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# HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: POTENTIALLY UNDERDIAGNOSED IN INTENSIVE CARE UNITS

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ABSTRACT—**Background:** Hemophagocytic lymphohistiocytosis in adults (aHLH) is a rare life-threatening hyperinflammatory syndrome caused by excessive activation of macrophages and CD8+ T-cells. Due to the clinical overlap with severe sepsis, aHLH often remains undiagnosed resulting in poor outcome. Here, we present a retrospective study of incidence, clinical findings, and the outcome of aHLH in intensive care units (ICUs). **Methods:** This retrospective analysis was performed at the university hospital Charité – Universitätsmedizin Berlin. We gathered data from 556 out of 46,532 patients admitted to our anesthesiological ICUs between 2006 and 2013, who had at least one plasma ferritin measurement during ICU treatment, and were at least 18 years old. Of these, 244 patients with ferritin at least 500 μg/L and available datasets of at least 4 HLH-2004 criteria were included. HLH-2004 diagnostic criteria and the recently published HScore were used. An aHLH expert team retrospectively reviewed the potential aHLH cases. **Results:** Seventy-one of the included 244 patients died; 9 out of the 244 patients were retrospectively classified as aHLH of whom 4 patients had died (44.4%). Two of the 9 aHLH patients had been correctly diagnosed and had received specific aHLH treatment. Thus, 7 out of 9 patients (77.8%) remained undetected. ICU patients with at least 1 captured ferritin value and hyperferritinemia showed an aHLH rate of 3.7%, which rises up to 5.6% when only deceased patients are considered. Mortality in this selected cohort is 44.4%. **Conclusions:** Overall, 7 out of 9 patients (77.8%) suffering from aHLH remained undiagnosed. Awareness of this life-threatening syndrome, especially in ICUs, should be raised. The inclusion of ferritin into the admission lab panel for ICU is warranted. Clinical trial registered with www.ClinicalTrials.gov (NCT02854943) on August 1, 2016. As this is a retrospective study, trial registration was after final data collection date.

KEYWORDS—Hemophagocytic lymphohistiocytosis (HLH), hemophagocytic syndrome (HPS), intensive care unit, macrophage activation syndrome (MAS), sepsis, undiagnosed

ABBREVIATIONS—aHLH—hemophagocytic lymphohistiocytosis in adults; AIDS—acquired immune deficiency syndrome; ALL—acute lymphatic leukemia; AML—acute myeloid leukemia; ARDS—acute respiratory distress syndrome; ASAT—aspartate aminotransferase; AUC—area under the curve; CD—cluster of differentiation; CI—confident interval; CLL—chronic lymphatic leukemia; CMV—cytomegalovirus; CT—computed tomography; ctl—cytotoxic T-lymphocytes; EBV—Ebstein–Barr virus; FUO—fever of unknown origin; Hb—hemoglobin; HIV—human immunodeficiency virus; ICU—intensive care unit; IFN-γ—interferon γ; MAS—macrophage activation syndrome; mM—mmoles/liter; MODS—multiorgan dysfunction; NHL—non-Hodgkin lymphoma; NK—natural killer cell; PET—positron emission tomography; plt—platelets; ROC—Receiver Operating Characteristics; SD—standard deviation; sIL-2R—soluble interleukin 2 receptor; SIRS—systemic inflammatory response syndrome; SLE—systemic lupus erythematosus; TNF-α—tumor necrosis factor alpha; U—units

## BACKGROUND

Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome or macrophage activation syndrome (MAS; HLH-subtype in autoimmune/autoinflammatory disease), is a rare life-threatening hyperinflammatory syndrome with a high fatality rate. It is caused by an excessive immune activation of benign macrophages and T-cells with an extreme cytokine production of interferon γ (IFN-γ) and tumor necrosis factor α (TNF-α), and subsequent hemophagocytosis (1–3). Although congenital HLH due to several genetic defects is well investigated (2), little is known about adult HLH (aHLH), which can occur at any age and is associated with a wide spectrum of underlying conditions mainly triggered by infectious diseases, malignancies (particularly leukemia and lymphoma), immunodeficiency and autoimmune disorders that lead to an impaired ability of cytotoxic T-lymphocytes (ctl),

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The study was performed at the Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité - Universitätsmedizin Berlin, Berlin, Germany.

Declarations: Ethics approval was obtained from the institutional review board (Ethikkommission der Charité – Universitätsmedizin Berlin, EA1/176/16). As of its retrospective design, no consent was needed from the patients.

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Authors' contributions: Conceived and designed the experiments—GL, CS, FMB, and PL; performed the experiments—GL, TS, FB, and PL; analyzed the data—GL, TS, and PL; wrote the manuscript—GL and PL.

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and natural killer (NK) cells to kill target cells (4–6). Patients suffering from aHLH can rapidly deteriorate within a few days. Clinical signs are prolonged fever, unexplained acute cytopenias, hyperferritinemia, hepatomegaly and/or splenomegaly, and nonresponse to anti-infectious treatment. Multiorgan dysfunction is the result of the cytokine storm with highly activated macrophages and T-cells that infiltrate lymphoid and nonlymphoid tissues in a diffuse or tumorous pattern (6–8).

The diagnosis of aHLH is challenging as most symptoms and laboratory findings of this hyperinflammatory state are nonspecific and are also found in sepsis, multiorgan dysfunction (MODS), and other cytokine storm disorders. Hence, missed diagnosis due to misclassification exposes patients to risk (9–12). Without specific treatment, aHLH results in multiple organ failure and death (13, 14). Early diagnosis and treatment is pivotal to improve outcome (15). Diagnostic criteria developed for the pediatric HLH-2004 protocol have been widely adopted in adult medicine without systematic validation (6). French investigators have therefore proposed an adapted web-based diagnostic tool, the HScore, which comprises selected criteria from HLH-2004 with grading according to severity (16). Yet, appropriate diagnosis still requires a high level of clinical vigilance and expertise (5, 17). Treatment is often adapted from the pediatric HLH-2004 protocol containing dexamethasone, etoposide, and cyclosporine A with an overall poor outcome. Although HLH-2004 includes a bridging strategy to allogeneic stem cell transplant due to high frequency of hereditary disease in children, aHLH on grounds of various trigger diseases requires an individualized approach (18). The outcome depends on the trigger disease with worst results in malignancy-associated aHLH and a mortality rate of up to 75% (19). Beyond immunosuppression, the treatment contains disease-specific chemotherapy, antimicrobial therapy, anti-inflammatory therapeutic antibodies (Anakinra, Tocilizumab) (20–22), application of polyvalent immunoglobulins, and plasmapheresis or cytokine adsorption (23, 24). Treatment recommendations are not based on prospective trials but rather on case series and expert opinion.

Due to the overlap with systemic inflammatory response syndrome (SIRS), severe sepsis and septic shock, failed or delayed diagnosis of aHLH particularly in intensive care units (ICUs) impose a fatal risk on patients (5, 8, 9, 12, 25, 26). The true incidence of aHLH in ICUs is unclear. Our study therefore aimed to retrospectively detect undiagnosed cases of aHLH in ICUs of a German university hospital between 2006 and 2013.

## PATIENTS AND METHODS

### Study participants and data acquisition

This retrospective observational analysis was performed at the university hospital Charité – Universitätsmedizin Berlin, Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK). We reviewed clinical routine data derived from two electronic patient data management systems operated at the Charité – Universitätsmedizin Berlin (COPRA, Sasbachwalden, Germany and SAP, Walldorf, Germany). We collected data from all patients admitted to at least one of the multicampus anesthesiological ICUs between 2006 and 2013. Diagnosis of sepsis was adopted from the patient charts. All patients received guideline-based anesthesiological and surgical treatment in accordance to our standard operating procedures (27). The study period was defined from admission to our hospital until discharge, transfer, or death. All patients with available datasets of at least 4 HLH-2004 criteria and plasma ferritin at least 500 μg/L while on ICU treatment were included according to the HLH-2004 criteria (6). Age below 18 years and no measurement of ferritin during ICU stay were defined as exclusion criteria.

### Diagnosis of aHLH

Included patients were analyzed according to HLH-2004 criteria (6) (Suppl. Table 1, http://links.lww.com/SHK/A665) and HScore (16) (Suppl. Table 2, http://links.lww.com/SHK/A665). Therefore, charts were reviewed to determine body temperature, ferritin, blood counts, triglycerides, fibrinogen, soluble IL-2 receptor (sIL-2R), and aspartate aminotransferase (ASAT). Based on ultrasound and computed tomography (CT) scan findings as well as medical reports, hepatomegaly and/or splenomegaly and preceding immune suppression were analyzed. Bone marrow findings were reviewed to determine hemophagocytosis. All of the considered values and findings were taken from a time point close to the measurement of ferritin (maximum range ± 6 days). Patients with at least 4 out of 8 fulfilled HLH-2004 criteria and/or an HScore HLH probability of at least 80% were reviewed by aHLH experts (Paul La Rosée, Thomas Schenk), who retrospectively confirmed aHLH based on all collected data and clinical judgment.

### Statistical analysis

Results are expressed as means ± standard deviation (SD), median ± quartiles, or percentage, respectively. Differences between ICU survivors and nonsurvivors were calculated using nonparametric statistical tests. Receiver Operating Characteristics (ROC) analysis was performed to analyze best ferritin levels to predict aHLH. SPSS 23.0 software (IBM Corporation, Armonk, NY) was used for all statistical analysis. A $P < 0.05$ was considered statistically significant.

## RESULTS

### Study population

In total, 46,532 patients were admitted to our anesthesiological ICUs during 2006 and 2013. Thereof, 556 patients had at least one measurement of ferritin while in ICU and were at least 18 years old. Ferritin was elevated (≥500 μg/L) in 258 patients; 244 out of these patients had available datasets of at least 4 HLH-2004 criteria and were included in the final analysis; 173 out of 244 patients survived ICU treatment, and 71 patients died (Fig. 1). The basic patient characteristics and outcome parameters are shown in Table 1.

In 349 out of 556 patients, ferritin was measured in combination with transferrin (62.8%); 171 patients had more than one ferritin measurement (30.8%). Among all included patients, two patients were diagnosed with MAS and therefore treated. In one further patient who died, aHLH was suspected but not treated. Another deceased patient had histiocytosis X in his history.

### Analyses of all patients regarding aHLH

Patients' charts were reviewed based on HLH-2004 criteria and HScore (Table 2). Blood counts and body core temperature were measured in all of the 244 patients. Triglycerides were available for 157 (64.3%), fibrinogen in 221 (90.6%), sIL-2R in 8 (3.3%), and ASAT in 243 patients (99.6%). Ultrasound or CT scan to detect hepatomegaly and/or splenomegaly was performed in all of the 244 patients. Bone marrow biopsy was conducted in 15 patients (6.1%).

### Analyses of patients with suspected aHLH

Twenty-three patients fulfilled at least four HLH-2004 criteria. Eleven patients scored at least 80% in the HScore. These patients were reviewed by the aHLH expert team and aHLH

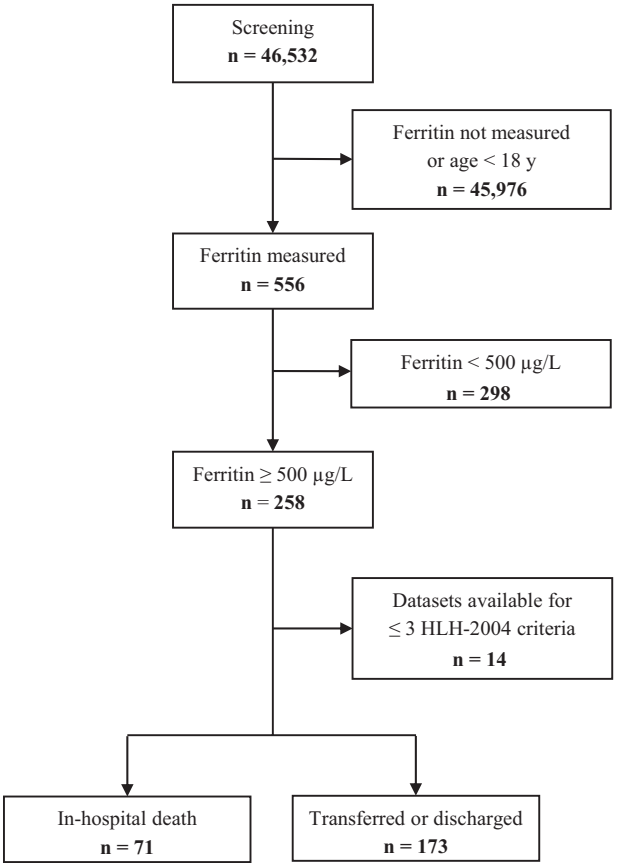


Fig. 1. **Consort diagram.** A total of 244 patients were included to the final analyses.

was retrospectively diagnosed in nine patients of whom four patients had died (44.4%; Table 3). In two of these patients, MAS was diagnosed and treated (one patient was treated shortly before death with a significant delay of 9 weeks after admission, the other patient survived). Hence, 7 out of 9 cases remained undiagnosed during ICU treatment (77.8%). Furthermore, aHLH was not confirmed retrospectively in the patient who was suspected for aHLH but left untreated. The deceased patient with histiocytosis X in his history was not scored as aHLH. Three additional deceased patients scored positive with 5 out of 8 HLH-2004 criteria or had an HScore of at least 90%, but were reviewed as being unlikely to have suffered from aHLH. These patients are listed in Suppl. Table 3, http://links.lww.com/SHK/A665. Overall, ICU patients with measured ferritin and hyperferritinemia showed an aHLH rate of 3.7%, which rises up to 5.6% when only deceased patients are considered. Mortality in this selected cohort was 44.4%.

Table 1. **Basic patient characteristics and outcome parameters**

| | ICU survivors (n = 173) | Death (n = 71) |
|---|---|---|
| Age (yr) | 61.0 (42.0–73.0) | 60.0 (49.0–70.0) |
| Sex, male/female (n) | 101/72 | 40/31 |
| Body mass index (kg/m$^2$) | 25.7 (23.1–30.8) | 24.7 (21.3–27.6) |
| Sepsis (n) | 90 | 63 |
| ICU duration (d) | 36.0 (14.0–70.0) | 39.5 (16.0–75.5) |
| In-patient duration (d) | 55.0 (27.0–89.0) | 51.5 (23.0–82.8) |

Continuous quantities in median with quartiles; ICU, intensive care unit. Significant differences occurred for body mass index ($P = 0.045$) and sepsis ($P < 0.001$).

Over all 244 patients, ROC analysis of ferritin levels predictive for aHLH revealed 100% sensitivity and 82.6% specificity for a ferritin value of 3,095 µg/L (Fig. 2; AUC 94.7%, 95% CI 0.900–0.994, $P < 0.001$). Looking at the underlying conditions, 4 out of 9 patients (44%) suffered from malignant disorders (AML, ALL, CLL, and NHL). Two patients (22%) presented with autoimmune/autoinflammatory disease (SLE and M. Still), and three patients (33%) suffered from infections (HIV, tuberculosis, and pneumonia). Mortality data at specific ferritin cutoffs are shown in Suppl. Table 4, http://links.lww.com/SHK/A665.

## DISCUSSION

In this retrospective observational study, we screened for aHLH in anesthesiological ICUs to determine the rate of undetected aHLH patients. Case-by-case analysis revealed a total of 9 aHLH patients detected via retrospective ferritin-based screening of a 244 patients cohort with hyperferritinemia (3.7%). Seven out of 9 aHLH patients were never considered to suffer from aHLH. If only deceased patients are considered, the aHLH rate rises up to 5.6%. To the best of our knowledge, no other study investigated the estimated number of undiagnosed cases of aHLH in ICUs.

Adult HLH is a rare life-threatening hyperinflammatory syndrome due to uncontrolled immune regulation causing MODS with fatal outcome (19). Little is known about its epidemiology in ICUs, though an increasing number of case reports and series were published during the last decade (9, 28–31). Barba et al. (29) and Buyse at al. (30) reported 71 and 56 ICU patients, respectively, suffering from aHLH with mortality rates of 68% and 52%. All of these patients were admitted due to acute multiple organ failure. A recent study of Halacli et al. (32) investigated HLH-2004 criteria in 10 patients suffering from severe sepsis and septic shock. All had at least 5 out of 8 positive criteria but only one was correctly diagnosed and treated. This study exluded patients with malignancies, which constitute a major proportion of adult patients with aHLH as shown by us and others (33, 34). As malignant disorders and anticancer treatment predispose patients to develop aHLH, excluding those patients ignores a significant risk population.

Tothova et al. (8), Okabe et al. (9), Machowicz et al. (35), and our research group (36) suggest aHLH being underdiagnosed in ICUs due to overlap with septic shock and MODS. In patients with progressive fever, cytopenia, and organomegaly, an aHLH work-up is recommended by expanded laboratory testing. Routine ICU lab panels should be expanded by white blood differential, ferritin, triglycerides, fibrinogen, ASAT, and sIL-2R.

A very valuable, easily available and cost-effective marker in the clinical context is serum ferritin. Eighty-four percent sensitivity was calculated for the 500 µg/L cutoff in the pediatric HLH-1994 trial (6). This trial included children with the age up to 18 years and may therefore not be representative for adult patients with HLH. Pediatricians have revisited their

TABLE 2. **HLH-2004 criteria and HScore in 244 ICU patients with ferritin at least 500 μg/L**

| | ICU survivors (n = 173) | Death (n = 71) |
|---|---|---|
| Hemoglobin (g/dL), n = 173\|71 (normal range: 11.8–15.8 (f), 14.0–17.5 (m)) | 8.6 (8.0–9.2) | 8.7 (8.2–9.3) |
| Platelet count (/nL), n = 173\|71 (normal range: 150–400) | 204.0 (131.0–284.5) | 91.0 (55.0–156.0) |
| Leukocyte count (/nL), n = 173\|71 (normal range: 4.5–11.0) | 8.3 (5.8–12.4) | 9.7 (6.4–14.6) |
| Ferritin (μg/L), n = 173\|71 (normal range: 30–400) | 1,158.0 (714.0–1,878.5) | 1,923.0 (1,061.0–5,380.0) |
| Triglycerides (mg/dL), n = 106\|51 (normal range: <180) | 147.0 (94.8–204.5) | 168.0 (99.0–300.0) |
| Fibrinogen (mg/dL), n = 154\|67 (normal range: 150–400) | 440.0 (315.8–561.8) | 349.0 (233.0–477.0) |
| ASAT (U/L), n = 172\|71 (normal range: <35) | 36.5 (25.0–64.8) | 59.0 (34.0–97.0) |
| sIL-2R (IU/mL), n = 4\|4 (normal range: <1,000) | 1,826.5 (842.3–2,401.3) | 2,332.5 (808.0–6,366.5) |
| Maximum core body temperature (°C), n = 173\|71 | 37.7 (37.2–38.4) | 38.5 (37.1–38.8) |
| Hepatomegaly and/or splenomegaly (yes/no), n = 141\|60 | 35/106 | 28/32 |
| Hemophagocytosis* (yes/no), n = 8\|7 | 0/8 | 0/7 |
| Fulfilled HLH-2004 criteria (n) | 2 (1–2) | 3 (2–3) |
| HScore probability (%) | 0.1 (0.02–0.6) | 3.5 (0.3–40.0) |
| At least 4 fulfilled HLH-2004 criteria (n) | 6 | 17 |
| At least 80% of HScore probability (n) | 4 | 7 |

Diagnostic parameters with n representing the number of patients with available data in each group; continuous quantities in median with quartiles; ASAT, aspartate aminotransferase; sIL-2R, soluble IL-2 receptor.
*Bone marrow biopsy was conducted in 15 patients (5.8%). Significant differences were seen for platelet count ($P < 0.001$), ferritin ($P < 0.001$), fibrinogen ($P = 0.008$), ASAT ($P < 0.001$), maximum core body temperature ($P = 0.003$), hepatomegaly and/or splenomegaly ($P = 0.003$), fulfilled HLH-2004 criteria ($P < 0.001$), and HScore probability ($P < 0.001$).

databases by thorough calculations and improved sensitivity/specificity by providing a threshold of more than 10,000 μg/L in children (37). The use of ferritin as a highly predictive laboratory test for aHLH recently was challenged by retrospective large-scale analysis of hospital databases screened for hyperferritinemic all-age patients (38, 39). Schram et al. and Sackett et al. pointed out that ferritin as high as more than 10,000 μg/L is a poor predictive biomarker in the context of multiple pathophysiologic conditions causing a hyperferritinemic state (liver damage, hemolytic conditions, hemodialysis, hemosiderosis in transfusion dependent patients, malignancy, infections, and others). However, hyperferritinemia in the clinical context of progressive fever, cytopenia, and splenomegaly is highly valuable in particular in ICUs, where sepsis is the major overlapping clinical condition (40). In accordance to previous case series in ICUs (31, 41), ferritin ranged between 3,102 and 107,470 μg/L in our study. Saeed et al. (42) found a ferritin of 3,951 μg/L in ICUs with 88% sensitivity and 82% specificity, whereas a cutoff value of 3,095 μg/L was at 100% sensitivity and 82.6% specificity in our case series. In analogy to ferritin in aHLH, procalcitonin is a widely used biomarker to identify bacterial infections in critically ill sepsis patients. Yet, procalcitonin can be upregulated in cancer and other cytokine storm disorders without bacterial blood stream infections, leaving us with the notion of a large metaanalysis that test results ''must be interpreted carefully in the context of medical history, physical examination, and microbiological assessment'' (43). This, in our opinion, is a core message for improving diagnostic vigilance in ICUs: 1. Focus on medical history: Almost half of our aHLH patients had a previously

TABLE 3. **aHLH patients, case review**

| Case-Id | Age | Sex | Underlying condition | Ferritin (μg/L) | Max. core body temperature (°C) | Hb (g/dL)/ platelets (/nL)/leuko (/nL) | Triglycerides (mg/dL)/ fibrinogen (mg/dL) | sIL-2R (IU/mL) | ASAT (U/L) | Hepato- and/or splenomegaly | Hemopha-gocytosis | ICU/ hospital stay (d) | Fulfilled HLH-2004 criteria | HScore probability (%) | Outcome | Undiag-nosed |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 38 | Male | ARDS, septic shock, H1N1 infection, HIV | 8,878 | 38.8 | 8.4/89/7.19 | 402/408 | – | 31 | Yes | No | 360/389 | 5 | 98.1 | Survived | Yes |
| 2 | 25 | Female | SIRS, Pneumonia, SLE | 3,102 | 39.4 | 7.2/79/3.69 | 563/230 | – | 37 | No | – | 38/81 | 3 | 94.4 | Survived | Yes |
| 3 | 65 | Female | ARDS, septic shock, AML | 15,920 | 38.7 | 8.5/39/3.83 | 158/214 | – | 130 | Yes | – | 29/29 | 4 | 99.8 | Survived | Yes |
| 4 | 37 | Male | ARDS, miliary tuberculosis | 3,115 | 38.8 | 9.0/50/2.93 | 425/170 | – | 214 | Yes | – | 160/217 | 5 | 99.5 | Survived | Yes |
| 5 | 27 | Female | SIRS, FUO, Still's disease, MAS | 9,110 | 38.2 | 7.9/99/2.01 | 168/147 | 1,949 | 105 | No | No | 3/13 | 3 | 64.2 | Survived | No |
| 6 | 49 | Male | Septic shock without focus, CLL, autoimmune hemolytic anemia | 107,470 | 41.3 | 8.1/82/0.81 | 327/146 | – | 377 | Yes | No | 64/79 | 5 | 99.8 | Dead | Yes |
| 7 | 20 | Male | Septic shock, ARDS, state by ALL with allogenic stem cell transplantation | 40,800 | 38.4 | 7.8/94/9.6 | 184/343 | – | 3,274 | No | – | 24/24 | 4 | 88.2 | Dead | Yes |
| 8 | 59 | Male | Septic shock, pneumonia, NHL with antibody deficiency syndrome | 30,420 | 38.5 | 9.0/32/8.1 | 171/144 | – | 17,414 | Yes | – | 3/3 | 5 | 99.0 | Dead | Yes |
| 9 | 29 | Female | Septic shock, pneumonia, MAS | 18,978 | 39.3 | 8.5/60/2.8 | 299/185 | >7,500 | 499 | Yes | – | 70/74 | 6 | 99.7 | Dead | No |

ALL, acute lymphatic leukemia; AML, acute myeloid leukemia; ARDS, acute respiratory distress syndrome; ASAT, aspartate aminotransferase; CLL, chronic lymphatic leukemia; FUO, fever of unknown origin; HIV, human immunodeficiency virus; MAS, macrophage activation syndrome; NHL, non-Hodgkin lymphoma; sIL-2R, soluble IL-2 receptor; SIRS, systemic inflammatory response syndrome; SLE, systemic lupus erythematosus.

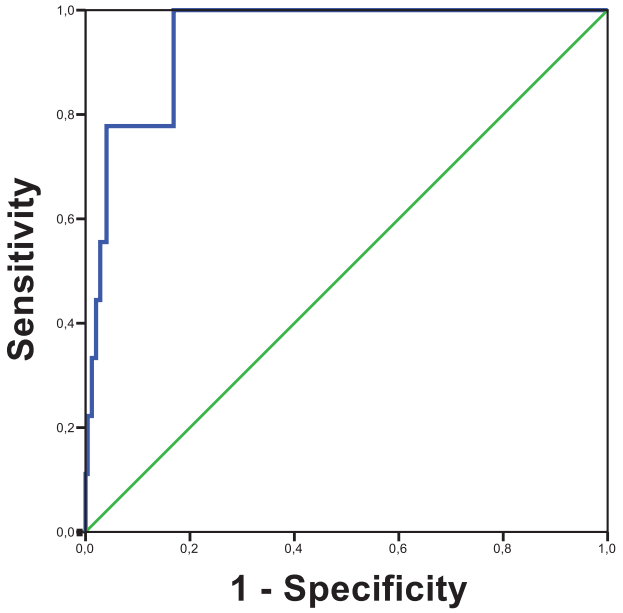


Fig. 2. **ROC analysis of ferritin levels predictive for aHLH.** Over all 244 patients, a ferritin value of 3,095 μg/L was at 100% sensitivity and 82.6% specificity (AUC 94.7%, 95% CI 0.900–0.994, $P < 0.001$).

diagnosed hematologic malignancy. Two additional patients had autoimmune/inflammatory conditions, and only a third of the patients developed aHLH without a known immune affection. 2. Repeatedly focus on physical examination and follow-up diagnostic procedures: As overt inflammation obscures histopathology, malignant lymphoma may remain undetected and may require repeated follow-up invasive diagnostic procedures (liver, skin, lymph node, spleen, liquor) guided by sequential imaging procedures including positron emission tomography (PET) (44, 45). Adult HLH is not a disease by itself, but rather an inflammatory tip of an iceberg of an underlying disorder. It is enriched in patients with acquired or induced immunosuppression (46, 47). In summary, it cannot be overemphasized to assess ferritin in every patient with unexplained cytopenia, organomegaly, or fever refractory to antibiotics, and to include ferritin to the sepsis work-up.

Bone marrow diagnostics are needed as part of the HLH-2004 criteria to search for hemophagocytosis. Yet, hemophagocytosis may only be detectable in 60% to 80% of patients with HLH despite its name-giving role (1). To perform, a bone marrow biopsy is not only mandatory in the search for hemophagocytosis, but also required as part of a thorough lymphoma and infectious disease (tuberculosis, leishmaniasis) work-up. In contrast, functional NK cell diagnostics, which are part of the HLH-2004 criteria, are usually dispensable, as most patients enter ICUs deeply cytopenic, and may be pretreated with lymphocyte depleting steroids. Fardet et al. also excluded measurement of NK cell function from the diagnostic panel (Suppl. Table 2, http://links.lww.com/SHK/A665) (16). Tests are time consuming and costly and should never cause delayed treatment due to pending test results (20).

It is important to reflect on patient age in our and many other patient series of aHLH: age in this series ranges from 20 to 65 years, median age in the German aHLH registry is about 50 years (17–80) (34). Hence, elderly patients should not be withheld from aHLH work-up.

Almost all of our undiagnosed patients were primarily diagnosed with septic shock highlighting the capability of imitation and the difficulty in recognition (12, 40). Underlying conditions could be identified in all seven undiagnosed cases, i.e., H1N1 infection, miliary tuberculosis, SLE, and hematological malignancy in four patients. The four undiagnosed survivors in our study most likely survived because of combined life support measures (SOP-guided intensive care) with disease-specific treatment of the underlying trigger despite aHLH remaining undetected. Thus, in adults, diagnosing aHLH should not trigger unreflected treatment according to the standard pediatric HLH-1994 protocol, but rather focus on treatment of the disease that is causing aHLH by close interaction of intensive care specialists, hematologists, rheumatologists, and clinical infectious disease specialists (20).

Treatment of aHLH is aimed to interfere with self-sustaining aberrant inflammation and the trigger condition identified to being causative for the cytokine storm. Hence, it cannot be standardized. Effective inhibition of cytotoxic T-lymphocyte proliferation and macrophage activity is imparted by corticosteroids and etoposide. Polyvalent immunoglobulins are administered to neutralize cytokines and splenic phagocytosis (48). In patients with steroid refractory aHLH not amenable to etoposide due to organ failure, cytokine adsorption or plasmapheresis may be considered (49). As soon as the patient is stabilized, treatment has to focus on the infection, malignant disorder, or autoimmune/inflammatory disease (20). Contact to the respective national aHLH reference center with involvement of aHLH experts is highly recommended (20). In patients with suspected aHLH, the authors recommend the following scheme (Fig. 3).

Mortality of our selected cohort is 44%. In previous ICU studies, mortality of aHLH ranged between 52% and 68% (29, 30). However, our case series comprises only nine aHLH patients and most of these remained undiagnosed preventing us from computing meaningful statistics. Nonetheless, the consistent high mortality rate of aHLH in the available literature reminds us to improve our diagnostic vigilance not to miss timely onset of therapeutic measures against the fatal aHLH cytokine storm. A time-dependent prognosis (initiation of aHLH treatment <4 weeks after symptom onset) has consistently been published (50, 51).

It is of note that a recently published subgroup analysis of a large randomized controlled multicenter trial that tested interleukin-1 receptor blockade via Anakinra in sepsis demonstrated potential use of Anakinra in patients with aHLH symptoms, i.e., hepatobiliary dysfunction and disseminated intravascular coagulation (52). Although Anakinra failed to demonstrate beneficial effects in the entire sepsis cohort, this subgroup analysis shed further light on potentially undetected aHLH patients in ICUs.

Our study has some obvious limitations: first, this is a retrospective chart review analysis. It depends on patchy data documentation in particular with regard to HLH-2004 diagnostic criteria. Second, aHLH diagnosis from charts only has the limitation of being devoid of the full clinical picture. Third, due

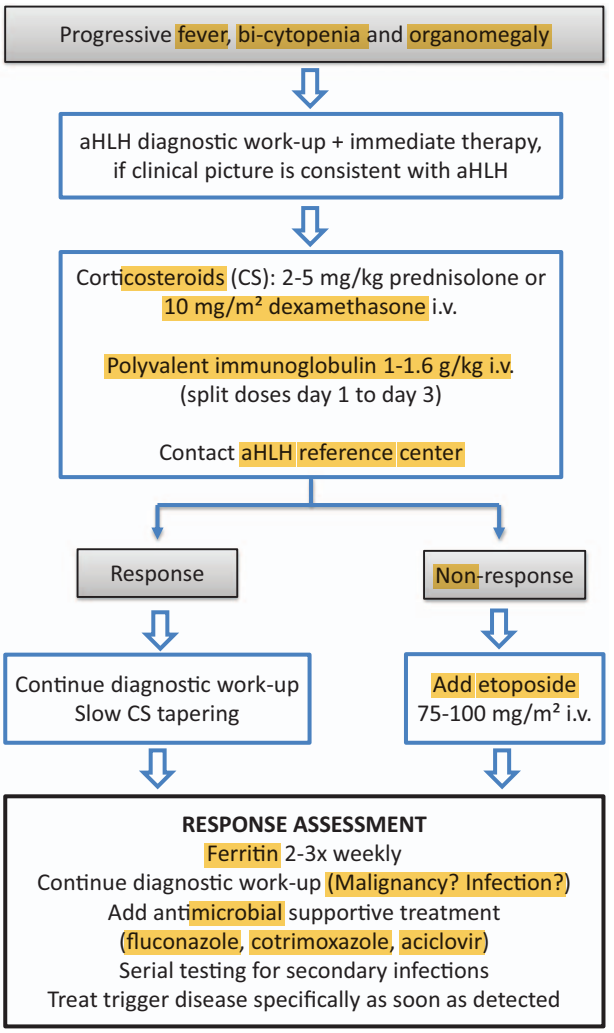


FIG. 3. **aHLH flow.** In patients with suspected aHLH, the authors recommend immediate therapy, if the clinical picture is consistent with aHLH.

to the time lapsing between start of symptoms and sampling for ferritin measurement, it is probable that patients with hyperferritinemia were lost. Nonetheless, our data bare comparison with the available literature and provide evidence that undetected aHLH patients do not receive appropriate treatment with subsequent fatal outcome.

## CONCLUSIONS

In conclusion, 7 out of 9 patients (77.8%) suffering from aHLH remained undiagnosed. Awareness of this life-threatening syndrome, especially in ICUs, should be raised. Patients with bicytopenia, treatment resistant fever, and splenomegaly are highly suspicious for aHLH. aHLH work-up including routine assessment of serum ferritin is warranted.

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