Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

**An open access, online journal • www.smw.ch**

**Original article** | Published 22 June 2015, doi:10.4414/smw.2015.14152

**Cite this as:** Swiss Med Wkly. 2015;145:w14152

# Patients with an extraordinarily elevated serum ferritin: think of haemophagocytic lymphohistiocytosis

*Marc Schweizer*[a], *Jeroen S. Goede*[b], *Verena Briner*[c]

[a] Department of Anaesthesiology and Intensive Care Medicine, University of Tübingen, Germany

[b] Division of Haematology, University Hospital of Zurich, Switzerland

[c] Department of Medicine, Cantonal Hospital of Lucerne, Switzerland

## Summary

BACKGROUND: We retrospectively analysed charts of patients with blood ferritin level >5000 µg/l. The aim of the study was to look for the likelihood of haemophagocytic lymphohistiocytosis (HLH) in these patients.

METHODS: Forty-two patients demonstrated hyperferritinaemia and could be evaluated. The diagnosis of HLH was based on a recently published HScore and an earlier diagnostic algorithm.

RESULTS: According to the algorithm, 20 patients fulfilled the criteria for a diagnosis of HLH. However, patients with Still's disease have macrophage activation and, in this context, a rise in ferritin without having HLH. Fourteen patients with carcinoma, haematological malignancies or infection and hyperferritinaemia remained. Signs and symptoms were: systemic inflammatory response syndrome (SIRS 100%), fever (95%), cytopenia of ≥2 lines (70%), immunosuppression (61.5%), splenomegaly (50%), elevated liver enzymes (45%), lymphadenopathy (35%), hepatomegaly (30%). These are nonspecific parameters. Therefore HLH may be overdiagnosed. Using the HScore, only 10 patients had >80% probability of having HLH. Patients demonstrating cytopenia of ≥2 cell lines had a >60% mortality rate. Time to death was 13.8 days; death was most often due to multiorgan failure.

CONCLUSION: HScore reflects a higher specificity than the algorithm for diagnosing HLH. The discrepancy may indicate the difficulty that a specific marker still is missing. Hyperferritinaemia was strongly associated with HLH in patients with haematological or oncological malignancies. HLH may be underdiagnosed because the majority of these patients suffer from a severe underlying disease, which easily might suggest a flare or infection. In this population, hyperferritinaemia and SIRS should rise suspicion because mortality in HLH is high.

***Key words:*** *hyperferritinaemia; systemic inflammatory response syndrome; Still's disease; HLH; haematological and solid neoplasm*

## Introduction

Markedly elevated ferritin levels in the blood may be a marker of severe underlying disease such as haemophagocytic lymphohistiocytosis (HLH) (for review see [1]). In children, a ferritin level >10'000 µg/l has been shown to have a 90% sensitivity and 96% specificity for a diagnosis of HLH [2]. The Histiocytic Society classifies the syndrome as primary (genetic) and secondary (reactive) forms [3]. Genetic defects result in T-cell lymphocyte or natural killer cell dysfunction [3, 4]. In adults, secondary HLH or the reactive macrophage activation syndrome is more frequent and has been described in association with various causes, e.g. autoimmune disease, infections, neoplasms, drugs, etc. [5–7]. More recently, various genetic defects causing HLH also have been described in adults [8]. Regardless of its aetiology, dysfunctional regulation of cytokines leads to a cytokine storm clinically resembling systemic inflammatory response syndrome (SIRS). In some cases this may result in multiple organ dysfunction or failure, and even death [9]. The diagnosis of HLH is challenging owing to the lack of pathognomonic clinical and laboratory markers. Diagnostic criteria mainly define the primary form of the syndrome. In HLH, the serum ferritin level may be disproportionately elevated [10]. This finding contrasts to other inflammatory diseases. Hyperferritinaemia may be the most prominent biochemical abnormality in patients with HLH. Additional abnormal findings include cytopenia of several cell lines, elevated concentration of lactate dehydrogenase (LDH) and liver enzymes, hypertriglyceridaemia and a low fibrinogen level. However, all these markers are nonspecific. A rise in soluble interleukin-2 (IL-2) receptor α chains (sCD25) and CD163 are promising markers with more specificity [11, 12].

In children, the incidence of HLH or MAS is 1:800'000 in Sweden [13]. In adults, malignancy-associated HLH has been estimated to occur in 3.6:1'000'000 patients per year [14]. Even though its course is often lethal HLH is underdiagnosed [15] because a flare of the underlying disease or infection can explain many signs and symptoms of HLH. Only enhancing the awareness and systematic measurement of a cheap and easily available, specific marker of

HLH will shed light on the real incidence of this syndrome. For screening, ferritin seems accurate in patients with SIRS and sepsis-like syndrome. Early diagnosis is critical in order to start treatment of HLH before deterioration of the patient's condition. Improvement of outcome has been demonstrated with glucocorticoids [5], etoposide [16], immunoglobulins (IGs) [17], anti-CD20 antibody rituximab, ciclosporin and tacrolimus [18], etc.

The aim of the present study was to look for patients with excessive ferritin levels who were hospitalised in a tertiary hospital in Switzerland between 1996 and 2011. In addition, we looked for the aetiology, clinical, haematological and biochemical parameters, and outcome in these patients.

## Methods

Retrospectively, charts of patients with serum ferritin level >5'000 µg/l admitted to the Department of Medicine of a tertiary hospital in Switzerland were analysed. Some patients were hospitalised more than once. The first hospitalisation during which such an elevated ferritin level was found, we called the patient's index hospitalisation. Ferritin was measured by means of the chemiluminiscence method (ECLIA) Cobas 6000 system by Roche (normal range: 13–150 µg/l).

The diagnosis of HLH was based on the algorithm of Emmenegger et al. [15]. There were three major screening markers: (1) SIRS (temperature >38 °C or <36 °C, heart rate >90 bpm, hyperventilation, white blood cells >12 G/l or <4 G/l); (2) peripheral blood cytopenia affecting at least two of the three blood cell lines; (haemoglobin <90 g/l, neutrophils <1.0 G/l, platelets <100 G/l); (3) underlying disorder increasing the risk of HLH, and in addition morphological evidence of haemophagocytosis, soluble CD163, soluble CD25, elevated liver enzymes and LDH. The ferritin level was set arbitrarily, since in other inflammatory diseases ferritin levels >5'000 µg/l are rare. Splenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, haemophagcytosis in bone marrow, spleen, lymph node, or liver and elevated sCD25 >2,400 U/l were supportive of the diagnosis of HLH [12], but analyses were not done routinely for our patients. A total of 44 patients had a serum ferritin >5'000 µg/l. Data for two patients were omitted from further analysis because only a single blood sample was available. The remaining 42 patients were assigned to groups A to C, according to the likelihood of them suffering from HLH (tables 3–5). In addition, a recently published score "HSocre" [19] (http://saintantoine.aphp.fr/score/) included temperature, immunosuppression, organomegaly, hyperferritinaemia, hypofibrinogenaemia, low triglyceride level, elevated liver enzyme, haemophagocytois in bone marrow, in order to diagnose HLH.

The approval of the ethics committee of the canton of Luzern was obtained before data evaluation.

## Results

More than 70'000 patients were hospitalised at the Luzerner Kantonsspital between 1996 and 2011. Forty-four patients featured a ferritin level >5'000 µg/l during this period. Ferritin testing was performed at the treating physicians' discretion and for whatever reason. Forty-two patients were enclosed for further analysis. Baseline characteristics are shown in table 1.

### Grouping of the patients by use of the Emmengger algorithm [15]:

*Group A (tables 1–3)*

Twenty of 42 patients did fulfil the required five of eight criteria. Twelve patients (60%) suffered from haematological or oncological malignancy and two patients from an infection. Six patients (numbers 11–16, mean age 50.2 years) fulfilled the criteria but suffered from adult Still's disease (one patient in addition to a myelodysplastic syndrome). Patients with Still's disease have macrophage activation and in this context hyperferritinaemia (mean 28,052 µg/l). This group represents a different entity from classical HLH. Patient number 11 presented with a sepsis-like condition with pancytopenia and ciprofloxacin-resistant *Escherichia coli*. Despite appropriate antibiotic therapy he only improved four days later, when steroids were added. In patient 12 serology for Epstein Barr virus (EBV) viral capsid antigen IgG and EBV IgM were positive. Ret-

**Table 2:** Symptoms of patients of group A.

| | |
|---|---|
| Systemic inflammatory response syndrome | 100% |
| Ferritin >5'000 µg/l | 100% |
| Temperature (>38 °C or <36 °C) | 95% |
| Cytopenia of at least two cell lines | 70% |
| Splenomegaly | 50% |
| Elevated transaminases | 45% |
| Lymphadenopathy | 35% |
| Rash | 35% |
| Hepatomegaly | 30% |
| Arthritis | 25% |
| Neurological manifestation | 15% |

**Table 1:** Grouping of the patients suffering from haemophagocytic lymphohistiocytosis (HLH) using HScore and the algorithm of Emmenegger [15], fulfilling at least five of eight required criteria: (A) with and without patients suffering from Still's disease (B) fewer than five of eight criteria and thus HLH is less probable, (C) patients most likely suffer from another disease with liver injury.

| | HScore | A without Still's disease | A Still's Disease only | Total A | B | C | Total A–C |
|---|---|---|---|---|---|---|---|
| Number of patients | 10 | 14 | 6 | 20 | 6 | 16 | 42 (100%) |
| Mean age (years) | 56.8 | 57.1 | 50.2 | 55.1 | 63.5 | 66.1 | 58.8 |
| Sex | | | | | | | |
| Female | 4 | 7 | 2 | 9 | 1 | 6 | 16 (38.1%) |
| Male | 6 | 7 | 4 | 11 | 5 | 10 | 26 (61.9%) |
| Ferritin max (µg/l) | 122'600 | 122'600 | 80'660 | 122'600 | 45'400 | 23'970 | 122'600 |
| Ferritin peak mean (ely s | 41'484 | 35'396 | 28'052 | 33'193 | 16'750 | 12'976 | 23'237 |
| Number of deaths | 6 (60%) | 9 (64.3%) | 0 | 11 (55%) | 3 (50%) | 5 (31.3%) | 19 (45%) |

rospectively, high numbers of EBV copies could be demonstrated in stored serum of this patient. In our area primary infection in adults is very rare. More frequently reactivation is seen.

Nine of the 14 HLH patients died (64%), all of them had an underlying haemato-oncological disease. The average timespan from hospital admission to death due to HLH was 13.8 days. Of the five survivors, four were treated with glucocorticoids and one of them in addition with intravenous immunoglobulin (IG). None received chemotherapy with the intention of treating HLH. Two patients (10%) died of other causes (one from progression of the underlying B-cell lymphoma 7 months after HLH, one from a traumatic intracranial haemorrhage 1 year later). Patients demonstrating cytopenia of two or three cell lines showed a high risk for death (five of nine patients with pancytopenia and four of five patients with bicytopenia). In contrast, all patients solely with anaemia survived (table 3). All patients with Still's disease survived.

*Group B (table 4)*

Patients in group B had hyperferritinaemia but did not fulfil at least five of the required eight criteria of the HLH algorithm. There was, for example, a lack of various chemical markers of HLH at the time of hyperferritinaemia. In three patients an infection was confirmed by blood cultures or at autopsy (*Mycobacterium avium* complex, mucormycosis, and *Pasteurella multocida*). Three patients (50%) died during the index hospitalisation. In contrast with use of the criteria of the HScore [19], two patients of group B suffered from HLH with >80% probability.

*Group C (table 5)*

All 16 patients of group C had liver injuries of different aetiologies. Peak plasma ferritin levels in this group were lower than group A and B (range 8'700 to 23'970 µg/l; median 11'660 µg/l). Liver injury (e.g. ischaemia, severe congestion) may cause a rise in ferritin level without HLH. The algorithm did not suggest HLH in this group. None of the patients had >80% likelihood of HLH in the HScore. Five patients (31.3%) in group C died. Three of them had liver metastases.

**HScore**

The HScore selected 10 patients with hyperferirtinaemia and a probability of >80%, and 14 of the 42 patients with

**Table 3**: Details of patients in group A.

| No. | Disease | Maximum ferritin level (µg/l) | H Score | Age years / sex | Cytopenia | Treatment: Steroids (S) Intravenous immunoglobulin (IG) | Outcome (survived HLH) |
|---|---|---|---|---|---|---|---|
| | *I. Haematological malignancies* | | | | | | *3 out of 10* |
| 1 | Acute monocytic leukaemia (FAB M5b) | 53'427 | 4.9 | 81 / F | Yes (anaemia, thrombocytopenia) | S/IG | No |
| 2 | Acute myeloid leukaemia (FAB M5) | 42'840 | 30.1 | 73 / M | Yes (all 3 cell lines) | S | No |
| 3 | Myelodysplastic syndrome with transformation into acute myeloid leukaemia | 18'071 | 82.8 | 68 / F | Yes (all 3 cell lines) | S | Yes (died of other cause) |
| 4 | Acute myeloid leukaemia (FAB M5) | 17'740 | 49.1 | 29 / M | Yes (all 3 cell lines) | S | Yes |
| 5 | B-cell chronic lymphocytic leukaemia with transformation into B-cell prolymphocytic leukaemia | 15'590 | 86.8 | 60 / M | Yes (anaemia, thrombocytopenia) | S | No |
| 6 | B-cell acute lymphoblastic leukaemia | 15'295 | 64.2 | 43 / F | Yes (all 3 cell lines) | S/IG | No |
| 7 | Chronic myelogenous leukaemia | 9'470 | 99.4 | 57 / M | Yes (anaemia, thrombocytopenia) | S/IG | No |
| 8 | Anaplastic T-cell non–Hodgkin's lymphoma | 122'600 | 99.9 | 45 / F | Yes (all 3 cell lines) | S/IG | No |
| 9 | Anaplastic large cell B-cell non-Hodgkin's lymphoma | 81'500 | 99.9 | 45 / F | Yes (all 3 cell lines) | S/IG | No |
| 10 | Large cell centroblastic B-cell non-Hodgkin's lymphoma | 64'700 | 90.5 | 46 / M | Yes (all 3 cell lines) | S/IG | Yes (died of other cause) |
| | *II. Systemic inflammatory disorders* | | | | | | *2 out of 2* |
| 11 | *E. coli* sepsis | 12'495 | 98.8 | 77 / F | Yes (all 3 cell lines) | S | Yes |
| 12 | Epstein-Barr virus infection | 9'259 | 32.7 | 51 / M | Yes (anaemia, thrombocytopenia) | – | Yes |
| | *III. Solid tumours* | | | | | | *0 out of 2* |
| 13 | Metastasised prostate cancer | 19'090 | 30.1 | 70 / M | Yes (all 3 cell lines) | S | No |
| 14 | Metastasised renal cell carcinoma | 13'470 | 13.1 | 55 / F | Yes (anaemia, thrombocytopenia) | S | No |
| | **Total** | | | | | | **5 out of 14** |
| | *IV. Still's disease* | | | | | | |
| 15 | No malignant disease | 80'660 | 44.5 | 53 / M | Yes (anaemia) | S | Yes |
| 16 | No malignant disease | 35'720 | 96.5 | 55 / M | Yes (anaemia) | S/IG | Yes |
| 17 | Still's disease and myelodysplastic syndrome | 19'640 | 4.4 | 75 / F | Yes (anaemia) | S | Yes |
| 18 | No malignant disease | 13'786 | 16.1 | 39 / M | Yes (anaemia) | S | Yes |
| 19 | No malignant disease | 10'390 | 12.4 | 56 / M | Yes (thrombocytopenia) | S | Yes |
| 20 | No malignant disease | 8'120 | 16.9 | 23 / F | Yes (anaemia) | S | Yes |
| | **Total** | | | | | | **6 out of 6** |

<50% probability of suffering from HLH (tables 1–5). One patient with Still's disease also had a 96.5% probability of suffering from HLH although the clinical findings did not differ from the other Still's disease patients. Taken together, the algorithm suggested 14 patients were suffering from HLH and the HScore suggested 10 patients with >80% probability of HLH. The discrepancy may be the result of using different but still nonspecific, markers of HLH.

## Discussion

During a 15 year period (1996 to 2011), 42 patients had a high ferritin level >5'000 µg/l and 30 patients >10'000 µg/l at our tertiary hospital in Central Switzerland. In another single centre 43% of patients with ferritin levels >10'000 µg/l suffered from HLH [20]. According to Ma et al. [21], after excluding sickle cell anaemia, liver disease and graft versus host disease, HLH should be suspected in >80% of patients with a ferritin level above that range. However, in our series, the diagnosis of HLH was very likely in only 14 cases (12 patients with ferritin >10'000 µg/l). They ful-

**Table 4:** Details of patients in group B.

| No. | Primary disease | Additional diagnosis | Maximum ferritin level (µg/l) | H Score | Age years sex | Treatment: Steroids (S) Intravenous immunoglobulin (IG) | Outcome (survived) |
|---|---|---|---|---|---|---|---|
| | *I. Haematological malignancies* | | | | | | *1 out of 4* |
| 21 | Myelodysplastic syndrome with refractory anaemia with excess blasts | Mucormycosis | 45'400 | 82.8 | 71 / M | S/IG | No |
| 22 | Hodgkin's lymphoma | Antifreeze poisoning, aspiration pneumonia | 10'250 | 59.8 | 68 / M | S | No |
| 23 | Waldenström's disease with pancytopenia | Purported urinary tract infection, multiple transfusions | 9'795 | 1.8 | 75 / F | S | Yes |
| 24 | Hairy cell leukaemia | MAC infection, pseudomonal sepsis, pulmonary aspergillosis | 9'290 | 96.5 | 44 / M | S/IG | No |
| | *II. Solid Tumours* | | | | | | *1 out of 1* |
| 25 | Metastasised prostate cancer | – | 13'290 | 0.3 | 63 / M | S | Yes |
| | *III. Haematological disorders* | | | | | | *1 out of 1* |
| 26 | Aplastic anaemia | Sepsis due *to P. multocida* | 12'479 | 18.8 | 60 / M | – | Yes |
| | **Total** | | | | | | **3 out of 6** |

MAC = *Mycobacterium avium* complex

**Table 5:** Details of patients in group C.

| No. | Primary disease | Maximum ferritin level (µg/l) | H Score | Age years / sex | Outcome (survived) |
|---|---|---|---|---|---|
| | *I. Hepatic metastasis* | | | | *1 out of 4* |
| 27 | Colon cancer | 23'370 | 5.3 | 74 / M | Yes |
| 28 | Breast cancer with acute liver failure | 15'735 | 18.8 | 48 / F | No |
| 29 | Breast cancer | 13'330 | 0.9 | 72 / F | No |
| 30 | Small cell lung cancer | 8'700 | 3.7 | 64 / M | No |
| | *II. Drug related liver injury most likely* | | | | *4 out of 4* |
| 31 | Phenytoin side effect likely | 23'600 | 22.9 | 56 / F | Yes |
| 32 | Diclofenac | 23'970 | 47.5 | 50 / M | Yes |
| 33 | Paracetamol and ethanol | 14'880 | 5.9 | 38 / M | Yes |
| 34 | Gemcitabine in breast cancer | 8'340 | 12.4 | 76 / F | Yes |
| | *III. Severe heart failure* | | | | *1 out of 2* |
| 35 | Hepatic congestion | 11'540 | 0.2 | 75 / M | No |
| 36 | Hepatic congestion | 12'053 | 0.2 | 80 / M | Yes |
| | *IV. Infection of the hepatobiliary tract* | | | | *2 out of 3* |
| 37 | Cholangitis and alcoholic liver disease | 11'780 | 12.4 | 72 / M | No |
| 38 | Chronic hepatitis B and alcoholic liver disease | 9'170 | 0.9 | 52 / M | Yes |
| 39 | Acute hepatitis B | 8'990 | 75.8 | 36 / F | Yes |
| 40 | Hepatic candidiasis after bone marrow transplantation for AML and immunosuppression | 5'571 | 18.8 | 64 / F | Yes |
| | *V. Haematological disorders* | | | | *1 out of 1* |
| 41 | Myelodysplastic syndrome and mutiple transfusions | 8'480 | 0.4 | 59 / M | Yes |
| | *VI. Metabolic disorders* | | | | *1 out of 1* |
| 42 | Haemochromatosis and relapsing fever of unknown origin | 8'100 | 0.2 | 62 / M | Yes |
| | **Total** | | | | **11 out of 16** |

filled five of eight clinico-pathological criteria of a HLH algorithm [15] and 10 patients fulfilled the criteria of the HScore (8 patients with ferritin >10'000 µg/l). Patients with liver injury and very high level of ferritin were excluded although it is possible that some also had HLH. HLH occurred in our patients in fewer than 0.2‰ of all inpatients at our hospital (70'000 patients, 500'000 inhabitants of central Switzerland) and about 2 cases per million people, which is below a previous estimate of 3.6 per million per year [14]. The real incidence of HLH is probably greater, when considering patients with plasma ferritin peaks below 5'000 µg/l and those in whom the diagnosis was never considered or ferritin never measured. In the present study population, the diagnosis of HLH was missed in 45% of cases during their index hospitalisation. Since the vast majority of patients with HLH suffered from a severe underlying disease, HLH easily is overlooked. We noticed an increased incidence of HLH in our series towards the end of our observational period. This was most likely due to a growing awareness of this syndrome among clinicians.

In the present series, the most common diseases associated with HLH were haemato-oncological in origin. This contrasts with HLH in children, in whom genetic defects and viral infections are the main causes of HLH [22–24]. Earlier reports in adults as well as in our series have shown HLH occurring most often with malignant non-Hodgkin lymphoma [25–27]. In our series, in addition acute myeloid leukaemia (AML) was also a frequent underlying disease. The cornerstones for diagnosing HLH were SIRS, marrow haemophagocytosis and very high ferritin levels in our patients. The diagnosis of a haematological malignancy had previously been established, with HLH being a new, uncontrolled complication. In two patients, however, HLH was diagnosed first and the work-up elucidated the underlying haematological cancer. In patient number 1 with AML, HLH was probably triggered by induction chemotherapy. Soaring ferritin levels and SIRS were noted during both cycles of induction chemotherapy. The second cycle proved to be fatal. Delavigne [28] suggests up to 10% of AML patients have HLH, which is triggered in the majority of patients by an infection. Interestingly enough, our patients with AML and bone marrow haemophagocytosis but without HLH did exceptionally well in terms of complete remission. Thus, haemophagocytosis *per se* is not an ominous sign. In HLH, uncontrolled activation of lymphocytes and macrophages release large amounts of cytokines to cause cytokine storm and multiorgan dysfunction. Malignant haematological diseases were most frequent and these patients did markedly worse compared with patients with a nonmalignant cause in our series. Other series have shown similar aetiology and an even higher fatality rate [26, 27, 29]. Outcome is worse than in children with HLH.

The second largest group of patients demonstrating hyperferritinaemia in our series had Still's disease. Already previously it has been argued that a subgroup of adult Still's disease might be identical with HLH [9]. HLH complicating rheumatic disorders in children has been found to follow a severe course and may be fatal [30]. The mean age of our patients with Still's disease was lower (50 years) compared with the HLH patients with haematological neoplasia (57 years). The serum ferritin level was in the same high range in both groups. Maybe some share a common pathway, causing clinical and laboratory findings such as SIRS and very high ferritin level [31]. It is interesting that the HScore suggests one patient with Still's disease had HLH with >80% probability. These data may reflect a higher specificity of the HScore, which includes additional criteria compared with the algorithm proposed by Emmenegger et al. However, this discrepancy may also point towards a fundamental difference that may exist between patients with Still's disease and the other patients in our cohort. Still's disease represents an autoinflammatory disorder and activation of the innate immune system. Particularly the macrophage system is an inherent component of this entity. The distinct pathophysiology of Still's disease may also explain the high ferritin plasma levels that are usually observed already during relatively mild disease. It is therefore likely that the population of patients with Still's disease represents a continuum of macrophage activation states, which is difficult to segregate into a dichotomous model of patients with or without HLH. In addition, even those Still's disease patients with the highest ferritin levels usually have a good prognosis and respond to moderate-intensity immunosuppression. Nevertheless, ferritin levels >10'000 µg/l may still identify a group of Still's disease patients with a higher probability to develop overt HLH, which may require closer clinical and laboratory follow-up.

In our series, there were only 14% of patients with infection- (EBV and *E. coli*) associated HLH. According to the literature, viruses (e.g. cytomegalovirus, human immunodeficiency virus), bacteria (including mycobacteria), fungi, and parasites are known to cause HLH [32]. EBV has been described as a trigger for HLH frequently in children and Asian adults but rarely in adults of western countries [15, 33]. It is interesting to note that the infectious agents found in patients of group B fitted the spectrum of known triggers of HLH (e.g. atypical mycobacteria, fungi, Gram-negative bacteria) [32], thus raising the question, if some of these cases, were not indeed cases with infection related HLH.

In the present series, patients with EBV or *E. coli* sepsis and HLH had a good prognosis. In contrast, 75% of patients with malignancy-associated, excessive hyperferritinaemia and HLH died. Peripheral cytopenia of two cell lines or more was an ominous sign heralding death. We did not note a correlation between other laboratory parameters and the likelihood of progression to death. In part, this might be due to the retrospective nature of the study and a lack of systematic analysis of blood samples during the course of the disease. Since hepatocytes store high level of ferritin, excessive hyperferritinaemia may also occur in patients with acute hepatic injury. Severe liver injury of any aetiology such as metastasis, hepatitis, etc. may therefore cause a rise in serum ferritin concentration when hepatic cytolysis occurs even without HLH [34]. Therefore the data of patients with some kind of hepatopathy have to be interpreted with caution.

## Conclusion

High levels of hyperferritinaemia may be an ominous sign in adult inpatients. Excluding patients with Sill's and liver

disease, a majority of these patients have HLH. However, the diagnosis is missed very often. This most likely is due to the difficulties distinguishing it from the underlying disease, which may mask the life-threatening HLH. Insufficient knowledge of the syndrome and the lack of a pathognomonic marker of HLH delay the diagnosis and appropriate treatment. A high index of suspicion in a patient suffering from unexplained fever, cytopenia and hyperferritinaemia is still the key to recognising HLH. For screening, the analysis of ferritin should be performed in all patients with SIRS of unknown aetiology. It is cheap and easy to measure. Until we have specific diagnostic criteria or a specific marker, HLH remains challenging to clinicians. Our study has limitations: it is a retrospective analysis and blood samples were not drawn systematically and not at the same time. Therefore statistical comparison of data might be false negative.

**Acknowledgement:** The authors thank Prof. Klaus Neftel and Prof. Dominique Schaer for their critical reading of the paper and advices.
**Disclosures:** Financial support from Verein zur Förderung der Wissenschaft am Departement Medizin, Luzerner Kantonsspital, CH-6000 Luzern, Schweiz

***Correspondence:*** *Professor Verena Briner, MD, Department of Medicine, Luzerner Kantonsspital, CH-6000 Luzern, Switzerland, verena.briner[at]luks.ch*
*Marc Schweizer, Med. pract., Klinik für Anästhesiologie und Intensivmedizin, Hoppe-Seyler-Strasse 3, DE-72076 Tübingen, Germany, marc.schweizer[at]med.uni-tuebingen.de*

## References

1 Ramos-Casals M, Brito-Zerón P, López-Guillermo A., Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014;383:1503.

2 Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 200850;1227.

3 Henter JI, Elinder G, Söder O, Hansson M, Andersson B, Andersson U. Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. Blood. 1991;78:2918.

4 Osugi Y, Hara J, Tagawa S, Takai K, Hosoi G, Ohta H, et al. Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohisticytosis. Blood. 1997;89:4100.

5 Dhote R, Simon J, Papo T, Detournay B, Sailler L, Andre MH, et al. Reactive hemophagocytic syndrome in adult systemic disease: report of twenty-six cases and literature review. Arthritis Rheum. 2003;49(5):633.

6 Shimazaki C, Inaba T, Nakagawa M, et al. B-cell lymphoma-associated hemophagocytic syndrome. Leuk Lymphoma. 2000;38(1-2):121.

7 Falini B, Pileri S, De Solas I, Martelli MF, Mason DY, Delsol G, et al. Peripheral T-cell lymphoma associated with hemophagocytic syndrome. Blood. 1990;75(2):434.

8 ZhangK, Jordan MB, Marsh RA, Johnson JA, Kissell D, Meller J, et al. Hypomorphic mutations in PRF1, MUNC13-4, and STXBP2 are associated with adult-onset familial HLH. Blood. 2011;118:5794.

9 Emmenegger U, Reimers A, Frey U, Fux C, Bihl F, Semela D, et al. Reactive Macrophage Activation Syndrome: a simple screening strategy and its potential in early treatment initiation. Swiss Med Wkly. 2002;132:230.

10 Emmenegger U, Frey U, Reimers A, Fux C. Semela D, Cottagnoud P, et al. Hyperferritinemia as indicator for intravenous immunoglobulin treatment in reactive macrophage activation syndromes. Am J Hematol. 2001;68:4.

11 Schaer DJ, Schleiffenbaum B, Kurrer M, Imhof A, Bächli E, Fehr J, et al. Soluble hemoglobin-haptoglobin scavenger receptor CD163 as a lineage-specific marker in the reactive hemophagocytic syndrome. Eur J Haematol. 2005;74:6.

12 Imashuku S, Hibi S, Sako M, Ishida Y, Mugishima H, Chen J, et al. Soluble interleukin-2 receptor: a useful prognostic factor for patients with hemophagocytic lymphohistiocytosis. Blood. 1995;86:4706.

13 Henter JI, Elinder G, Söder O, Ost A. Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand. 1991;80:428.

14 Machaczka M, Vaktnäs J, Klimkowska M, Hägglund H. Malignancy-associated hemophagocytic lymphohistiocytosis in adults: a retrospectice population-based analysis from a single center. Leuk Lymphoma. 2011;52(4):613.

15 Emmenegger U, Schaer DJ, Larroche C, Neftel KA. Haemophagocytic syndromes in adults; current concepts and challenges ahead. Swiss Med Wkly. 2005;135:299.

16 Imashuku S, Kuriyama K, Teramura T, Ishii E, Kinugawa N, Kato M, et al. Requirement for etoposide in the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. J Clin Oncol. 2001;19:2665.

17 Rhoades CJ, Williams MA, Kelsey SM, Newland AC. Monocyte-macrophage system as targets for immunomodulation by intravenous immunoglobulin. Blood Rev. 2000;14:14.

18 Watanabe H, Hirase N, Goda H, Nishikawa H, Ikuyama S. Oral low-dose tacrolimus therapy for refractory hemophagocytic syndrome associated with systemic lupus erythematosus. Mod Rheumatol. 2012;22:284.

19 Faradet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arth & Rheumat. 2014;66:2613.

20 Parikh SA, Kapoor P, Letendre L, Kumar S, Wolanskyj AP Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis. Mayo Clin Proc. 2014;89:484

21 Ma A, Fedoriw YD, Roeders P. Hyperferritinemia and Hemophagocytic Lymphohistiocytosis. Single institution experience in adult and pediatric patients. Annual meeting 54th ASH, Abstract 2135.

22 Risma K, Jordan MB. Hemophagocytic lymphohistiocytosis: updates and evolving concepts. Curr Opin Pediatr. 2012;24:9.

23 Egeler RM, Shapiro R, Loechelt B, Filipovich A. Characteristic immune abnormalities in hemophagocytic lymphohistiocytosis. J Pediatr Hematol. Oncol. 1996;18:340.

24 McClain K, Gehrz R, Grierson H, Purtilo D, Filipovich A. Virus-associated histiocytic proliferations in children. Frequent association with Epstein-Barr virus and congenital or acquired immunodeficiencies. Am J Pediatr Hematol. Oncol. 1988;10:196.

25 Rivière S, Galicier L, Coppo P, Marzac C, Aumont C, Lambotte O, Fardet L. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. Am J Med. 2014;127:1118.

26 Chang CS, Wang CH, Su IJ, Chen YC, Shen MC. Hematophagic histiocytosis: a clinicopathologic analysis of 23 cases with special reference to the association with peripheral T-cell lymphoma. J Formos Med Assoc. 1994;93:421.

27 Li J, Wang Q, Zheng W, Ma J, Zhang W, et al. Hemophagocytic lymphohistiocytosis: Clinical Analysis of 103 adult patients. Medicine 2014;93:100.

28 Delavigne K, Bérard E, Bertoli S, Corre J, Duchayne E, Demur C, et al. Hemophagocytic syndrome in patients with acute myeloid leukemia undergoing intensive chemotherapy. Haematologica. 2014;99:474.

29 Takahashi N, Chubachi A, Kume M, Hatano Y, Komatsuda A, Kawabata A, et al. A clinical analysis of 52 adult patients with hemophagocytic syndrome: The prognostic significance of the underlying diseases. Intern J Hematol. 2001;74:209.

30 Sawhney S, Woo P, Murray KJ. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child. 2001;85:421.

31 Rosado FG, Kim AS. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. Am J Clin Pathol. 2013;139:713.

32 Fisman DN. Hemophagocytic syndromes and infection. Emerg Infect Dis. 2000;6(6):601.

33 Fox CP, Shannon-Lowe C, Gothard P, Kishore B, Neilson J, O'Connor N, et al. Epstein-Barr Virus-Associated Hemophagocytic Lymphohistiocytosis in Adults Characterized by High Viral Genome Load within Circulating Natural Killer Cells. Clin Infect Dis. 2010;51:66.

34 Bhagat CI, Fletcher S, Joseph J, Beilby JP. Plasma ferritin in acute hepatocellular damage. Clin Chem. 2000;46:885.