

WEST COAST TID CONFERENCE

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IMMUNOCOMPROMISED HOST INFECTIOUS DISEASE FELLOW

STANFORD UNIVERSITY

PMH

■-year-old ■ with a history of:

1. SLE on Hydroxychloroquine and monthly Anifrolumab
2. Sjogren's disease
3. Pulmonary coccidioidomycosis s/p 1 year fluconazole 2018 (no records available)

HPI (HD-I)

- Presented with fevers, jaundice, change in mental status
- Found to have shock and intubated for airway protection
- Started on Pip-tazobactam, IV Vancomycin
- Micro testing negative so far: blood cultures, urine culture, RPP, acute hepatitis panel, HIV ag/ab.

INVESTIGATIONS (HD-I)

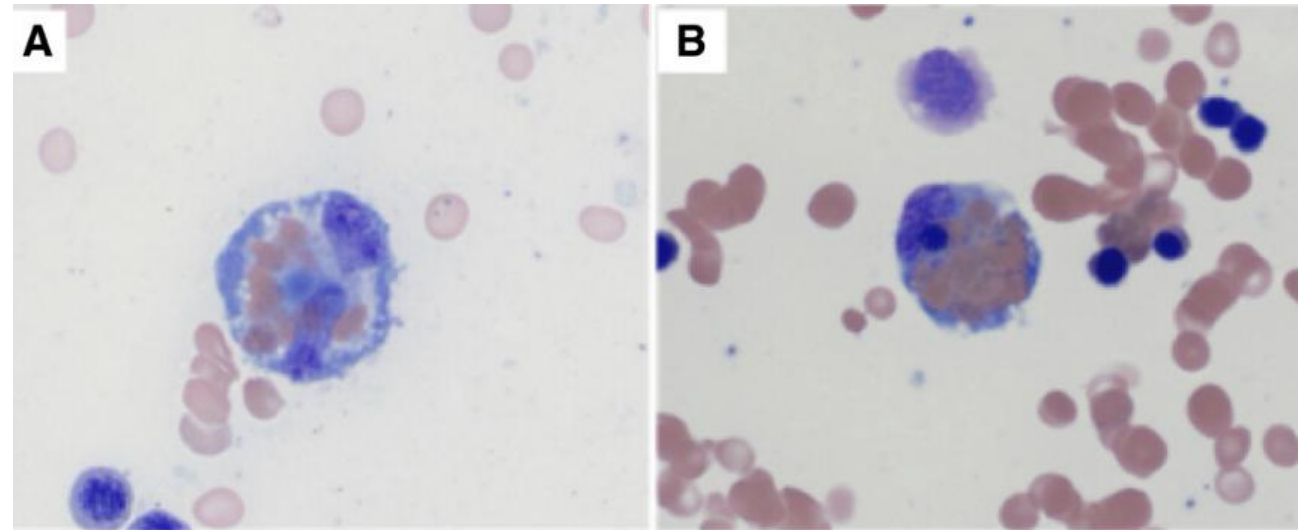
- LFT's AST >7000, ALT 5958, T bili 6.9, INR 4.6.
- CT CAP: no lung abnormalities, patchy abnormal hepatic enhancement, indeterminate for abscesses.
- MRI abdomen: multiple peripheral hypoattenuating areas in the liver with no corresponding T2 signal abnormalities, concerning for areas of infarct.

INFLAMMATORY MARKERS (HD-I)

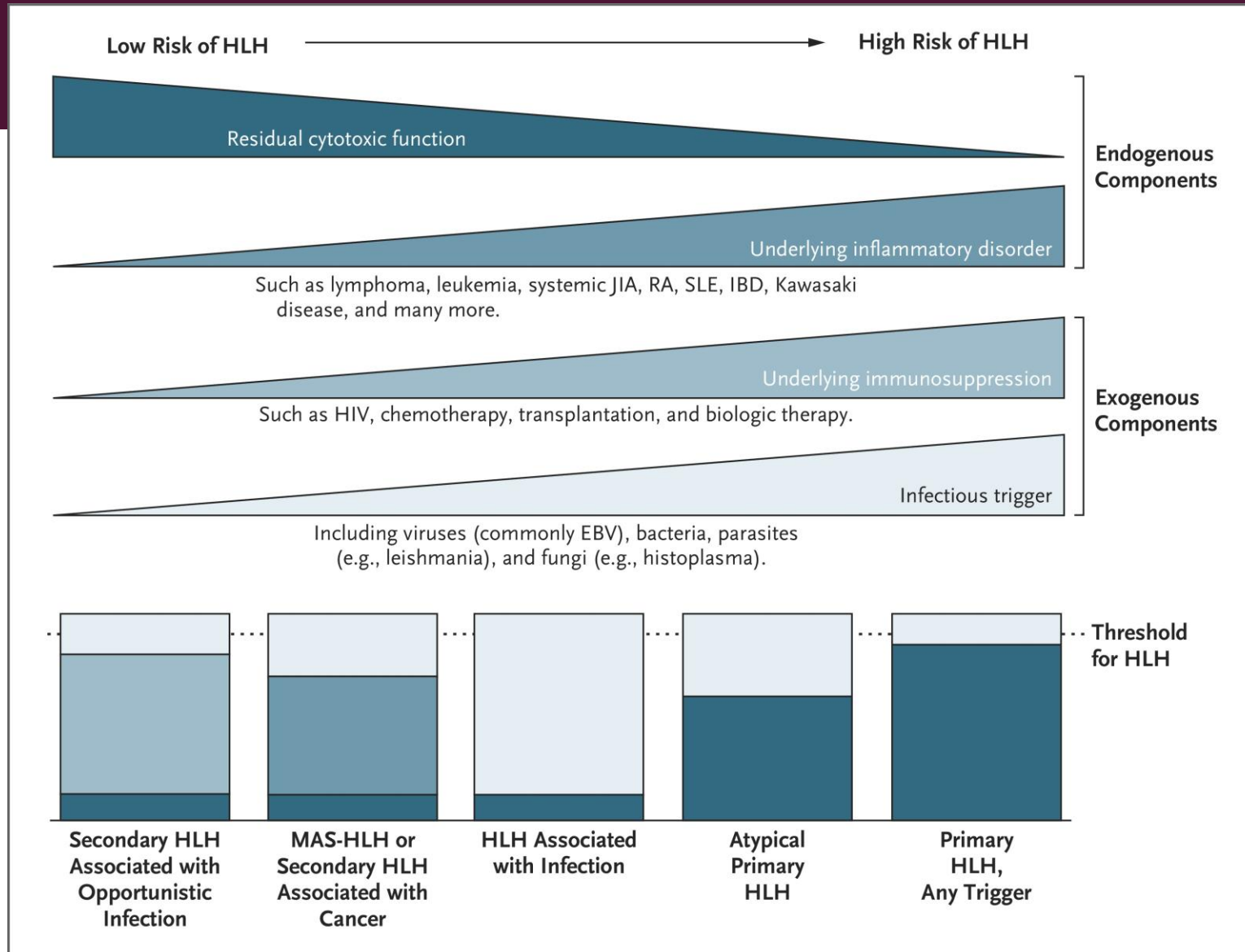
<u>Parameter</u>	<u>Result</u>	<u>Status</u>	<u>Reference Range</u>
Ferritin	28,854	(H)	13 - 150 ng/mL
Triglyceride	380	(H)	<150 mg/dL
Fibrinogen	56	(LL)	234 - 395 mg/dL
D-Dimer	>20.00	(H)	<0.50 ug/mL
CXCL9	45,878	(H)	<769 pg/mL
IL-2RA, soluble	17,851	(H)	214 - 1910 pg/mL
IL-18	5,823	(H)	82 - 344 pg/mL

BONE MARROW BIOPSY (HD-2)

- Florid nucleated hemophagocytosis
- No findings of malignancy
- Highly activated CD8 cells

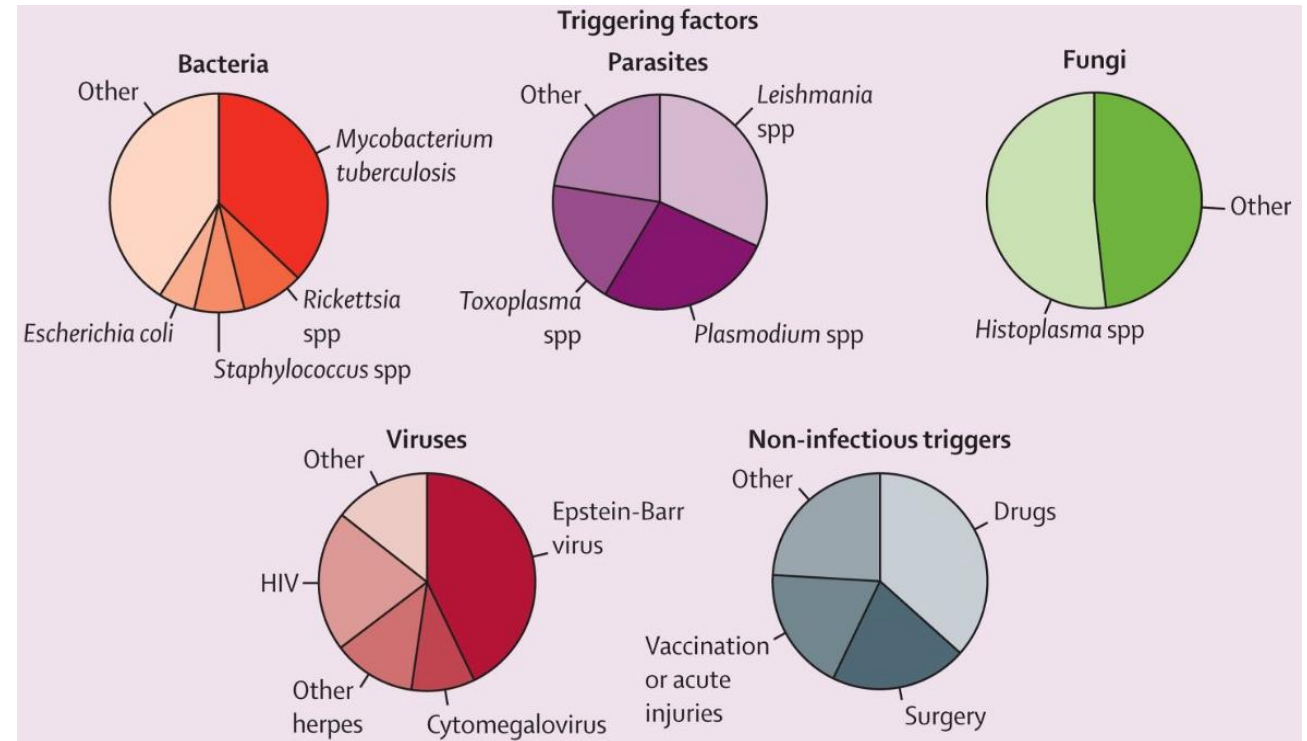


SOURCE: <https://onlinelibrary.wiley.com/doi/10.1111/his.14591>

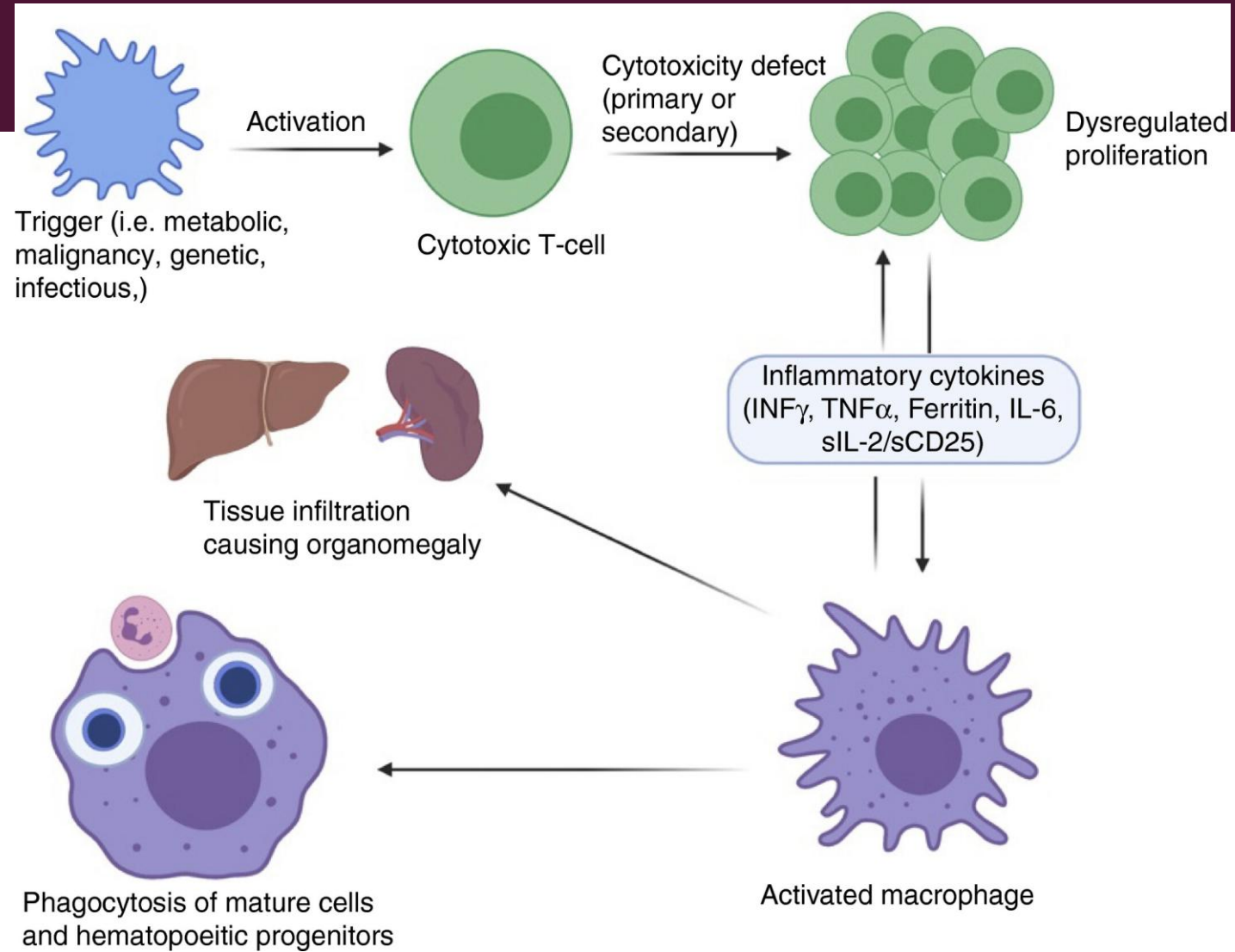


SECONDARY HLH TRIGGERS

- Infections (50%), cancers (28%), and autoimmune diseases (12%).
- The most common infectious triggers Epstein Barr virus (EBV) (25%), bacteria (20%), and cytomegalovirus (7%).



SOURCE: <https://onlinelibrary.wiley.com/doi/10.1111/his.14591>



HLH MANAGEMENT (HD-1, 2)

- Steroids (IV Solumedrol 1g/d)
- Anakinra (IL-1 receptor antagonist)
- IVIG 2g/kg over 2 days
- Emapalumab (IFN-Gamma neutralizing mAb)
- Etoposide (Topoisomerase II inhibitor)

Due to ALF (MELD 30) : Listed status 7 for OLT while awaiting HLH improvement

POLL QUESTION

What antimicrobial prophylaxis would you recommend in this patient?

- A)** PJP and mold
- B)** HSV/VZV prophylaxis and CMV monitoring
- C)** PJP, mold, and herpesvirus prophylaxis/surveillance
- D)** Bacterial (*Pseudomonas* coverage) and mold prophylaxis only

ANTIMICROBIAL PROPHYLAXIS

- **Secondary infections:** Major cause of fatality and may erroneously be diagnosed as HLH relapse.
- **The Challenge:** HLH treatments severely deplete leukocytes (T/B lymphocytes and granulocytes).
- **Recommended Prophylaxis:**
 - **Pneumocystis jirovecii**
 - **Fungal Infections:** Mold coverage recommended.
 - **Viral Infections:** HSV/VZV

EMAPALUMAB

- IFN-Gamma neutralizing mAb
 - IFN-Gamma critical against specific intracellular pathogens- Mycobacteria, HSV/VZV, Histoplasma (avoid)
 - Screen for latent TB
 - Do not administer live or live-attenuated vaccines for at least 4 weeks after the last dose

DURATION OF PROPHYLAXIS

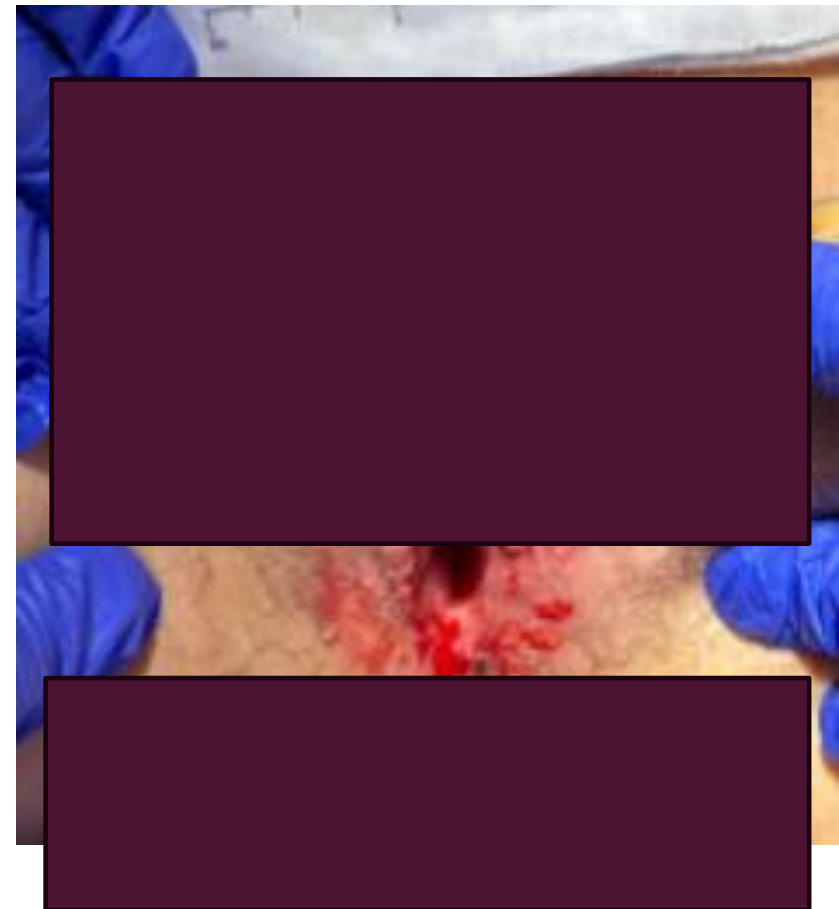
- Individualized based on the degree of ongoing immunosuppression, concurrent therapies (e.g., dexamethasone, etoposide).
- Whether proceeding to HSCT, which would carry its own prophylaxis requirements.

PROPHYLAXIS (HD-2)

- Viral: Acyclovir 125 mg/m² IV q12h (CRRT)
- PJP: Bactrim I SS daily
- Fungal: Caspofungin 50 mg daily

VULVOVAGINAL LESIONS (HD-3)

- Noted to have vulvovaginal erosions
- PTA HSV 1&2 IgG were negative.



POLL QUESTION

What is the most appropriate next step in managing this patient's vulvovaginal lesions?

- A)** Initiate empiric broad-spectrum antibacterial and antifungal therapy
- B)** Swab the lesions for HSV-1/2 PCR and continue antiviral prophylaxis.
- C)** Treat empirically with high-dose topical corticosteroids for suspected autoimmune ulceration.
- D)** Swab the lesions for HSV-1/2 PCR and initiate empiric intravenous Acyclovir.

VULVOVAGINAL LESIONS (HD-3)

- Swabbed for HSV
- Switched to IV Acyclovir 10 mg/kg every 12 hours (CRRT dosing)
- Discussion with hematology– held Emapalumab, Etoposide

RESULTS (HD-4)

- Swabs from vulvo-vaginal lesion: Positive for HSV-I
- Plasma HSV-I PCR positive (with very low CT)

HSV SHIFT

- Increased incidence of HSV-I genital herpes at sexual debut
 - Declining childhood seroprevalence of HSV-I (improved hygiene and living conditions reducing childhood oral HSV-I transmission)
 - Adolescents without protective antibodies

- HSV-I now accounts for at least half of all first-episode genital herpes cases in the U.S.
 - 70% in some populations (young heterosexual women aged 18–22, non-Hispanic whites, and men who have sex with men).

Component	Standard HLH (e.g., EBV)	HSV-Triggered HLH
Antiviral therapy	Supportive role	Primary treatment — high-dose IV acyclovir
Etoposide	First-line for severe/EBV-HLH	Generally avoid — not indicated for non-EBV infections
Glucocorticoids	Standard component	Cautious use; consider if severe inflammation persists
Anakinra	Emerging first-line for secondary HLH	Reasonable adjunct — immunomodulation without immunosuppression
IVIg	Adjunctive	Adjunctive — safe, no immunosuppression
Cyclosporine	Used in some protocols	Generally avoid in active infection
Emapalumab	Refractory HLH	Caution — herpes viruses listed as specific infection risk

CLINICAL COURSE (HD-5)

- Found to have bowel ischemia in the setting of shock and TMA
- S/p total colectomy and removal of terminal ileum

HISTOPATHOLOGY (HD-10)

- Intra-op liver biopsy:
 - Extensive coagulative necrosis with viral cytopathic changes in the necrotic cells.
 - Approximately 70% of the normal liver parenchyma replaced by necrosis.
 - IHC for HSV was positive.

- Intestinal biopsy: ischemic changes, HSV IHC negative

	Latest Reference Range & Units	01/12/26 19:36	01/13/26 03:40
Bilirubin Total	<1.2 mg/dL	14.8 (H)	14.3 (H)
AST	10 - 35 U/L	267 (H)	230 (H)
ALT	10 - 35 U/L	271 (H)	238 (H)
Alk P'TASE, Total, Ser/Plas	35 - 105 U/L	97	93

HISTOPATHOLOGY (HD-10)

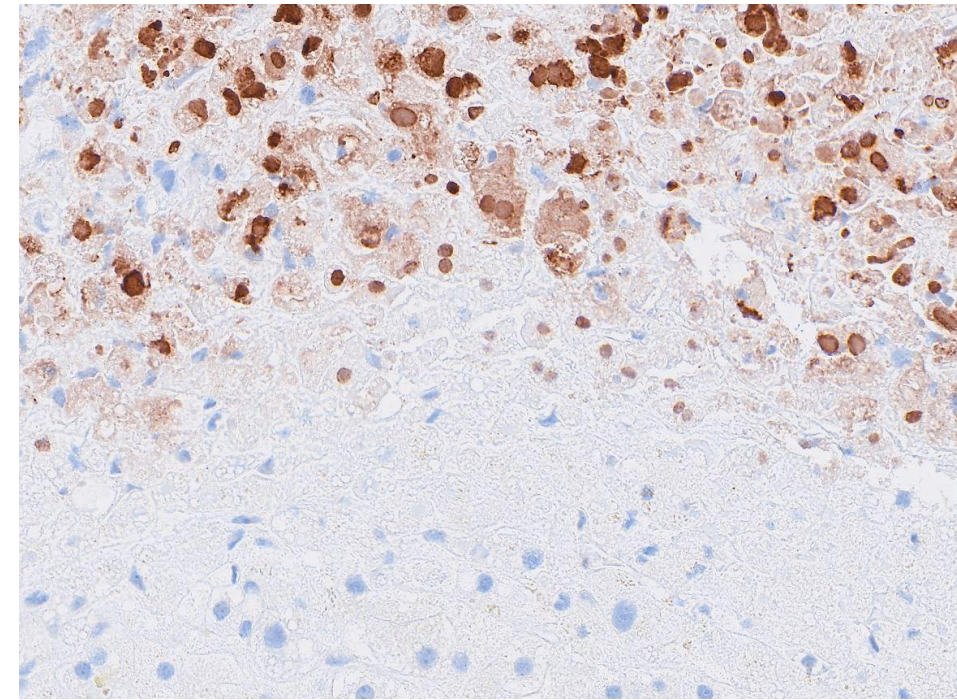
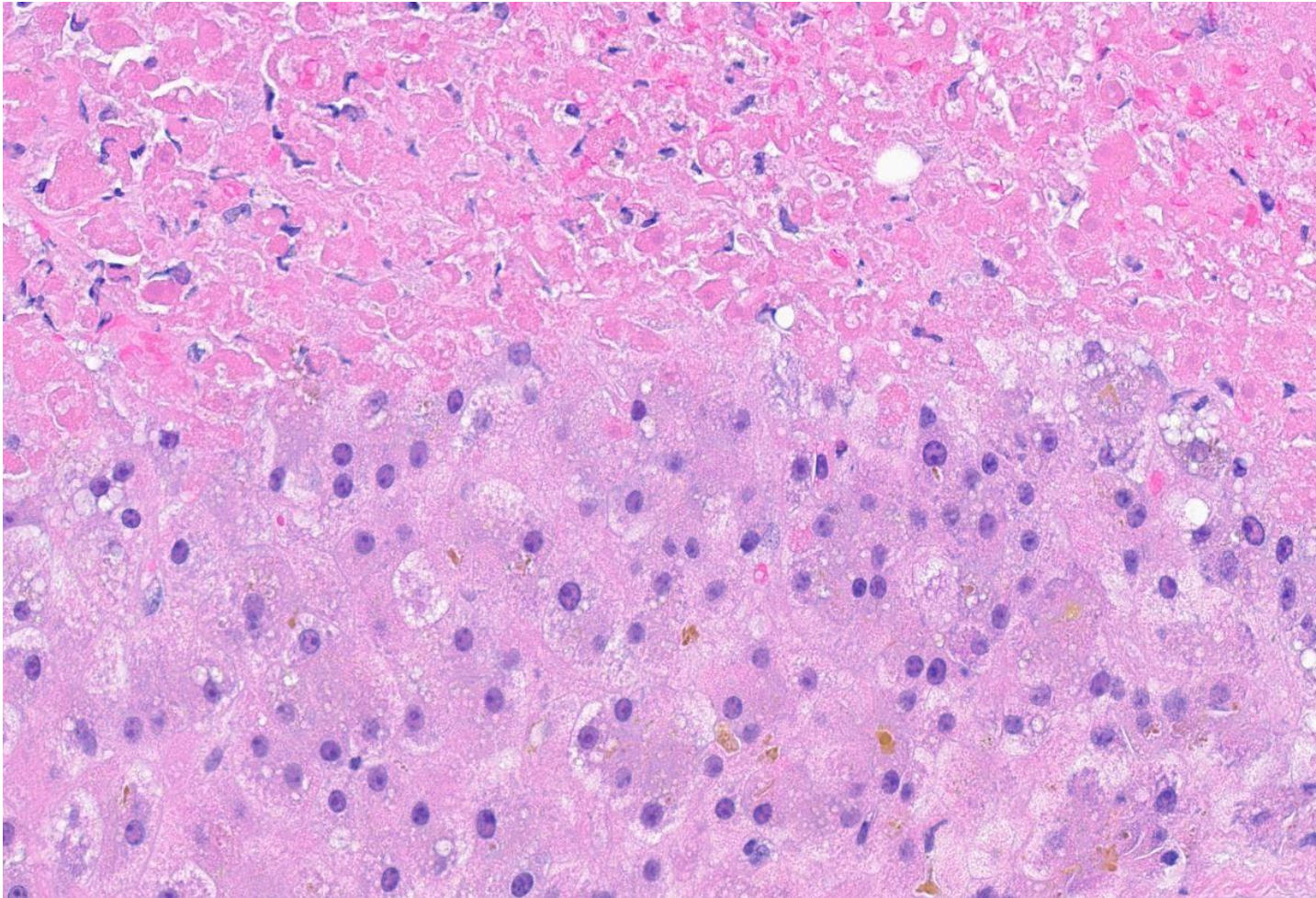
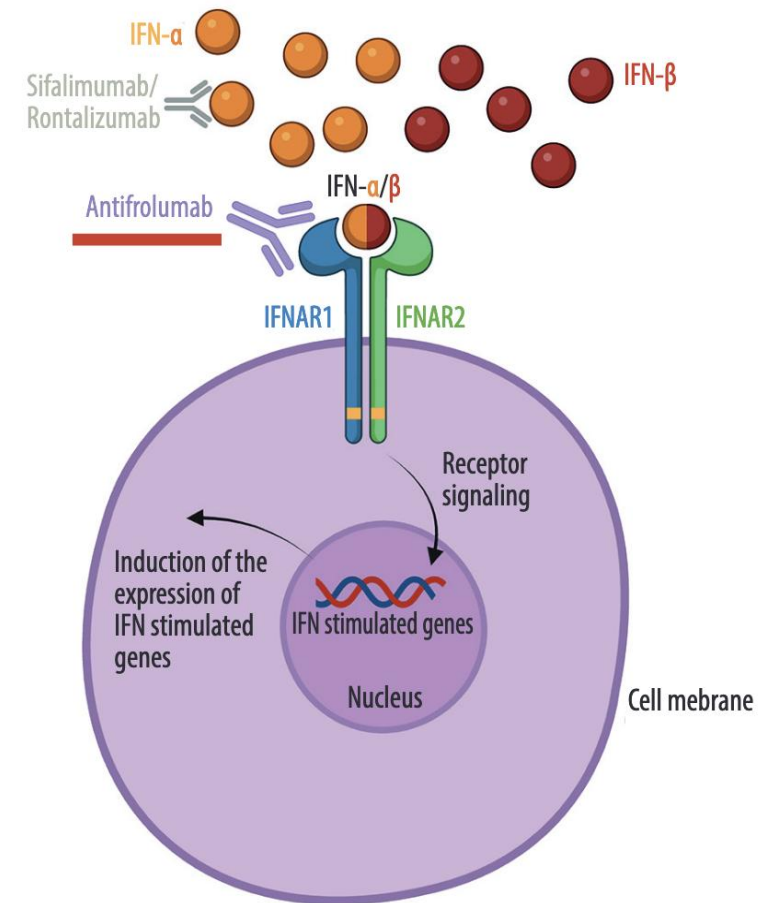


Image Courtesy: Dr. John Patrick Higgins, Professor of Pathology, Stanford Medicine.

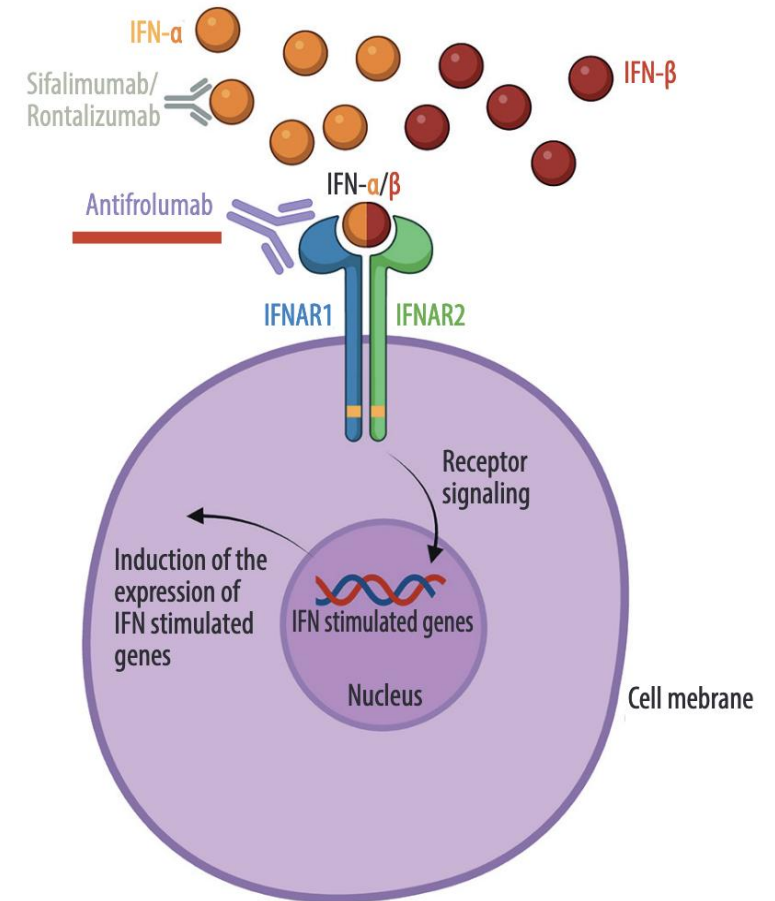
ANIFROLUMAB

- Antagonist of type I interferon receptor (IFNAR)
- Approved moderate to severe SLE (2021)
- Pooled 52-week data from 925 adults with moderate to severe SLE from across the TULIP 1, TULIP 2, and MUSE trials- AE
 - Anifrolumab vs placebo recipients included upper respiratory tract infection (34% vs 23%), herpes zoster (6.1% vs 1.3%).



ANIFROLUMAB

- Case report from Aarhus University, Denmark: 32-year-old woman on Anifrolumab for SLE with disseminated HSV-2, treated successfully with ACV.
- Disseminated HSV infection reported in children with complete deficiency of type I IFN receptor subunits.
- Also among the indigenous people of Polynesia and Arctic ancestry, where loss-of-function alleles of these genes are relatively common.



HSV-ACUTE LIVER FAILURE

- Early IV acyclovir is indicated if suspected, best chance for a good outcome.
- Carries a poor prognosis.
- Based on the analysis of reported cases from the early 2000s, risk factors for death or need for LT:
 - Male, older, or immunocompromised
 - ALT >5,000 IU/L, Platelets <75 × 10³/L, Coagulopathy
 - Encephalopathy

POLL QUESTION

What is the optimal timing for liver transplantation evaluation in a patient with HSV-induced acute liver failure?

- A)** After completing a 14-day course of intravenous acyclovir
- B)** Only after primary lesions have fully resolved
- C)** After demonstrating 7 days of clinical stability on intravenous acyclovir
- D)** As soon as possible

LIVER TRANSPLANT

- ACG/AGA recommend LT in HSV hepatitis as "rescue therapy" when patients progress to ALF.
- No defined optimal timing window, early transplant evaluation is critical given the rapid clinical deterioration.
- Children have significantly better survival after LT (69% vs 38% in adults, 5-year survival)
- The ACG recommends lifelong antiviral suppressive therapy after liver transplantation for HSV-induced acute liver failure due to the risk of recurrence.

HSV HEPATITIS CASE REVIEW

- A case report by Juan Ambrosioni et al (2011) reviewed 149 cases of HSV hepatitis that have been reported:
 - Most during primary infection
 - More frequent in immunocompromised hosts- 80 out of the 149 (54%)
 - 55% of cases (82/149) were diagnosed at autopsy.
 - Liver transplantation for HSV hepatitis was performed in 10 cases
 - Out of 10 LT, 6 died within the first year (85% expected 1-year survival after LT)
 - However, in only one case was death considered related to recurrent HSV infection and multi-organ failure.
 - Several cases showed a significant reduction in viral load post-LT. Could suggest liver being a major reservoir.

CLINICAL COURSE

AST		ALT		Alk P'TASE, Total, Ser/Plas		Bilirubin Total		Ferritin	
Ref. Range & Units	10 - 35 U/L	Ref. Range & Units	10 - 35 U/L	Ref. Range & Units	35 - 105 U/L	Ref. Range & Units	<1.2 mg/dL	Ref. Range & Units	13 - 150 ng/mL
01/12/26	19:36	267 ▲ *	01/12/26	19:36	271 ▲ *	01/15/26	03:30	10.5 ▲ *	
01/12/26	16:11	257 ▲ *	01/12/26	16:11	254 ▲ *	01/14/26	09:49	10.7 ▲ *	
01/12/26	09:18	312 ▲ *	01/12/26	09:18	303 ▲ *	01/14/26	03:36	11.6 ▲ *	
		312 ▲ 📄 *			303 ▲ 📄 *	01/13/26	20:19	13.1 ▲ *	
01/12/26	03:57	327 ▲ *	01/12/26	03:57	320 ▲ *	01/13/26	17:36	12.8 ▲ *	
01/11/26	23:33	466 ▲ *	01/12/26	03:57	320 ▲ *	01/13/26	09:29	13.7 ▲ *	
		466 ▲ *	01/11/26	23:33	392 ▲ *	01/13/26	03:40	14.3 ▲ *	
					392 ▲ *	01/12/26	19:36	14.8 ▲ *	
01/11/26	15:37	804 ▲ *	01/11/26	15:37	851 ▲ *	01/12/26	16:11	13.6 ▲ *	
01/11/26	09:33	861 ▲ *	01/11/26	09:33	837 ▲ *	01/12/26	09:18	14.7 ▲ *	
01/11/26	04:44	970 ▲ *	01/11/26	09:33	837 ▲ *			14.7 ▲ *	
01/10/26	23:35	1,112 ▲ *	01/11/26	04:44	844 ▲ *	01/12/26	03:57	13.4 ▲ *	
01/10/26	16:19	1,255 ▲ *	01/10/26	23:35	978 ▲ *	01/11/26	23:33	12.9 ▲ *	
01/10/26	09:16	1,504 ▲ *	01/10/26	23:35	978 ▲ *			12.9 ▲ *	
01/10/26	03:20	1,762 ▲ *	01/10/26	16:19	1,021 ▲ *	01/11/26	15:37	16.8 ▲ *	
01/09/26	21:35	1,923 ▲ *	01/10/26	16:19	1,021 ▲ *	01/11/26	09:33	14.5 ▲ *	
01/09/26	15:15	2,143 ▲ *	01/10/26	09:16	1,185 ▲ *	01/11/26	04:44	14.8 ▲ *	
01/09/26	09:54	2,207 ▲ *	01/10/26	03:20	1,293 ▲ *	01/10/26	23:35	13.2 ▲ *	
01/09/26	03:39	2,917 ▲ *	01/09/26	21:35	1,294 ▲ *	01/10/26	16:19	13.5 ▲ *	
01/08/26	21:30	3,648 ▲ *	01/09/26	15:15	1,365 ▲ *	01/10/26	09:16	12.1 ▲ *	
01/08/26	16:17	3,648 ▲ *	01/09/26	09:54	1,476 ▲ *				
01/08/26	09:37	4,419 ▲ *	01/09/26	03:39	1,843 ▲ *				
01/08/26	03:43	4,913 ▲ *	01/08/26	21:30	2,220 ▲ *				
01/07/26	21:46	5,766 ▲ *	01/08/26	16:17	2,019 ▲ *				
01/07/26	17:04	6,852 ▲ *	01/08/26	09:37	2,398 ▲ *				
01/07/26	10:01	>7,000 ▲ *	01/08/26	03:43	2,444 ▲ *				
			01/07/26	21:46	2,713 ▲ *				

CLINICAL COURSE (HD-16)

Patient passed from PEA arrest secondary to tension pneumothorax.

LEARNING POINTS

- HSV hepatitis is a rare but catastrophic cause of acute liver failure.
- Immunocompromised hosts face a substantially higher risk of rapid progression to fulminant hepatic necrosis.
- Infection is the leading trigger for secondary HLH.
- Proactively initiate antimicrobial prophylaxis for PJP, invasive mold, and HSV/VZV while treating HLH.

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