

RAISED **FERRITIN IN DENGUE** FEVER AND ITS IMPLICATIONS

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Patient	Age	Sex	DOA	Dengue test	Shock	Organ failure	
P1	8YR	M	D10	Positive	Yes	Liver/ Kidney/brain	
P2	9YR	M	D8	Positive	Yes	Liver/ kidney/Brain	
P3	10 M	M	D12	Positive	No	Worsening transaminase	
P4	11 M	M	D5	Positive	Yes	Liver/kidney	
P5	7M	M	D4	Positive	Yes	Liver/Brain	
P6	8M	F	D5	Positive	Yes	No	

Patient	Age	Sex	DOA	Dengue test	Shock	Organ failure	Peak ferritin
P1	8YR	M	D10	Positive	Yes	Liver/ Kidney/brain	71830 (D10)
P2	9YR	M	D8	Positive	Yes	Liver/ kidney/Brain	24125 (D6)
P3	10 M	M	D12	Positive	No	Worsening transaminase	19304 (D9)
P4	11 M	M	D5	Positive	Yes	Liver/kidney	85030 (D7)
P5	7M	M	D4	Positive	Yes	Liver/Brain	48900 (D5)
P6	8M	F	D5	Positive	Yes	No	23338 (D5)

ACUTE PHASE REACTANT

POSITIVE

- CRP
- Mannose binding protein
- **Ferritin**
- Complement factors
- Ceruloplasmin
- Haptoglobin
- ESR

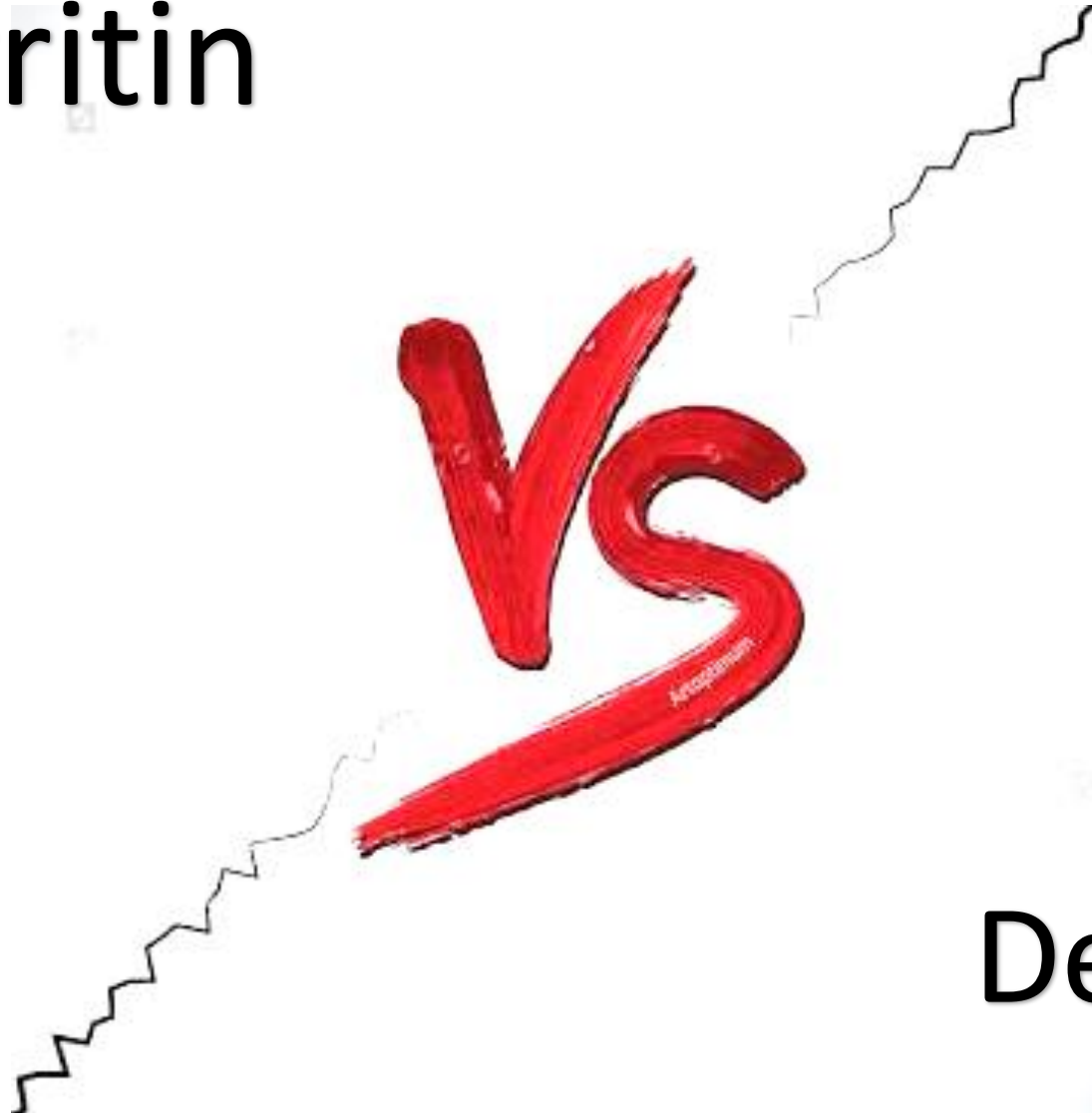
NEGATIVE

- Albumin
- Transferrin
- Retinol binding protein
- Antithrombin
- Transthyretin

Ferritin

vs

Dengue



1.High ferritin can be a marker to differentiate dengue fever from other febrile illnesses.

Ferritin serves as a significant marker for differentiating between dengue fever and fever of other etiology , even in absence of NS1 Ag or a positive IgM antibody for dengue

Serum ferritin: A backstage Weapon in diagnosis of dengue

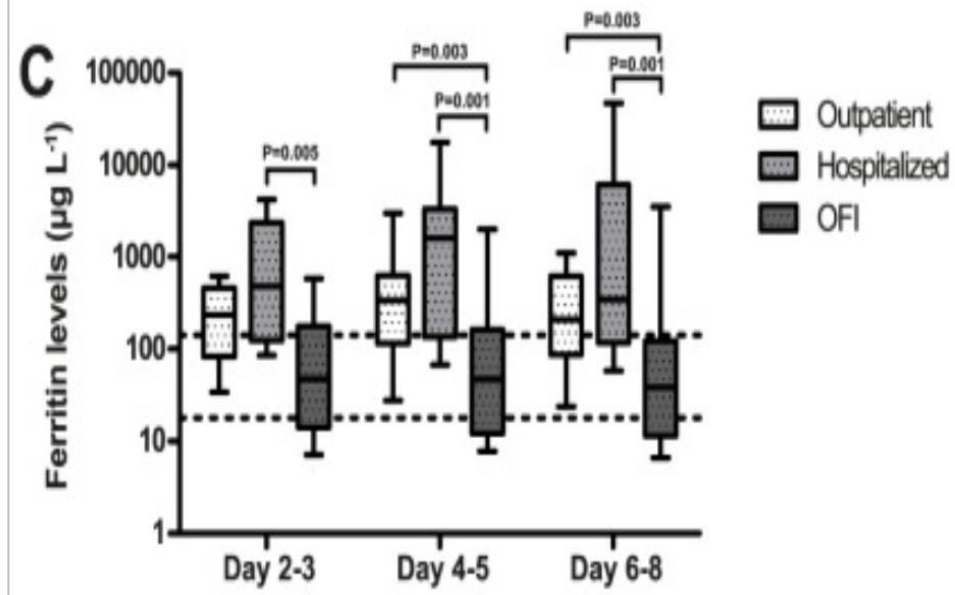
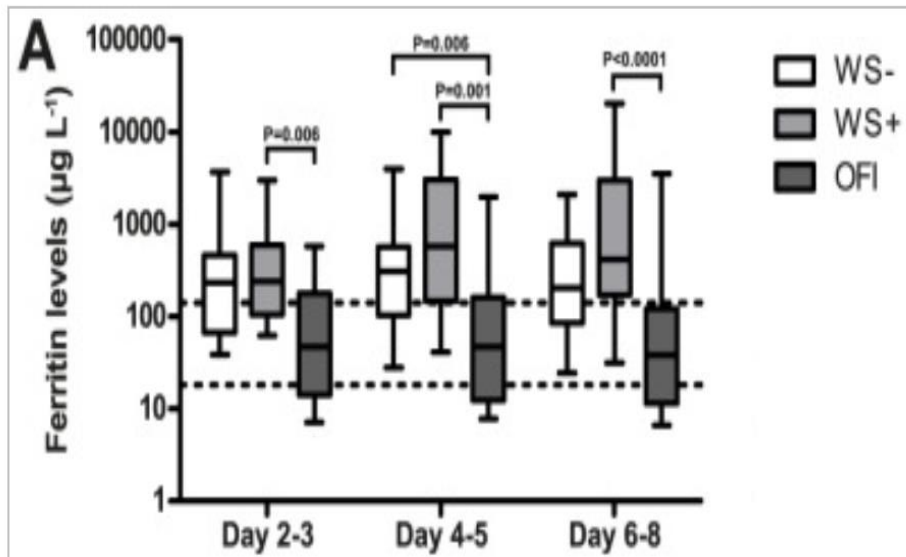
Chaoudhari SB, Bhattacharya S, Interdisciplinary perspective on infevctious disease, Volume 2017 (2017), article ID 7463489, 6 pg

2.High serum ferritin indicates severe dengue infection.

Ferritin level can predict disease severity in dengue fever with highest sensitivity and specificity 76.9 and 83.3 %, respectively.

Ferritin levels predicts severe dengue

Soundravally R, et al, infection 2015 Feb; 43(1): 13-9



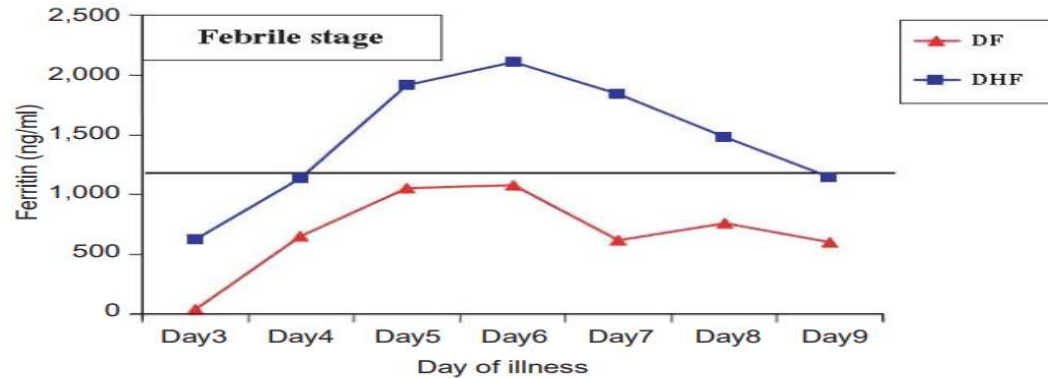


Fig 1—Comparison of median serum ferritin levels between patients with DF and DHF by day of illness after the onset of fever.

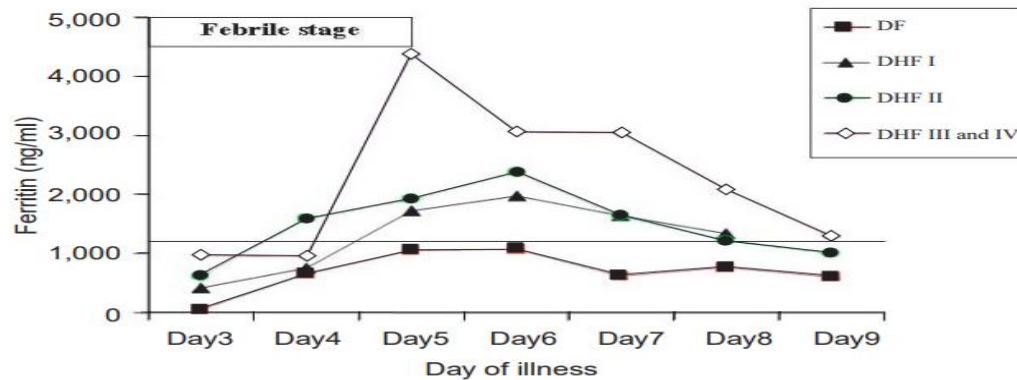


Fig 2—Comparison of median serum ferritin levels among patients with DF and DHF grades I, II, III and IV by day of illness after the onset of fever.

[Chaiyaratana W¹, Chuansumrit A, Atamasirikul K, Tangnararatchakit K. Serum ferritin levels in children with dengue infection. Southeast Asian J Trop Med Public Health. 2008 Sep;39\(5\):832-6.](#)

3. Hyperferritinaemia in Dengue Virus Infected Patients Is Associated with Immune Activation and Coagulation Disturbances

van de Weg CAM, Huits RMHG, Pannuti CS, Brouns RM, van den Berg RWA, et al. (2014) Hyperferritinaemia in Dengue Virus Infected Patients Is Associated with Immune Activation and Coagulation Disturbances. PLoS Negl Trop Dis 8(10): e3214. doi:10.1371/journal.pntd.0003214

4. Hyperferritinemia can indicate infection associated hemophagocytosis syndrome (IAHS) secondary to dengue

HLH

Macrophage activation syndrome or hemophagocytic syndrome is a severe systemic inflammatory condition due to excessive activation of T lymphocytes & macrophages leading to dysregulated immune responses.

**Hyperferritinemia is the most characteristic feature of
HLH**

[Machowicz R¹, Janka G², Wiktor-Jedrzejczak W³. Similar but not the same: Differential diagnosis of HLH and sepsis. Crit Rev Oncol Hematol. 2017 Jun;114:1-12](#)

Table 2. HLH-2004 diagnostic criteria

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:

1. A molecular diagnosis consistent with HLH is made.
2. Diagnostic criteria for HLH are fulfilled (5 of the 8 criteria below):*

Fever

Splenomegaly

Cytopenias (affecting ≥ 2 -3 lineages in the peripheral blood):

hemoglobin < 90 g/L (in infants < 4 weeks of age,

hemoglobin < 100 g/L), platelets $< 100 \times 10^9/L$,

neutrophils $< 1.0 \times 10^9/L$

Hypertriglyceridemia and/or hypofibrinogenemia: fasting

triglycerides ≥ 3.0 mmol/L (ie, ≥ 265 mg/dL), fibrinogen ≤ 1.5 g/L

Hemophagocytosis in BM, spleen, or lymph nodes

Low or absent NK-cell activity (according to local laboratory reference)

Ferritin ≥ 500 $\mu\text{g/L}$

Soluble CD25 (ie, sIL2r) ≥ 2400 U/mL†

*Supportive criteria include neurologic symptoms, cerebrospinal fluid pleocytosis, conjugated hyperbilirubinemia and transaminitis, hypoalbuminemia, hyponatremia, elevated D-dimers, and lactate dehydrogenase (see text for details). The absence of hemophagocytosis in the BM does not exclude a diagnosis of HLH.

Severe dengue... HLH?

As the dengue febrile period lasts 3-7 days, ongoing fever after 8 days with persistent cytopenias and MOD should alert clinician towards a diagnosis of HLH

Pal P, Giri PP, Ramanan AV. Dengue associated HLH: a case series. *Indian Pediatr* 2014;51:496-97.

Elevated serum ferritin > 10,000 mcg/dl – 90% sensitive and 96% specific for HLH. Should be used as screening tool for early detection of HLH, triggering further investigations.

M.R.GEORGE , Hemophagocytic lymphohistiocytosis: review of etiologies and management, *J Blood Med*, 5 (2014), pp. 69-86

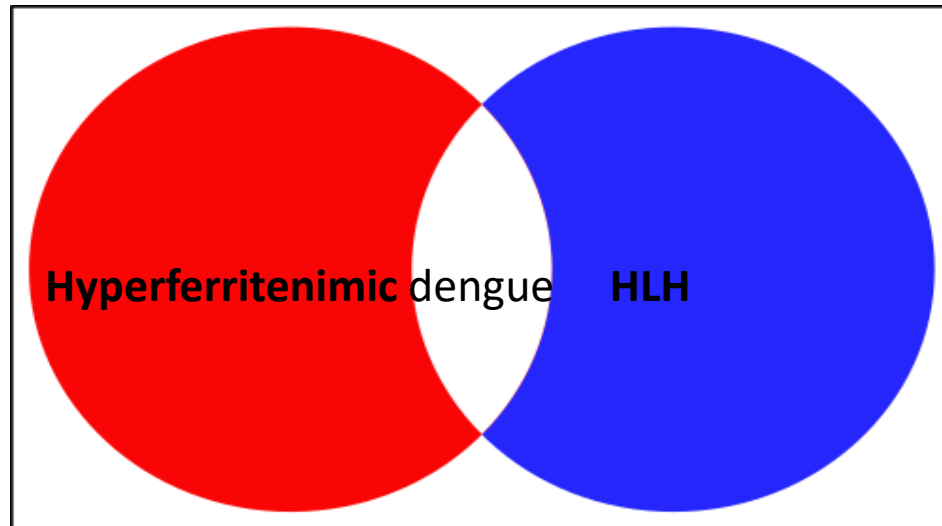
Patient	Persistent fever	Splenomegaly	Bicytopenia	Hyper TGL/ hypofibrinogenemia	BM	NK cell	Hyperferritinemia	CD 25	SUPPORTIVE	HLH Criteria (OUT OF 8)
P1	No	Yes	Yes	Yes	-	-	Yes	-	Transaminitis+ LDH +CB	4+S
P2	No	No	Yes	Yes	-	-	Yes	-	Transaminitis+ LDH +CB	3+S
P3	Yes	Yes	Yes	-	-	-	Yes	-	Transaminitis+ LDH	4+ S
P3	Yes	Yes	Yes	Yes	-	-	Yes	-	Transaminitis	5+S
P5	Yes	Yes	Yes	Yes	-	-	Yes	-	Transaminitis	5+S
P6	Yes	Yes	Yes	Yes	-	-	Yes	-	Transaminitis	5+S

Summary of clinical presentation

Patient	Age	Sex	DOA	Dengue test	Shock	Organ failure	Peak ferritin	Treatment	outcome
P1	8YR	M	D10	Positive	Yes	Liver/ Kidney/brain	71830 (D10)	IVIG + Steroids +Plasmapheresis	DIED
P2	9YR	M	D8	Positive	Yes	Liver/ kidney/Brain	24125 (D6)	IVIG + Steroids + plasmapheresis	DIED
P3	10 M	M	D12	Positive	No	Worsening transaminase	19304 (D9)	IVIG + Steroids (D9)	DC
P4	11 M	M	D5	Positive	Yes	Liver/kidney	85030 (D7)	IVIG + Steroids (D9)	DC
P5	7M	M	D4	Positive	Yes	Liver/Brain	48900 (D5)	IVIG + Steroids (D5)	DC
P6	8M	F	D5	Positive	Yes	No	23338 (D5)	IVIG + Steroids (D7)	On treatment

?Severe dengue ?HLH

- Though we treated all our patients, we admit that there is only a thin line between severe dengue with hyperferritinemia and dengue associated HLH.



- Appropriate decision should be made in each clinical situation.

Take home messages...

- High ferritin in dengue is a poor prognostic marker
- Dengue cases with high ferritin need close monitoring for progression into organ failure
- Consider HLH if fever spikes beyond 8 days, persisting cytopenias and multiorgan dysfunction
- Rule out other infectious causes of fever before diagnosing HLH
- All dengues with hyperferritinemias may not be HLH.

High ferritin in dengue - Significance....??

- ✓ ?? Magnitude of the problem in the community. Is it due to introduction of new serotype or variant of existing serotype.
- ✓ Why is there a poor outcome with MODS in these patients even when shock is controlled?
- ✓ What are the predictors of progress to fulminant liver failure?
- ✓ No current guidelines on management of these patients

Acknowledgements

- Dr.K.Satheesh, Intensivist, Apollo Children's hospital
- Dr.Saravanan Pandian, Intensivist , Apollo children's hospital

INDIVIDUAL CASE DETAILS

Persistent fever	Splenomegaly	Bicytopenia	HyperTGL/hypofibrinogenemia	BM	NK cell	Hyperferritinemia	CD 25	SUPPORTIVE	HLH Criteria (OUT OF 8)
No	Yes	Yes	Yes	-	-	Yes	-	Transaminitis+LDH+CB	4+S

- Supportive measures and CRRT were continued involving hepatology & nephrology team.
- Repeat serum ferritin was 71830 ng/ml. Haematologist was involved, etoposide was started.
- Suffered cardiac arrest on day 12 of illness within 36 hrs of stay in our hospital.

P2

Patient	Age	Sex	DOA	Dengue test	Shock	Organ failure	Peak ferritin	Treatment	outcome
P2	9YR	M	D11	Positive	Yes	Liver/ Kidney/ brain	24125 (D6)	IVIG + Steroids +Plasmapheresis	DIED

- Similar picture as P1
- Received plasmapheresis, CRRT, IVIG and steroids in referring hospital
- Shifted to our hospital for liver transplantation on D10 of illness.
- Counselling for liver transplantation, parents refused.
- Got shifted to another hospital, died within few hours.

P3

Patient	Age	Sex	DOA	Dengue test	Shock	Organ failure	Peak ferritin	Treatment	outcome
P3	10M	M	D12	Positive	No	Worsening transaminase	19304 (D13)	IVIG + Steroids	Discharged

- H/O biphasic fever & abdominal distension for 1 day.
- Malaria & scrub were ruled out. Blood cultures were sterile.
- He remained unwell, continued to have fever spikes.
- Worsening transaminases.

Persistent fever	Splenomegaly	Bicytopenia	Hyper TGL/ hypofibrinogenemia	BM	NK cell	Hyperferritinemia	CD 25	SUPPORTIVE	HLH Criteria (OUT OF 8)
Yes	Yes	Yes	-	-	-	Yes	-	Transaminitis + LDH	4+ S

P4

Patient	Age	Sex	DOA	Dengue test	Shock	Organ failure	Peak ferritin	Treatment	outcome
P4	11M	M	D5	Positive	Yes	Liver /Kidney	85030 (D7)	IVIG + Steroids (D7)	Discharged

- He had signs of circulatory shock , fluid overload and lactic acidosis (highest was 7). Not responding to fluids & blood products.
- He showed worsening bicytopenia, significant elevation in liver enzymes , prerenal AKI & significant coagulopathy.

Persist ent fever	Spleno megaly	Bicyto penia	Hyper TGL/ hypofi brinogi nemia	BM	NK cell	Hyperf erritin emia	CD 25	SUPPOR TIVE	HLH Criteri a (OUT OF 8)
Yes	Yes	Yes	Yes	-	-	Yes	-	Transami nitis	5+S

P5

Patient	Age	Sex	DOA	Dengue test	Shock	Organ failure	Peak ferritin	Treatment	outcome
P5	7M	M	D4	Positive	Yes	Liver/brain	48900 (D5)	IVIg + Steroids (D5)	DC

- Had circulatory shock with severe lactic metabolic acidosis (lactate 6).
- He also had coagulopathy (INR 2.46) & elevated liver enzymes/encephalopathy after shock resolved.
- He continued to have fever spikes.

Persistent fever	Splenomegaly	Bicytopenia	HyperTGL/hypofibrinogenemia	BM	NK cell	Hyperferritinemia	CD 25	SUPPURATIVE	HLH Criteria (OUT OF 8)
Yes	Yes	Yes	Yes	-	-	Yes	-	Transaminitis	5+S

P6

Patient	Age	Sex	DOA	Dengue test	Shock	Organ failure	Peak ferritin	Treatment	outcome
P6	8M	F	D5	Positive	Yes	No	23338 (D5)	IVIG + Steroids (D7)	On treatment

- Had persistent fever spikes >7 days , bicytopenia.
- No fever for >36 hrs
- Again spiking temperatures
- Urine cultures E.Coli ... Receiving antibiotics

Persistent fever	Spleno megaly	Bicytopenia	Hyper TGL/ hypofibrinogenemia	BM	NK cell	Hyperferritinemia	CD 25	SUPPURATIVE	HLH Criteria (OUT OF 8)
Yes	Yes	Yes	Yes	-	-	Yes	-	Transaminitis	5+S