Hemophagocytic LymphoHistiocytoctosis

a simple summary of a complicated problem

BACKGROUND:

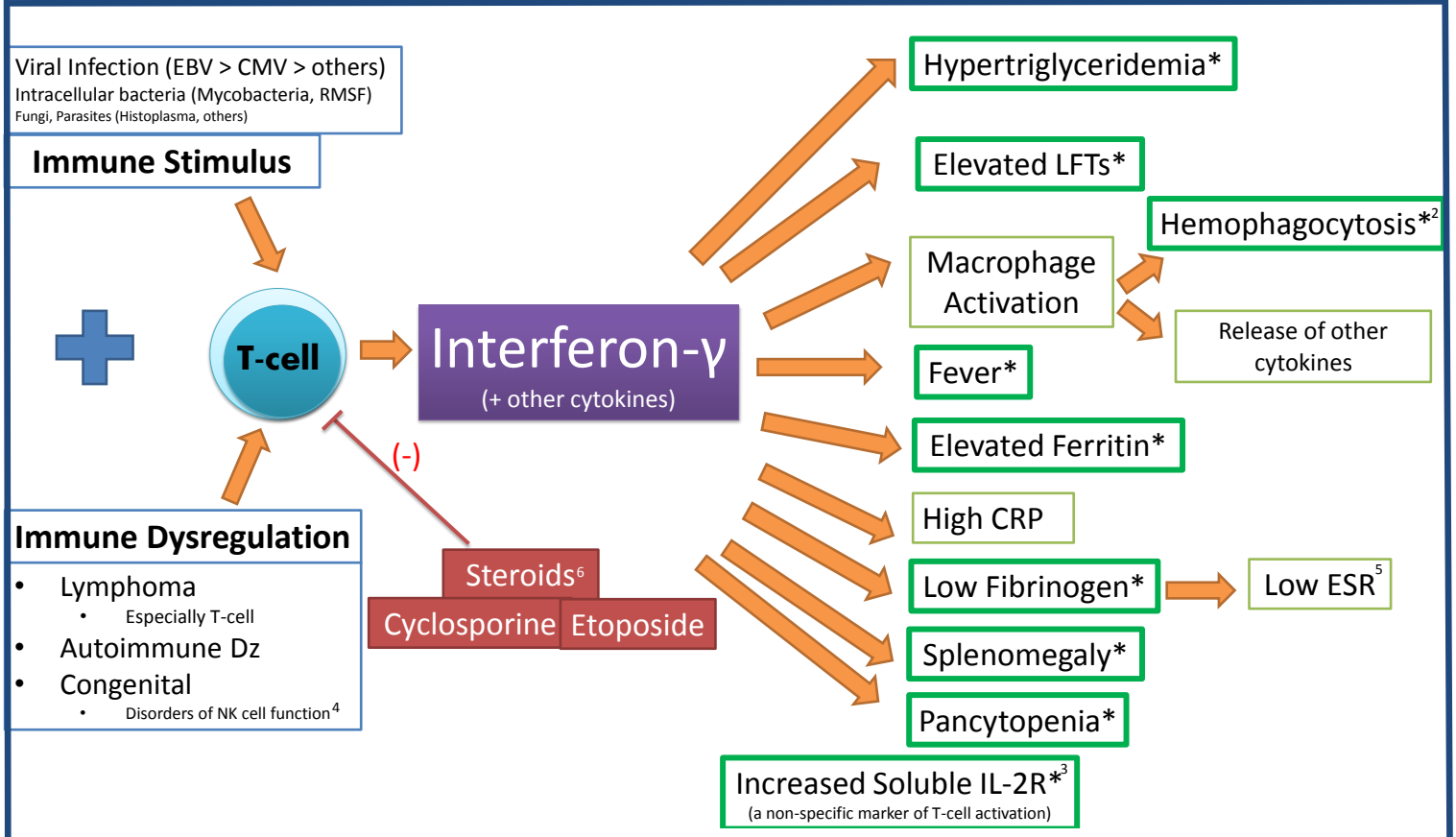
- When normal individuals are infected by a virus or an intracellular pathogen (e.g TB, anaplasma, histoplasma, etc.) their T-cells release **Interferon Gamma** to *activate their macrophages*.
- Interferons are responsible for the "flu-like illness" that you can see in many infections. In conditions with sustained high levels of interferon you can see pancytopenia (due to **interfer**ence with bone marrow production), transaminase elevation, and high triglycerides.

DEFINITION:

- HLH (hemophagocytic lymphohistiocytosis) is a *syndrome* characterized by an **excessive inflammatory response** (usually to an infection) where the inflammation becomes worse than the infection itself. HLH occurs in patients who have some kind of immune dysregulation at baseline (autoimmune dz, lymphoma, etc.).
- The inclusion criteria for the HLH-2004 study are commonly used as diagnostic criteria; see **HLH-2004 Diagnostic Criteria*** below

PATHOPHYSIOLOGY:

- Interferon Gamma is one of the central mediators of HLH. We infer this because patients given Interferon Gamma can develop all the signs and symptoms of HLH (see the drug information sheet for IFN-γ on the next page).



NOTES:

1. "Macrophage activation syndrome" or "hemophagocytic syndrome" are older terms for HLH. These terms are often still used to refer to HLH that occurs in patients with an underlying autoimmune disease. The terminology is unimportant, the pathophysiology is the same… IFN-γ mediated cytokine storm.
2. The Hemophagocytosis you can see in the bone marrow of HLH is just a marker of excessive macrophage activation. It is not the cause of the disease and is not specific and only ~70-80% sensitive. It can also be seen in situations where macrophages are being appropriately activated (e.g severe infection)
3. One of the diagnostic criteria for HLH is Increased soluble IL-2 receptor (CD25). Soluble IL-2R is a marker of T-cell activation, but it is not the cause of or a mediator of the disease.
4. Kids with familial HLH are born with a problem with their NK cells (due to various mutations that affect the function of perforin or granzymes). There are NK cells around but they don't work. Paradoxically, this results in overwhelming immune responses. There are various hypotheses about why this occurs, perhaps the NK cells can't clear virally infected cells so the t-cells keep pumping out interferon. Perhaps the normally activated macrophages aren't being eliminated by the NK cells so they stay activated too long.
5. HLH is one of the conditions that can cause discordant ESRs and CRPs. The CRP is high due to release in the liver from the acute phase response. ESR is low because fibrinogen is low. Lupus is the opposite where ESR is typically elevated, but CRP is often normal unless the SLE patient concurrently has an infection.
6. HLH is treated with **T-cell suppressive** therapies to block the IFN release such as steroids, cyclosporine, and etoposide. It's not clear that these drugs directly affect the macrophages.

Hemophagocytic LymphoHistocytoctosis

a simple summary of a complicated problem

Interferon gamma-1b: Drug information Lexicomp®

Fever (52%),

Additional adverse reactions noted at doses >100 mcg/m^2 administered 3 times weekly: ALT increased, AST increased, autoantibodies increased, bronchospasm, chest discomfort, confusion, dermatomyositis exacerbation, disorientation, DVT, gait disturbance, GI bleeding, hallucinations, heart block, heart failure, hepatic insufficiency, hyperglycemia, hypertriglyceridemia, hyponatremia, hypotension, interstitial pneumonitis, lupus-like syndrome, MI, neutropenia, pancreatitis (may be fatal), Parkinsonian symptoms, PE, proteinuria, renal insufficiency (reversible), seizure, syncope, tachyarrhythmia, tachypnea, thrombocytopenia, TIA

Concerns related to adverse effects:

- Bone marrow suppression: Dose-related reversible neutropenia and thrombocytopenia (may be severe) have been reported; use caution in patients with myelosuppression.
- CNS effects: Neurologic disorders (ie, decreased mental status, gait disturbances, dizziness) have been noted at the higher doses (>250 mcg/m^2/day); most of these abnormalities were reversible within a few days after dose reduction or discontinuation. Use with caution in patients with a history of seizure disorder or compromised CNS function.
- Flu-like symptoms: Acute and transient flu-like symptoms (eg, fever, headache, chills, myalgia, fatigue) have been noted at the higher doses (>250 mcg/m^2/day) and may exacerbate preexisting cardiovascular disorders; some of the flu-like symptoms may be minimized by bedtime administration.
- Hepatotoxicity: Elevations of AST and/or ALT (up to 25-fold) have been observed and were reversible with dose reduction or interruption of treatment. Incidence may be increased in children <1 year of age; perform monthly liver function assessments in this age group; modify dosage if severe elevations of liver enzyme develop.

Useful tables from "Adult Haemophagocytic Syndrome" *Lancet* April 2014

Diagnostic guidelines for haemophagocytic lymphohistiocytosis used in the HLH-2004 trial

Molecular diagnosis consistent with HLH

- Pathological mutations of *PRF1*, *UNC13D*, *STXBP1*, *RAB27A*, *STX11*, *SH2D1A*, or *XIAP*

OR

Five of the following criteria

- Fever of 38·5°C or more
- Splenomegaly
- Cytopenias (affecting at least two of three cell lineages in the peripheral blood)
  - Haemoglobin <5·59 mmol/L (infants <4 weeks, <6·21 mmol/L)
  - Platelets <100 cells per 10^9/L
  - Neutrophils <1 cell per 10^9/L
- Hypertriglyceridaemia (fasting, >3 mmol/L) and hypofibrinogenaemia (<1·7 mmol/L), or both
- Haemophagocytosis in bone marrow, spleen, lymph nodes, or liver
- Low or absent natural killer-cell activity
- Ferritin greater than 1123·5 pmol/L
- Increased soluble CD25 concentration (alpha chain of soluble interleukin 2 receptor)

	Patients (N=775)
Epidemiological features	
Mean age (range)	49·03 years (41–67 years)
Women	275/746 (37%)
Clinical features	
Fever	524/546 (96%)
Splenomegaly	420/609 (69%)
Hepatomegaly	389/580 (67%)
Pulmonary involvement	61/145 (42%)
Peripheral adenopathies	91/277 (33%)
Neurological involvement	41/161 (25%)
Skin lesions	63/250 (25%)
Gastrointestinal involvement	27/149 (18%)
Renal involvement	9/56 (16%)
Encephalopathy	9/102 (9%)
Haematological and coagulation features	
Anaemia	
Haemoglobin <5·6 mmol/L	122/181 (67%)
Haemoglobin <4·3 mmol/L	33/151 (22%)
Thrombocytopenia	
<100 000 cells per mm^3	178/227 (78%)
<10 000 cells per mm^3	10/168 (6%)
Leukopenia <4000 cells per mm^3	198/285 (69%)
Neutropenia	
<1000 cells per mm^3	61/144 (42%)
<500 cells per mm^3	15/64 (23%)
Coagulopathy	91/153 (59%)
D-dimer >54·8 mmol/L	24/49 (49%)
Fibrinogen <4·4 µmol/L	39/81 (48%)
Disseminated intravascular coagulation	40/101 (40%)