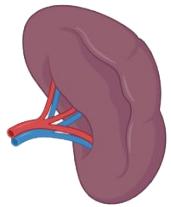
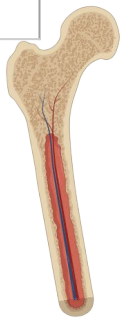
- Lungs

Part of the Hscore

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



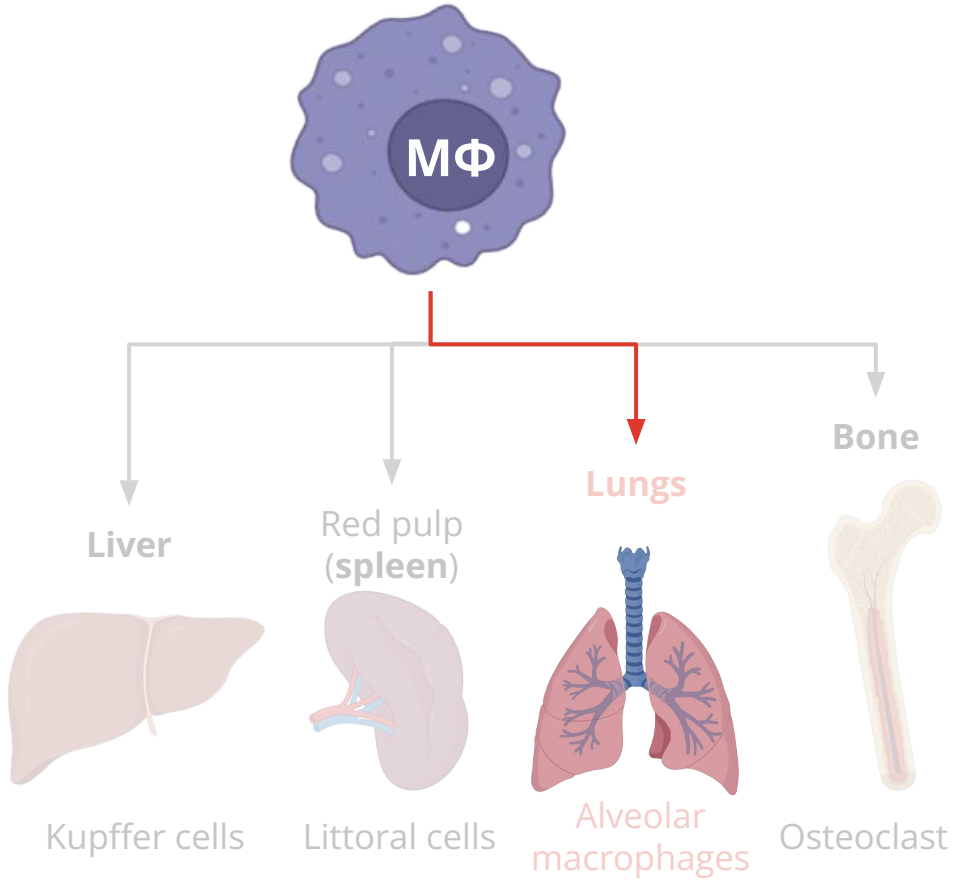
Macrophages

Macrophages live in...

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

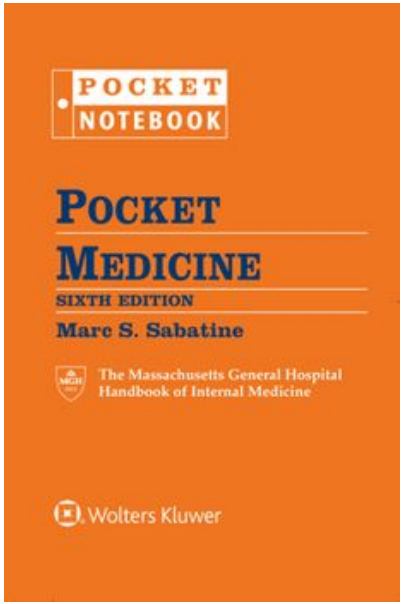
Part of the Hscore

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



HyperFerritinemia

IFN-γ → MΦ → 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)

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Causes of **ferritin >10,000**

- Rickettsial infection
- Histoplasmosis

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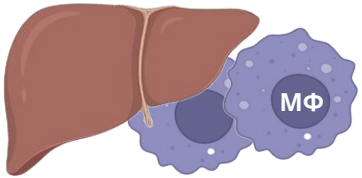
Clinical pearl (from MS3)

Causes of **ferritin >10,000**

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

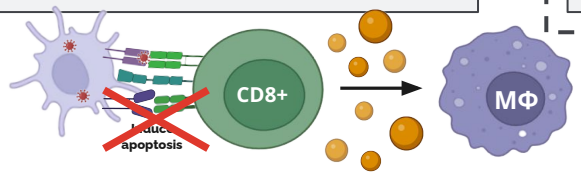


Conceptual overview

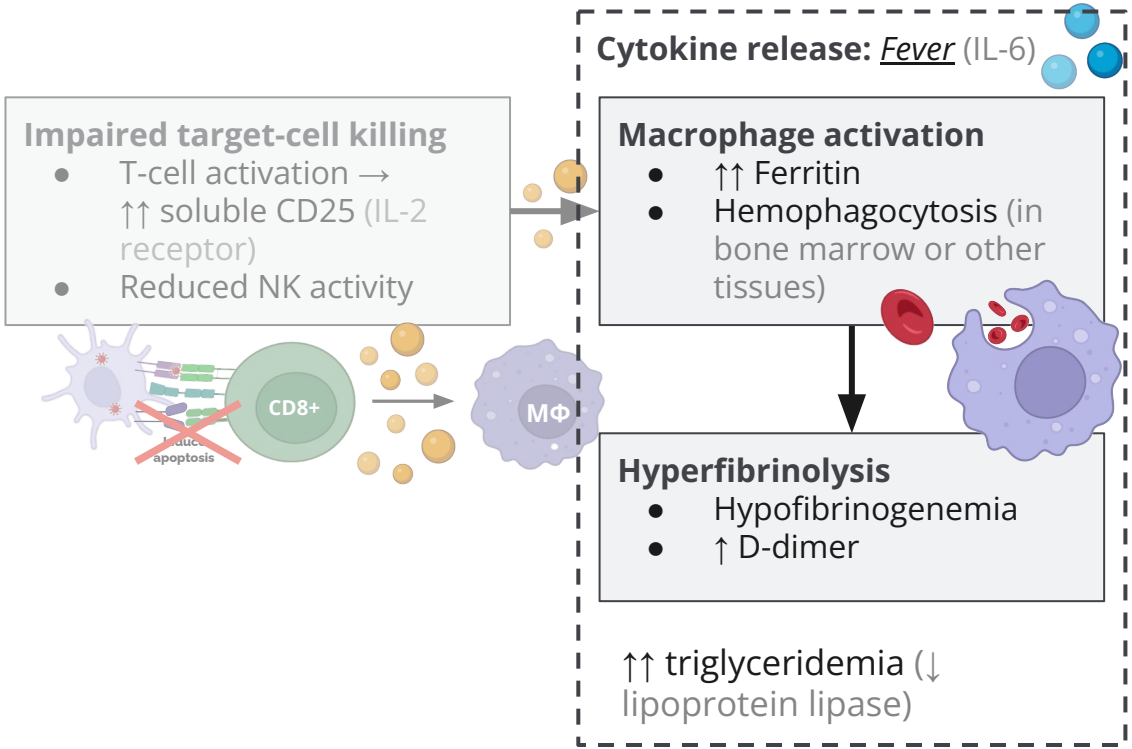
Impaired target-cell killing
- T-cell activation → ↑↑ soluble CD25 (IL-2 receptor)
- Reduced NK activity

Cytokine release: *Fever* (IL-6)

Macrophage activation
- ↑↑ Ferritin



Conceptual overview



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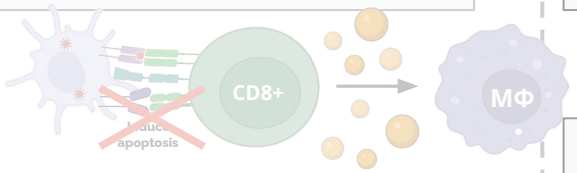


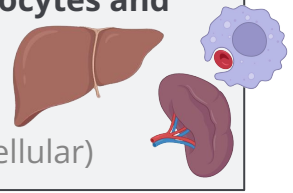
Cytokine release: *Fever* (IL-6)

Macrophage activation
- ↑↑ Ferritin
- Hemophagocytosis (in bone marrow or other tissues)

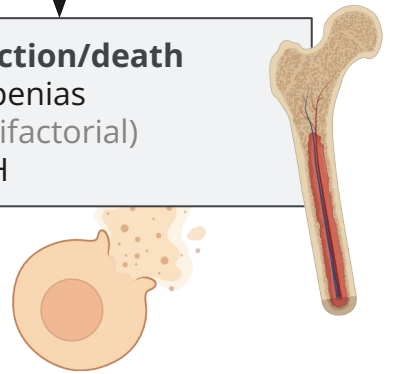
Hyperfibrinolysis
- Hypofibrinogenemia
- ↑ D-dimer

↑↑ triglyceridemia (↓ lipoprotein lipase)

Infiltration by lymphocytes and histiocytes
- Splenomegaly
- Hepatomegaly
- ↑ LFTs (hepatocellular)



Cell destruction/death
- Cytopenias (multifactorial)
- ↑ LDH



Conceptual overview

Impaired target-cell killing
- T-cell activation → ↑↑ *soluble CD25* (IL-2 receptor)
- Reduced NK activity

Included in **H-Score**
Included in *HLH-2004 criteria*

Cytokine release: *Fever* (IL-6)

Macrophage activation
- ↑↑ ***Ferritin***
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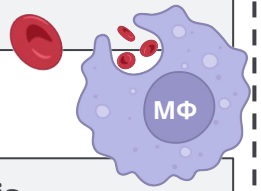

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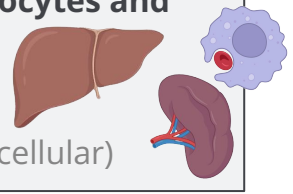

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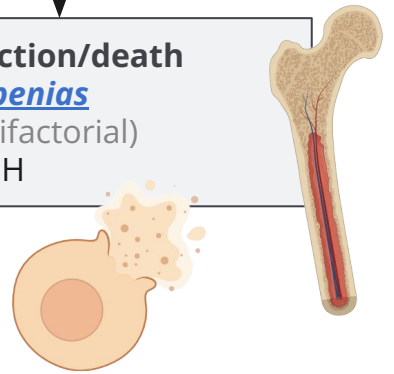


Conceptual overview

Cytokine release: *Fever* (IL-6)

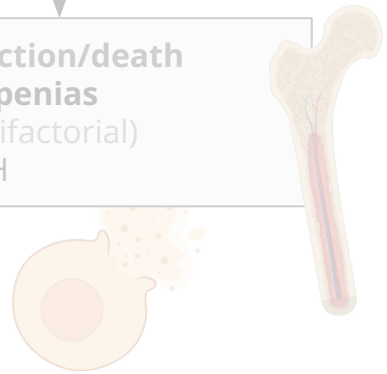
Admit labs	Our patient	Case report
WBC	3.0	3.3
Hgb	17.0	13.9
Platelets	72	16
Creat	1.7	3.96
AST	335	330
ALT	104	183
Ferritin	8,830 (**29** x ULN)	>33,511 (**>110** x ULN)
LDH	1,501	1,337

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
- Verus controls
  - Suspected to have anaplasmosis
  - But all lab testing indicated otherwise (negative serologies, PCR, smear)

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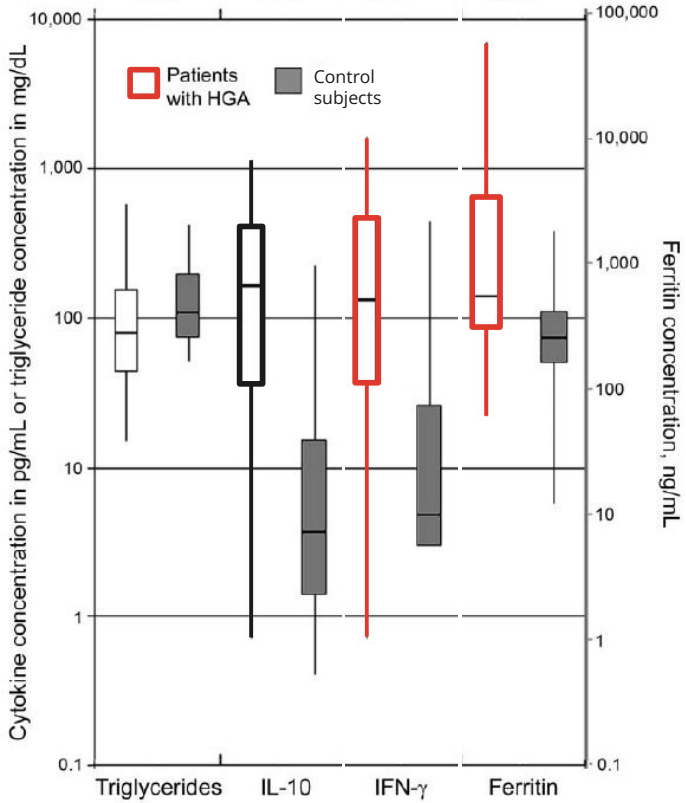
Patients with anaplasmosis had some cytokines elevated higher than would be expected

- Higher levels of **IL-10, IL-12, IFN-γ**



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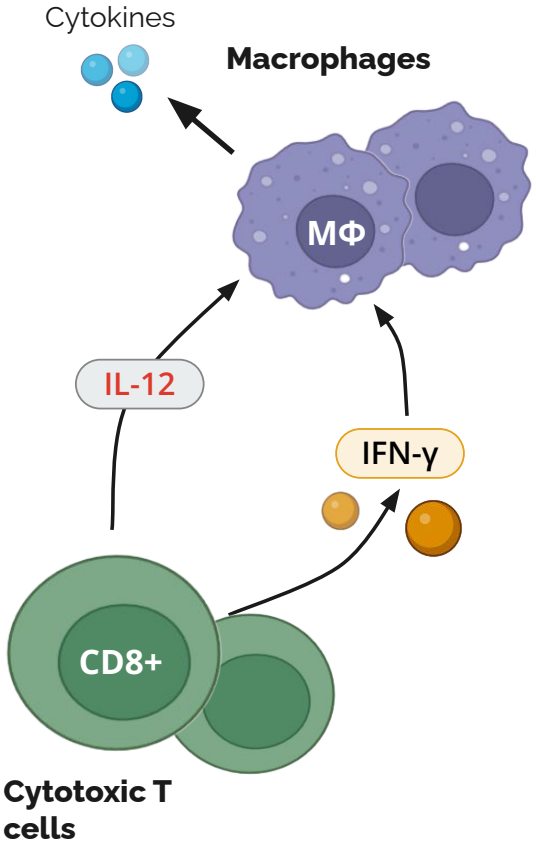

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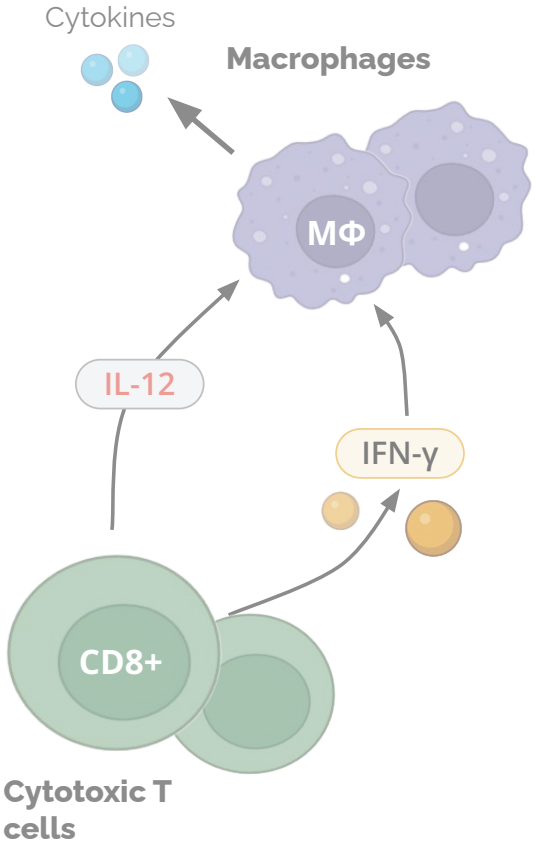
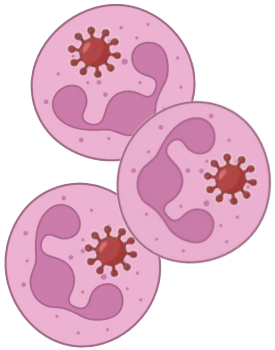
Patients with anaplasmosis had some cytokines elevated higher than would be expected

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



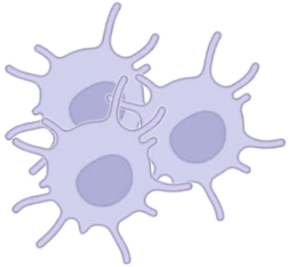
But...

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



Neutrophils

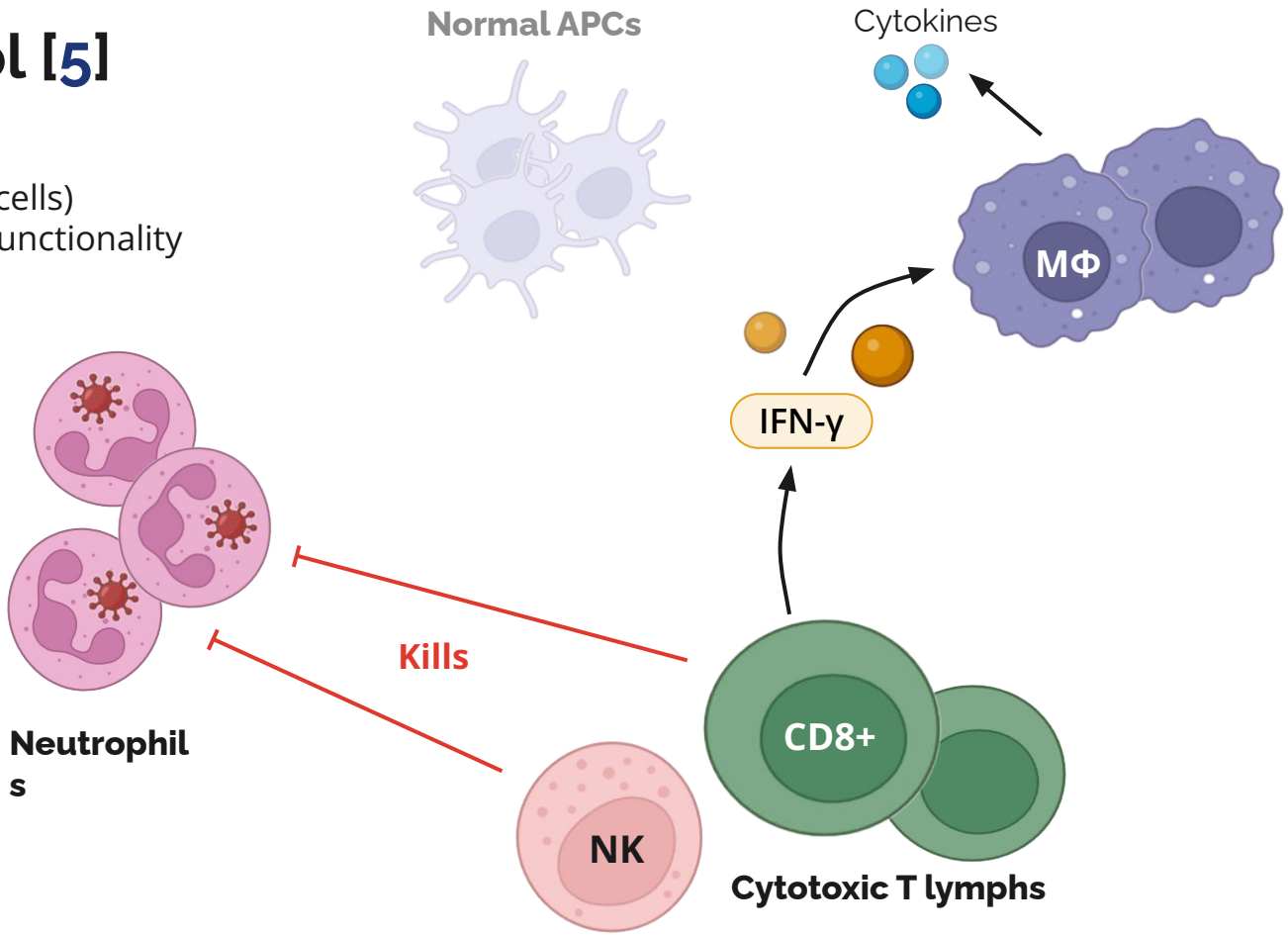
Normal APCs



Front Immunol [5]

Animal model (of human cells)

- Looking at cellular functionality



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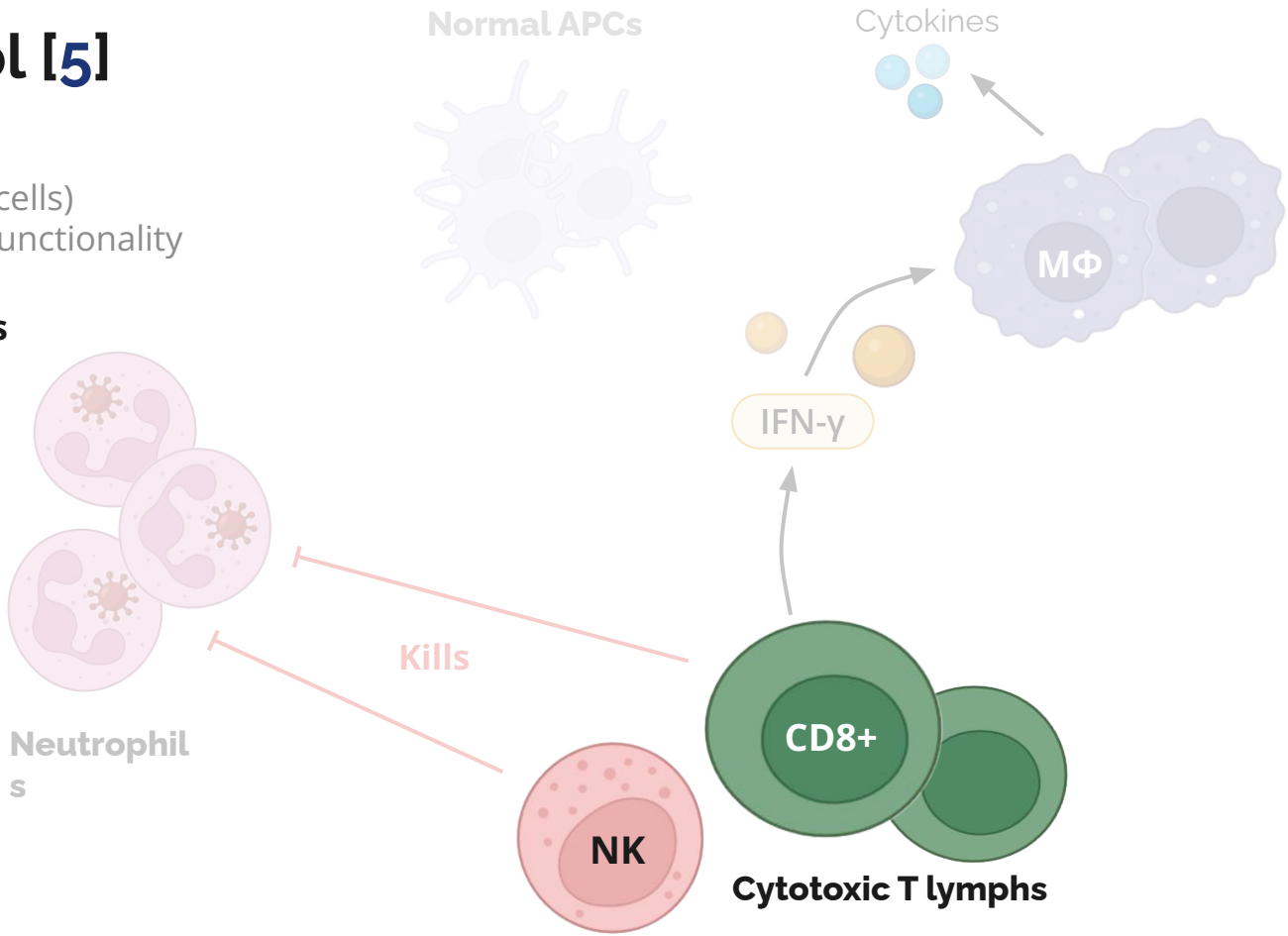
Cytotoxic T lymphocytes don't work when exposed to anaplasmosis



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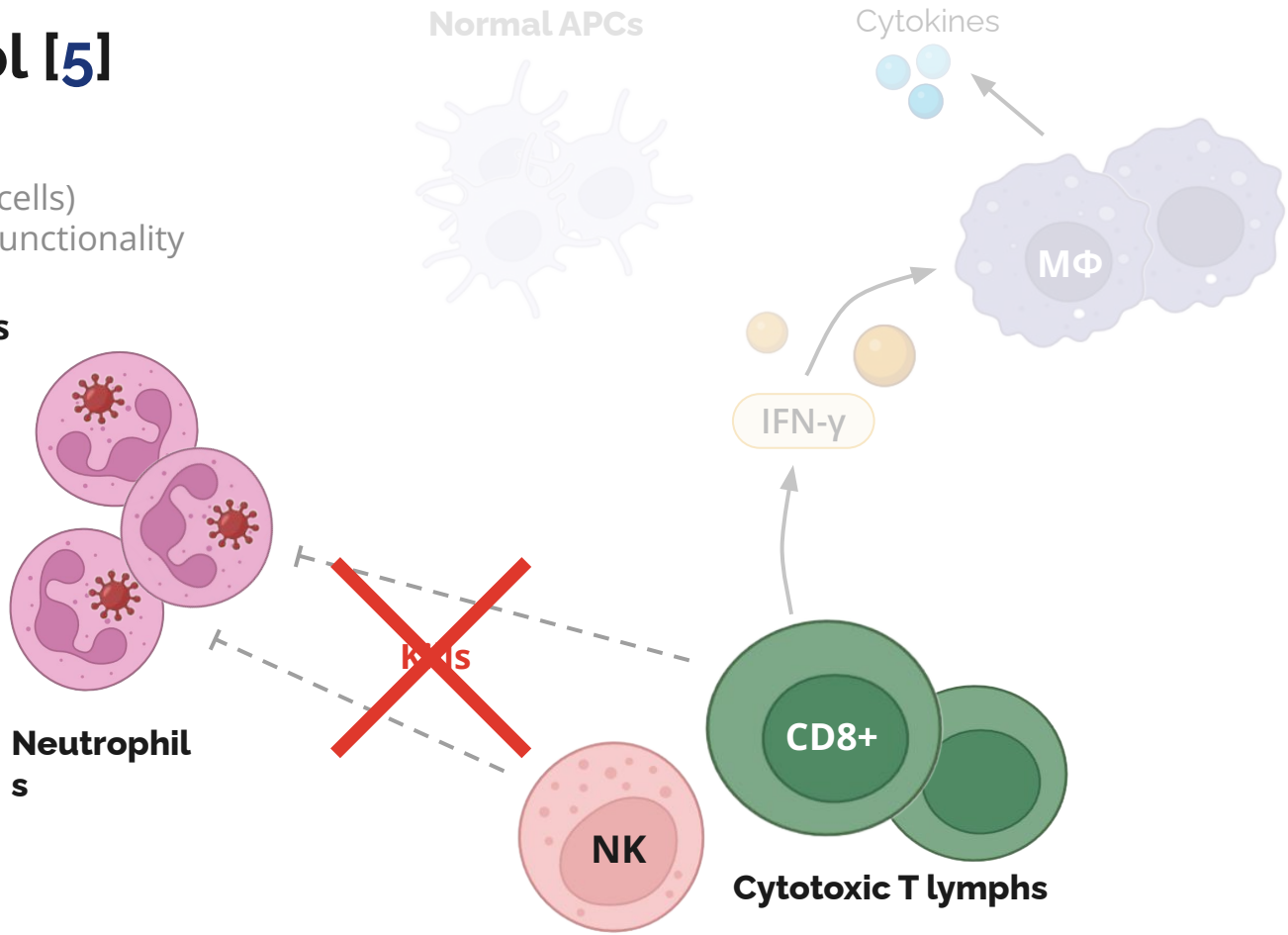

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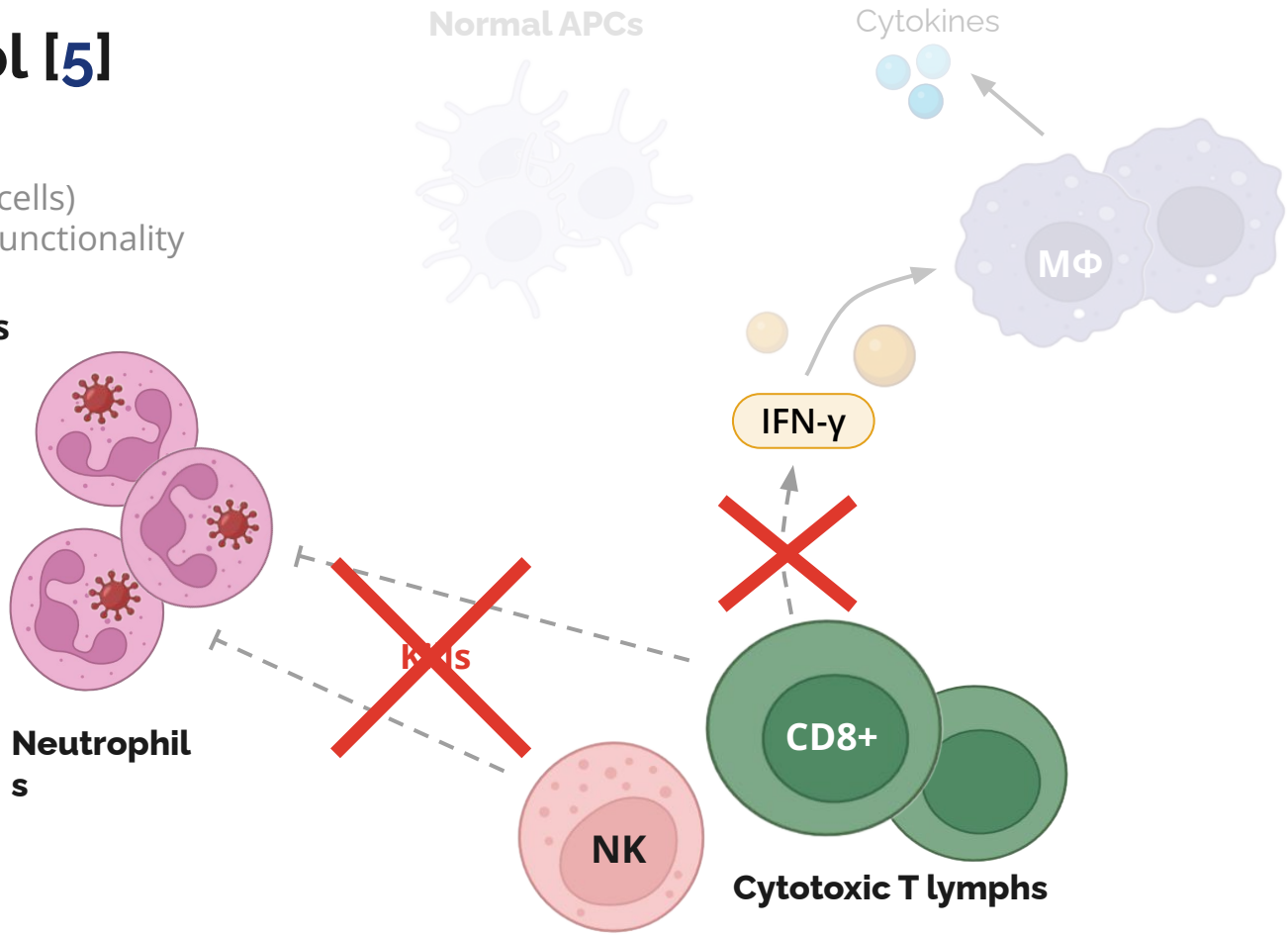
Cytotoxic T lymphocytes don't work when exposed to anaplasmosis

- Don't degranulate
- Also don't secrete IFN-γ



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Cytotoxic T lymphocytes don't work when exposed to anaplasmosis

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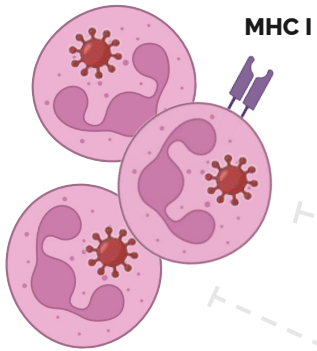
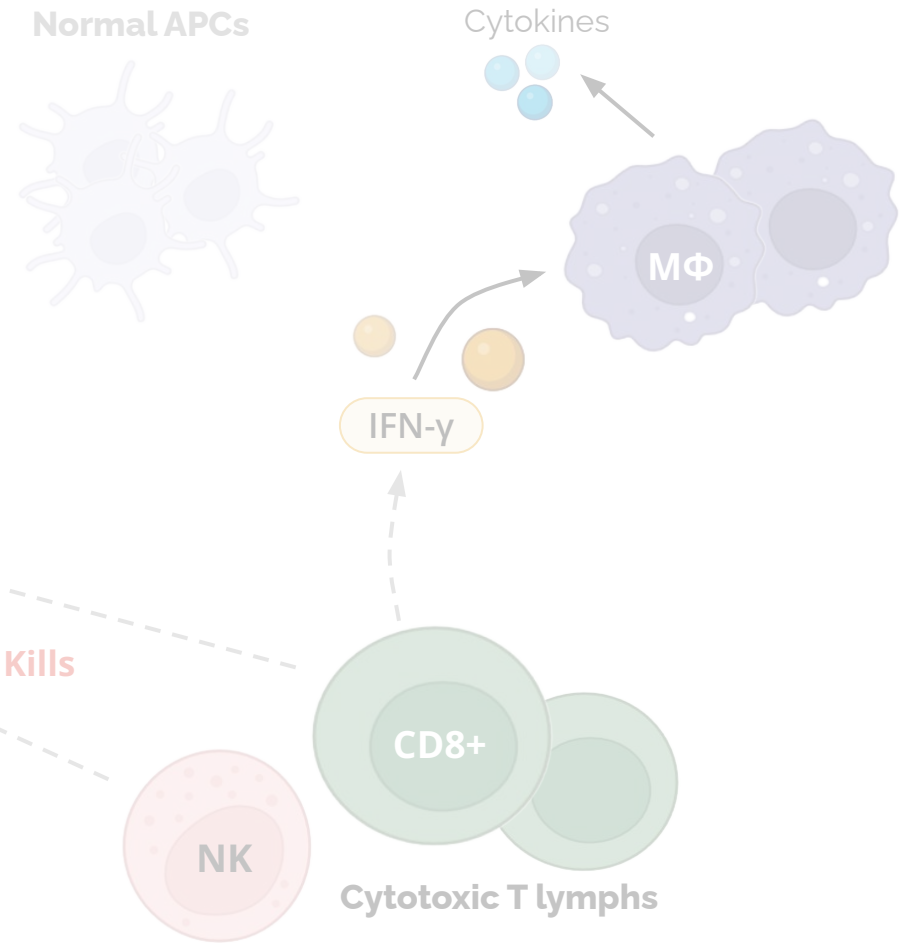
Possibly due **to poor presentation** by **MHC I** infected cells



Neutrophils



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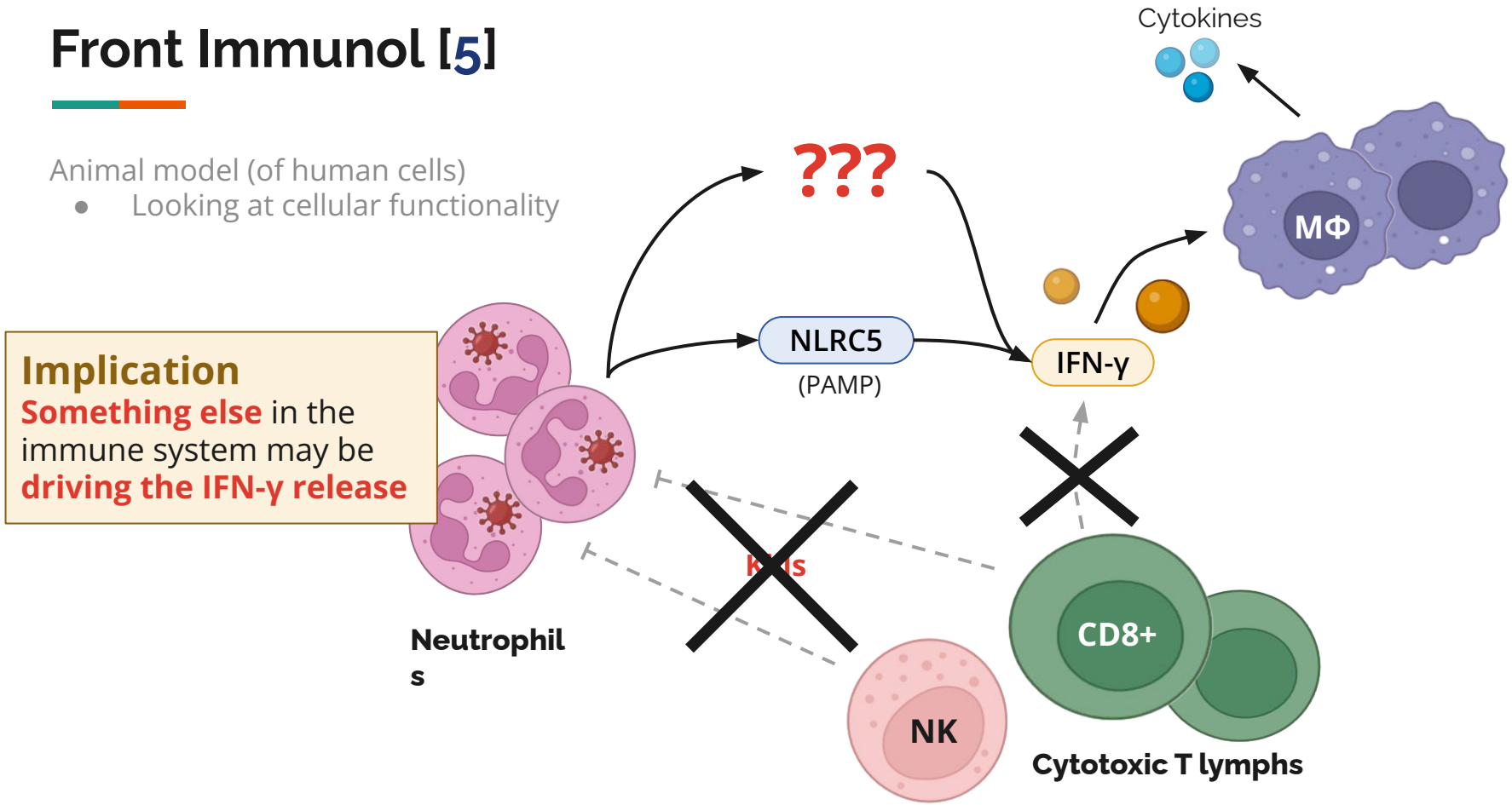
Implication
Something else in the immune system may be **driving the IFN-γ release**



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
Lyme	**Pos**	Neg
Ehrlichia	<1:20	<1:64
Anaplasma	<1:20	<1:64
RMSF	Neg	Neg

Other	Result
Parasite smear	Neg
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Serum PCR	Copies
Anaplasmosis	?
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Adenovirus	?
HSV	?
CMV	?
EBV	?

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

Case 1: Hospital course

PubMed®

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

Search

Advanced Create alert Create RSS User Guide

4 results

RMSF	Neg	Neg

Other	Result
Parasite smear	Neg
Monospot	Neg

HSV	?
CMV	?
EBV	?

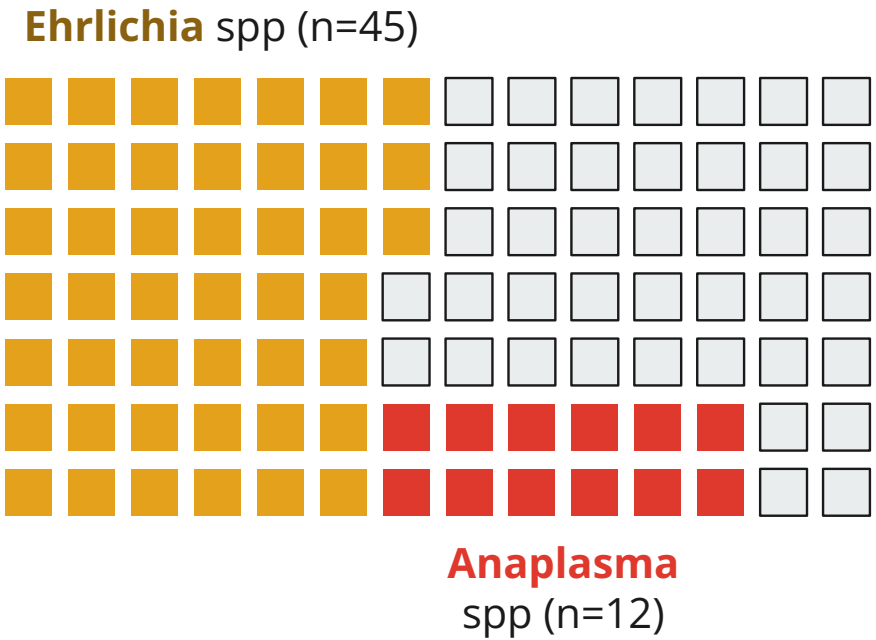
Well, then does Lyme cause HLH?

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)



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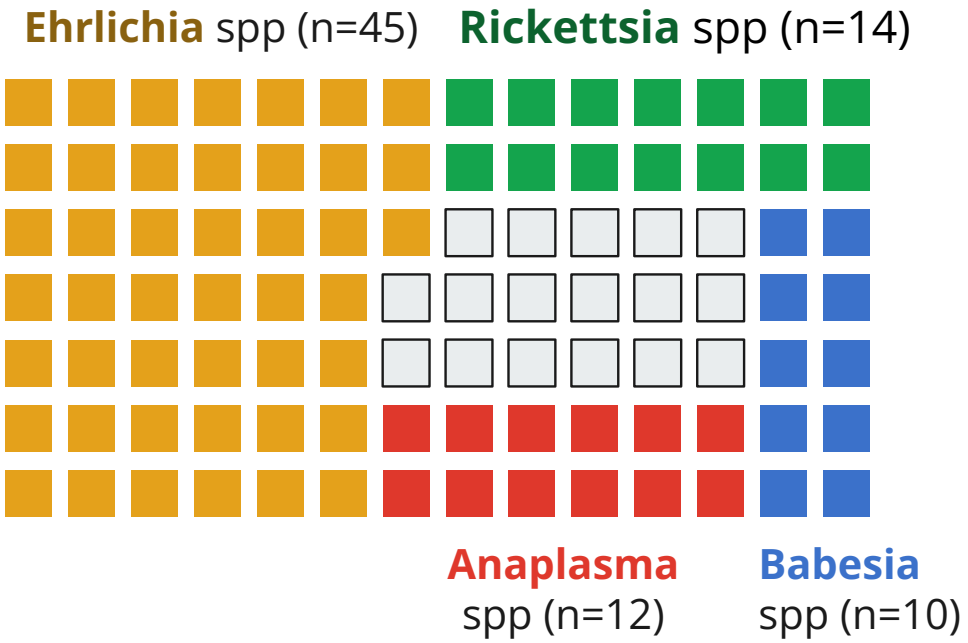

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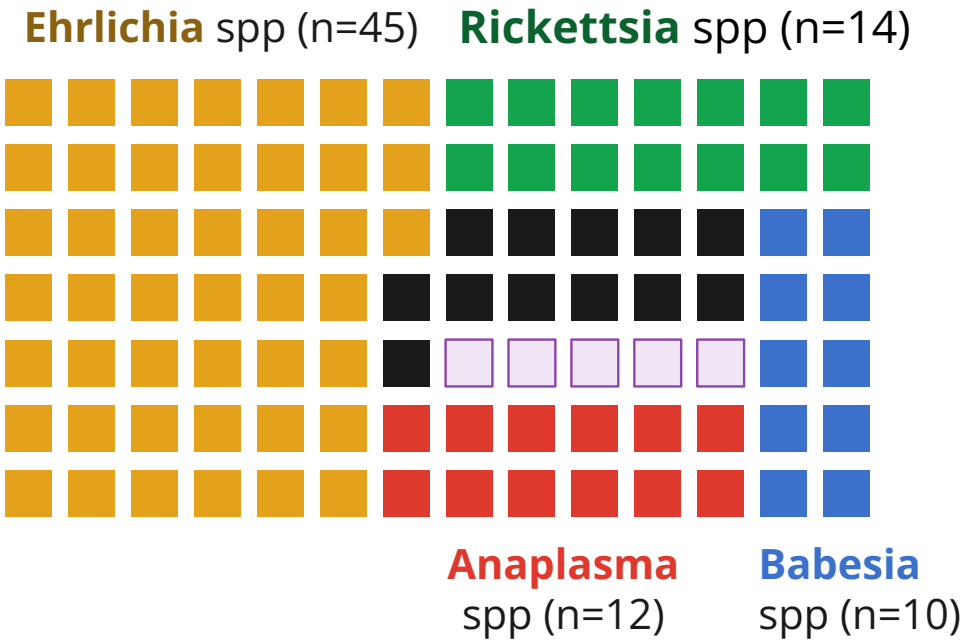
- **Babesia** spp (n=10)
- **Orientia** spp (n=8)
- **Coxiella** spp (n=5)
- **Heartland virus** (n=3)
- **Bunyavirus** spp (n=1)

But no Lyme!



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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
Lyme	**Pos**	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
EBV PCR	**Pos**
Flow cyto	Normal

Case 1: Hospital course

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Lyme	**Pos**	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	**23,648**
HSV	0
CMV	0
EBV	IgG+

Didn't send PCR :(

Bone marrow Bx	
CMV PCR	Neg
EBV PCR	**Pos**
Flow cyto	Normal

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

Learning points & take aways

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-γ / **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

Slides available on hunterratliff1.com/talk/; Citations available via QR code or via the "citations" button on the website