Adult Hemophagocytic Lymphohistiocytosis: More Data; Even More Questions*

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The diagnosis of hemophagocytic lymphohistiocytosis (HLH) and consideration of this diagnosis have skyrocketed in the past decade (1). It seems that no one can be admitted to the ICU with sepsis and thrombocytopenia without a bright resident, having studied for the board examination, proudly raising the specter of HLH. Yet, many adult hematologists would list this among their least favorite reasons to consult not because of the poor prognosis appended to this diagnosis (we are used to that). Their dismay is related to the nonspecific diagnostic criteria, which render the diagnosis unclear in many cases, and how and when to "specifically" intervene can be nebulous. The senior author has managed a number of clear-cut adult HLH cases, among them are a young man with underlying DiGeorge syndrome, another on immunosuppressive therapy for organ transplant, and a young woman with idiopathic Epstein-Barr virus-driven disease. Furthermore, hematologists do not relish confrontations with their rheumatology and internal medicine colleagues (case 2 below). Three of our cases illustrate some of the challenges.

CASE 1

A 44-year-old man became ill with fever, diarrhea, myalgia, and headache during a Mexican vacation. Symptoms repetitively recurred with temperatures above 40°C, resulting in two hospitalizations. Doxycycline and oseltamivir were not beneficial. Hemoglobin fell to 7.7 g/dL and leukocytes elevated to 18.5×10^9/L, platelets to 584×10^9/L, reticulocytes 0.2%, and ferritin 158 µg/L. Cultures and serologies for multiple organisms were negative. Bone marrow showed histiocytic hyperplasia and marked hemophagocytosis, officially interpreted as "HLH." The patient received corticosteroids and was scheduled for etoposide infusion. A second opinion found positive serology for *Salmonella typhi* H type B. After ciprofloxacin treatment, all symptoms and signs abated; the patient remains well 7 years later.

CASE 2

A 58-year-old woman, given trimethoprim-sulfa for a urinary tract infection, required ICU admission 10 days later for high fever, confusion, and severe pancytopenia. Bone marrow was 20% cellular with decreased megakaryocytes, virtually no granulocyte precursors, and debris-filled histiocytes (no hemophagocytosis). Treatment included antibiotics, granulocyte colony-stimulating factor, steroids, intubation, and pressors. White count rose to 37.6×10^9/L by hospital day 10, platelets recovered soon after, but high fever and signs of sepsis continued. Computed tomographic (CT) scan showed bilateral pulmonary infiltrates and colitis. Hospitalists and rheumatologists felt that criteria were satisfied for HLH and initiated IV immunoglobin G and cyclosporine, but hematologists (the two authors) argued that the problem was ongoing infectious sequelae from drug-induced marrow injury. Ferritin peaked at 2,494 µg/L, sIL2R was twice normal, and natural killer (NK) cell functional activity was 3.9 lytic units (normal, 5.8–59.2). Repeat CT scan showed lung abscess and free intraperitoneal air. Ischemic colon resected at emergent laparotomy stained positive for fungal elements; peritoneal fluid grew enterococcus and clostridium. The patient expired on hospital day 24.

CASE 3

A 14-year-old girl presented in 2004 with high fever, headache, hepatosplenomegaly, and pancytopenia. Ferritin was 10,297 µg/L, sIL2 receptor was 4,778 (normal, < 2,678), triglycerides were high, fibrinogen was low, and perforin and granzyme expression were low by flow cytometry; HLH genetic panel was negative. She achieved remission on the HLH-2004 protocol (steroids, etoposide, and cyclosporine). In 2008, she was retreated for relapse and then received a matched unrelated donor allogeneic bone marrow transplant. She did well (few managed complications) until 2013 when she was admitted to the ICU with fever and bilateral lung infiltrates. Platelets were 51×10^9/L, spleen was enlarged by imaging, ferritin was 11,661 µg/L (5 times > 2 mo earlier), triglycerides were 7.41 mmol/L, and sIL2 receptor was twice normal. Bone marrow performed for suspected HLH relapse was morphologically normal with 100% donor cells by short tandem repeat

*See also p. e1045.

Key Words: ferritin; hemophagocytic lymphohistiocytosis; hemophagocytosis; sepsis thrombocytopenia

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testing. Blood and urine cultures grew *Escherichia coli* (*E. coli*). All signs dramatically improved with antibiotic therapy over a 4-day hospital course. She remains well since.

HLH can be a devastating syndrome characterized by uncontrolled macrophage and lymphocyte activation leading to fever, hepatosplenomegaly, cytopenias, multiple-organ failure, and high mortality. Described in 1939, "histiocytic medullary reticulosis" was thought extremely rare (2). Subsequently HLH was linked to hematologic malignancies, particularly to non-Hodgkin lymphomas, portending a dismal prognosis. HLH was found to be more common in children where the primary form predominates because of inherited abnormalities in NK- or T-cell function. The Histiocytosis Society deserves congratulations for increasing awareness, establishing diagnostic criteria and treatment protocols, and thus improving the outlook for affected children (3, 4). We fully agree with Grange et al (5) that the diagnostic criteria extrapolate poorly to adult ICU patients and to adult patients in general. The criteria rely on markers of inflammation and cytokine release, which can occur in many highly inflammatory conditions, particularly sepsis. For example, markedly elevated ferritin (> 10,000 µg/L) was reported 90% sensitive and 96% specific for HLH in children (6), but levels of more than 50,000 µg/L predict HLH in less than 20% of adults (most with hematologic malignancy or sepsis) (7).

Case 1 (above) illustrates that hemophagocytosis is not specific (nor is it entirely sensitive) for HLH. The hematopathologist who interpreted the bone marrow might argue that this represents HLH secondary to typhoid fever, but most would probably agree that this constitutes typhoid fever period, a disease in which histiocytic hyperplasia and hemophagocytosis are characteristic, as with other intracellular pathogens (8). Certainly, therapy should be directed to the infection, and initiating HLH-specific treatment (as almost happened) might be disastrous. Cases 2 and 3 highlight that the criteria for HLH can characterize any severe acute infectious/inflammatory insult, where proinflammatory cytokine release can be expected. Case 3 is an HLH patient who exhibited signs compatible with relapse in the context of a septic event even after any genetic propensity had been corrected by bone marrow transplant! Is there anything to be gained by considering these cases as HLH secondary to infection and instituting HLH-directed therapy versus just treating the "triggering" problem?

In this issue of *Critical Care Medicine*, Grange et al (5) report the largest series of adult ICU patients with hemophagocytosis (5). Among more than 11,000 consecutive ICU admissions at Rouen University Hospital over a 12½-year period, 419 had bone marrow examinations performed generally for low platelets and/or other cytopenias. Excluding patients with known hematologic malignancy, 42% had hemophagocytosis visible on marrow examination. Thus, hemophagocytosis occurs in at least 1–2% of all ICU admissions, highlighting the importance of this problem for intensivists. Among these 106 patients with hemophagocytosis unrelated to malignancy, this most often occurred with bacterial sepsis (76%); *E. coli* was most commonly implicated (30%, as in case 3 above).

Thrombocytopenia occurs in 30–50% of ICU patients and is a major prognostic factor for survival (9, 10). Causes of thrombocytopenia include medication side effects, devices such as intraaortic balloon pumps, and heparin-induced thrombocytopenia (HIT; a small minority), but most commonly sepsis. The mechanism of sepsis thrombocytopenia has been debated for decades but is uncommonly related to overt or subclinical disseminated intravascular coagulation (9–11). More than a marker for severe disease, recent studies demonstrate important contributions of platelets to host defense in sepsis (9, 10). François et al (11) provocatively found visible hemophagocytosis in bone marrows from many sepsis thrombocytopenia patients. We differ from Grange et al (5) in that we do not routinely perform marrow examinations in septic patients with thrombocytopenia. As results rarely impact patient management, we reserve the examination for those with unusual features, such as signs of hematologic malignancy.

In adults with nonmalignancy-related secondary HLH (mostly sepsis patients), Grange et al (5) find that serum ferritin above 2,000 µg/L predicts 43% mortality. This high mortality could stimulate a multicenter exploration of whether specific intervention for hemophagocytosis is beneficial to such patients. Perhaps ferritin should be routinely measured in septic thrombocytopenic ICU patients, and one could randomize those with levels above 2,000 µg/L and hemophagocytosis on marrow examination (mandated by the clinical trial) to specific intervention (perhaps IVIG ± steroids) versus usual care. IVIG is a safer alternative to etoposide or cyclosporine-based regimens, with comparable efficacy in some reports for adult hemophagocytosis and/or macrophage activation patients. We are not the first to call for a prospective trial of IVIG in adult HLH although accomplishing such a trial could be challenging (12).

PENDULUMS SWING

HIT was long an underappreciated problem, limbs and lives lost as heparin continued to drip. One consequence of efforts to increase HIT awareness has been an epidemic of overdiagnosis with attendant patient harms (13). After years of exhortations for primary care and emergency physicians to be vigilant for thrombotic thrombocytopenia purpura (TTP), a disorder highly lethal if not promptly appropriately managed, this diagnosis is much less often missed, but hematologists pay a price in increased midnight calls to "rule-out TTP" in patients with decompensated cirrhosis, encephalopathy, and platelets of 80×10^9/L (platelets are always less than half this in TTP). At least with HIT and TTP, there are specific confirmatory laboratory tests, which is not the case with the nonspecific inflammatory markers of HLH. Others have begun to stress differences between adults and children in HLH causes and presentations (14) and to call for considered and sequential approach to therapy beginning with supportive care and addressing underlying causes (15). Our experience supports caution in making

the diagnosis of HLH in adults and in determining when and how to intervene.

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A Glimpse of Precision Medicine for Multiple-Organ Dysfunction Syndrome*

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In this issue of *Critical Care Medicine*, Abboud et al (1) working at the University of Pittsburgh report progress unraveling the riddles of multiple-organ dysfunction syndrome (MODS).The Pittsburgh group has been performing serial multiplex analysis of plasma sampled from patients with severe trauma. They accumulated 493 patients, looked at the outcomes, and saw that 19 died of (seemingly aseptic) MODS. They searched the pool of survivors, found the 19 closest matches, and asked of the data whether there were discernible patterns among the soluble signal molecules.

The first finding was that, compared with the survivors whose signal molecules seemed to be involved in a quiet, balanced conversation, there was commotion in the plasma of MODS. The second finding was that the commotion in the plasma preceded the progression of organ dysfunction. The third finding was that much of the commotion was concentrated in a signal network governed by a specific interleukin (IL). The fourth—and perhaps the most tantalizing—finding was that in a mouse model of trauma (a model known to reasonably reproduce the human condition, at least in its early escalation phase), squelching that governing IL with a specific antibody mitigated at least some organ dysfunction.

What precisely is new here that warrants a reader's attention, especially the attention of those who work at the bedside and not the bench? It is not the mere existence of "a commotion in the blood"—almost two decades ago, Hall (2) recounted the discovery of the molecules driving inflammation within the innate immune system. Neither is it the sequential aspect of MODS, which was recognized when "multiple-organ failure" was first described four decades ago (3). Neither is it a discovery of a "new" signal—IL-17 first came to light a quarter century ago during a differential screening experiment (4). Neither is it the now-familiar observation that neutralization of a signal molecule in a mouse can improve recovery from a modeled critical state: there have been hundreds of hopes around such observations later dashed at clinical trial (5).

There are at least three things that are new.

First, there is the method. The authors made no presupposition about important signals beyond the selection of molecules

***See also p. e1074.**

Key Words: immunology; multiple-organ dysfunction syndrome; network analysis

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The Use of Ferritin to Identify Critically Ill Patients With Secondary Hemophagocytic Lymphohistiocytosis*

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Objectives: Thrombocytopenia is a common, multifactorial, finding in ICU. Hemophagocytosis is one of the main explanatory mechanisms, possibly integrated into hemophagocytic lymphohistiocytosis syndrome, of infectious origin in the majority of cases in ICU. The hemophagocytic lymphohistiocytosis is probably underdiagnosed in the ICU, although it is associated with dramatic outcomes. The main objectives of this work were to identify the frequency of secondary hemophagocytic lymphohistiocytosis, and the main prognostic factors for mortality.

Design/Setting: We conducted a retrospective observational study in all adult patients admitted with suspected or diagnosed hemophagocytic lymphohistiocytosis, between January 1, 2000, and August 22, 2012.

Patients: A total of 106 patients (42%) had significant hemophagocytosis on bone marrow examination, performed for exploration of thrombocytopenia, bicytopenia, or pancytopenia.

Measurements and Main Results: The median age was 56 (45–68) and the median Simplified Acute Physiology Score 2 was 55 (38–68). The main reason for ICU admission was hemodynamic instability (58%), predominantly related to sepsis (45% cases). The main precipitating factor found was a bacterial infection in 81 of 106 patients (76%), including 32 (30%) with *Escherichia coli* infection. Forty six of 106 patients (43%) died in the ICU. They were significantly older, had higher Simplified Acute Physiology Score 2, plasma lactate dehydrogenase bilirubin, and serum ferritin. The fibrinogen and the percentage of megakaryocytes were significantly lower in nonsurvivors when compared with survivors. In multivariate analysis, only serum ferritin significantly predicted death related to hemophagocytosis. A serum ferritin greater than 2,000 µg/L predicted death with a sensitivity of 71% and a specificity of 76%. A decreased percentage of megakaryocytes also predicted patient death in the ICU.

Conclusions: Hemophagocytosis is common in thrombocytopenic patients with sepsis, frequently included in a postinfectious hemophagocytic lymphohistiocytosis setting. Our study reveals that ferritin could be a reliable prognostic marker in these patients, and hold particular interest in discussing a specific treatment for hemophagocytic lymphohistiocytosis. (*Crit Care Med* 2016; 44:e1045–e1053)

Key Words: ferritin; hemophagocytic lymphohistiocytosis; hemophagocytosis; intensive care unit; thrombocytopenia

Hemophagocytic lymphohistiocytosis (HLH) is characterized by clinical and biological abnormalities resulting from dysregulated activation and proliferation of lymphocytes, leading to the overproduction of cytokines (1–3). HLH can either be primary or secondary (4). Primary HLH is observed in malignant familial forms, which mainly occur in early childhood. Secondary HLH can be related to infectious diseases (viral, bacterial, or fungal), associated with malignancies, or due to other rare causes (toxic or metabolic). Secondary HLH in adults carry a poor prognosis, with a mortality rate between 20% and 60%, according to studies conducted primarily in oncohematology and internal medicine patients (5–8). ICU patients are particularly affected by the occurrence of this syndrome in sepsis (9–12). To date, a single study evaluating the frequency of HLH and the risk factors for death in this population has been conducted in the ICU setting, with a specific recruitment of oncohematology patients (13).

Some authors suggest that "hypercytokinemia" and possibly "hyperchemokinemia," generated by uncontrolled activation of histiocytes, are responsible for multiple organ dysfunction

*See also p. 2119.

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syndrome, which may require ICU admission (14–17). Bone marrow aspiration (BMA) is the gold standard for the detection of hemophagocytosis, and must be performed whenever HLH is suspected (**Fig. 1**). The hemophagocytosis usually observed during septic shock is a physiologic response and probably does not require a specific treatment. However, in more severe cases, HLH is in the foreground, and is associated with a catastrophic outcome in the absence of specific treatment. There are unfortunately no reliable diagnostic tests to identify this category of patients.

Data on the prevalence and risk factors of hemophagocytosis are scarce, especially in the medical ICU setting. The few frequency studies available are retrospective, and ICU populations studied are very different from one publication to another (18, 19). HLH is difficult to identify, because it can mimic septic shock with multiple organ failure (20). Patients receive care for the septic shock, leading to a diagnostic and therapeutic delay regarding HLH (21). The lack of specificity of biomarkers makes this diagnosis particularly difficult. To address this issue, we conducted an observational retrospective single-center study, in all patients diagnosed with thrombocytopenia/bicytopenia/pancytopenia and a bone marrow hemophagocytosis in Rouen University Hospital Medical ICU, between January 2000 and August 2012. The main objective of this study was to identify in this population highly suspected of having secondary HLH the main prognostic factors for mortality. We also focused on HLH related to microbial infection, which are particularly frequent in medical ICUs (22–25).

METHODS

We conducted a retrospective observational study in all adult patients admitted to the Medical ICU of Rouen University Hospital between January 1, 2000, and August 22, 2012, with highly suspected HLH. Census of suspected cases of HLH was possible, thanks to the consultation of BMA directory of the hematology laboratory. Hemophagocytosis was defined as the detection on BMA of activated macrophages engulfing erythrocytes, platelets, leukocytes, or their precursor cells. A semi-quantitative assessment of macrophages (1, few macrophages; 2, some macrophages; 3, fairly numerous macrophages; and 4, numerous macrophages) and megakaryocytes (0, none; 1, rare; 2, few; 3, normal; 4, many; and 5, numerous) was performed by a cytologist. BMA cellularity was satisfactory in all patients studied. We identified patients for whom the indication of bone marrow examination was the investigation of thrombocytopenia, bicytopenia, or pancytopenia. Thrombocytopenia was defined as a platelet count less than 150 G/L, anemia by transfusion need between the date of ICU admission and the date of BMA or hemoglobin less than 10 g/dL on the day of BMA, and leukopenia a count of total leukocytes less than $4 \times 10^9/mm^3$. Ferritin, plasma triglycerides, lactate deshydrogenase (LDH), fibrinogen, activated partial thromboplastin time (aPTT, compared to control values), prothrombin index, presence or absence of soluble fibrin, total bilirubin, aspartate aminotransferase, and creatinine were collected if the assay was performed on the day, the day before, or the day after the BMA. Patients with recently diagnosed and/or treated oncohematologic disease (chemotherapy within 6 mo prior to hospitalization), or benefiting from BMA for another indication than thrombocytopenia, or did not present hemophagocytosis were excluded from the study. Thus thrombocytopenia was considered to be independent of a neoplastic context and of chemotherapy. All clinical and biological data were collected from the patients' medical records in paper or electronic format. Patients were supported by physicians of the medical ICU, and by hematologists in the presence of an associated stable oncohematologic disease. The severity score used was the Simplified Acute Physiology Score (SAPS) 2. This study was reviewed by a local ethical board and was in full accordance with international ethical principles.

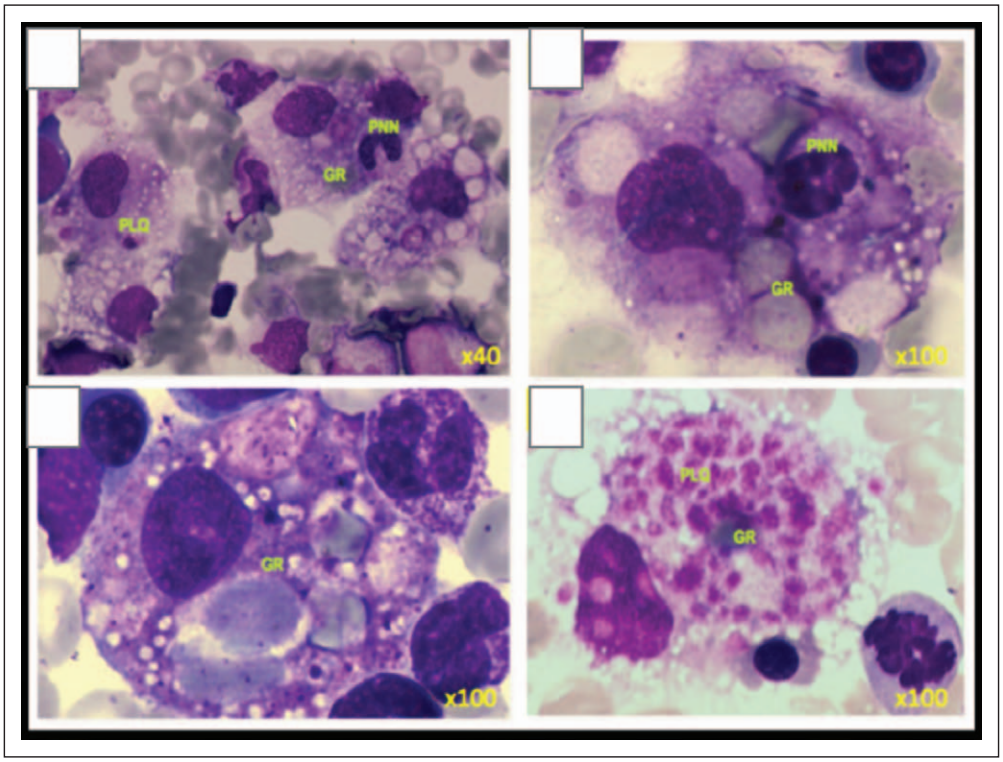

Figure 1. Morphology aspect of hemophagocytic syndrome. GR = RBCs, PLQ = platelets, PNN = neutrophils.

STATISTICS

The results are described as median (interquartile range) or number (%), unless otherwise stated. Patient characteristics were compared using the chi-square test or Fisher exact test for categoric variables, and Mann-Whitney *U* test for continuous variables. Associations linking patient characteristics

with hospital mortality were evaluated with a logistic regression model. All variables associated with hospital mortality in univariate analysis were entered into a model to perform multivariate analysis (model 1). A second multivariate model was used with the following variables: age, SAPS 2, ferritin, LDH, plasma fibrinogen, bilirubin, and number of megakaryocytes (model 2). In model 2, we kept variables with prognostic value for mortality in ICU HLH patients. All tests were two-sided, and the value of "*p*" was considered statistically significant if less than 0.05. Analyses were performed using STATA Version 9.1 (StataCorp, College Station, TX).

RESULTS

During the study period, 11,004 patients were admitted and we identified 460 BMAs, performed in 419 patients (**Fig. 2**). Based on the cytologic data, the biologist concluded to a single or multiple specific diagnoses, or to peripheral or central mechanism. Bone marrow examination was considered inconclusive in the presence of insufficient cytologic signs of deficiency or hemophagocytosis, and in the absence of argument for another diagnosis. Hemophagocytosis represented 42% of cytologic results, and acute folate deficiency 19%. The diagnosis could not be made in 10.6% of cases. The smear was defective or diluted in 14.4% of cases.

A total of 106 patients with hemophagocytosis were included. **Table 1** reports the main supportive treatments and

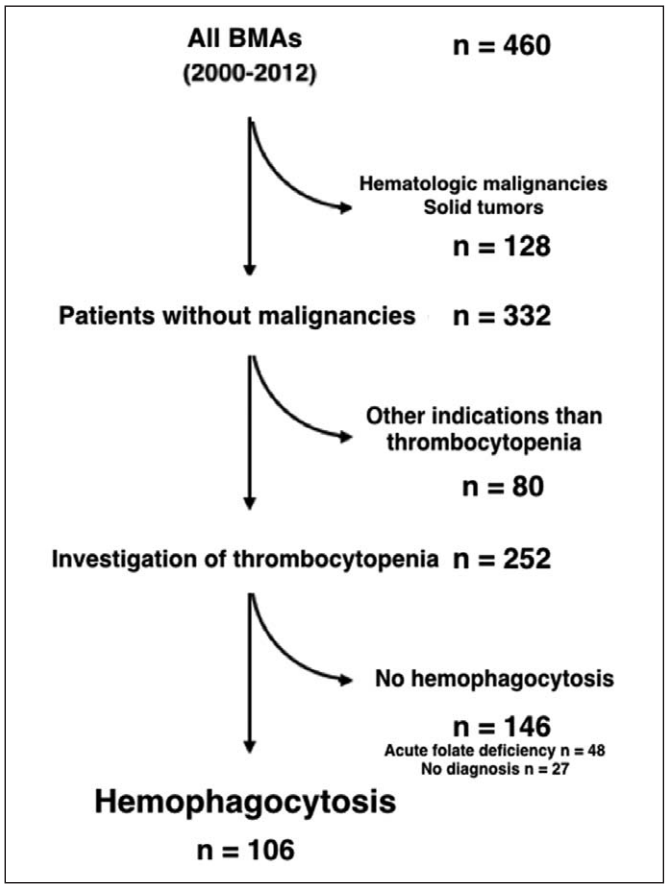

Figure 2. Study inclusion flowchart. BMA = bone marrow aspiration.

TABLE 1. Life-Supporting Treatments and Laboratory Criteria on the Day of Bone Marrow Aspiration and Outcome

BMA, *n* (%)	106 (100)
Mechanical ventilation, *n* (%)	83 (78)
Vasoactive drugs, *n* (%)	90 (85)
Renal replacement therapy, *n* (%)	66 (62)
Platelet units transfusion	3 (2–5)
Temperature (°C)	38.8 (38.2–39.4)
Laboratory criteria on the day of BMA	
Hemoglobin (g/dL)	9.2 (8.4–10.5)
Platelet count (× 10^9/L)	43 (24–58)
Neutrophil count (× 10^9/mm^3)	11.5 (7.3–20.6)
Patients with isolated thrombopenia	32 (30)
Patients with bicytopenia	56 (53)
Patients with pancytopenia	18 (17)
Ferritin (μg/L)	1,110 (631–4,460)
Triglyceridemia (mmol/L)	2.29 (1.38–3.7)
LDH (UI/mL)	798 (512–1,498)
Fibrinogen (g/L)	5.2 (3.5–7.1)
Bilirubin (μmol/L)	34 (18–85)
SGOT (UI/L)	76 (41–152)
SGOT > upper limit of the normal range	81 (76)
Creatinine (μmol/L) (nondialysed patients)	123 (71–179)
Time from admission to BMA	5 (2–10)
ICU length of stay (d)	15 (8–28)
Hospital length of stay (d)	25 (13–42)
Death in the ICU	46 (43%)
Prevalence of HLH-2004 and Imashuku-1997 HLH criteria, *n* (%)	
Fever (> 38.5°C)	62/89 (70)
Cytopenias	
Hemoglobin < 9 g/dL	46/106 (43)
Platelets < 100 × 10^9/L	100/106 (94)
Neutrophils < 1 × 10^3/mL	5/106 (6)
Bicytopenia or pancytopenia	74 (69)
Hypertriglyceridemia > 3 mmol/L	23/66 (35)
Hypofibrinogenemia < 150 mg/dL	5/75 (7)
Ferritin > 500 ng/mL	55/69 (80)
Ferritin > 1,000 ng/mL	40/69 (58)
LDH > 1,000 UI/mL	31/76 (41)

BMA = bone marrow aspiration, HLH = lymphohistiocytosis syndrome, LDH = lactate deshydrogenase, SGOT = serum glutamic oxaloacetic transaminase.

TABLE 2. Precipitating Factors *n* (%) (149 Factors in 106 Patients)

	n (%)
Gram-negative bacteria	
Escherichia Coli	32 (30)
Pseudomonas aeruginosa	14 (13)
Klebsiella Pneumoniae	7 (7)
Haemophilus influenzae	5 (5)
Acinetobacter Baumannii	2 (2)
Enterobacter cloacae	2 (2)
Serratia marcescens	2 (2)
Stenotrophomonas maltophilia	1 (1)
Enterobacter aerogenes	1 (1)
Bacteroides fragilis	1 (1)
Proteus mirabilis	3 (3)
Proteus vulgaris	1 (1)
Neisseria meningitidis	1 (1)
Klebsiella oxytoca	1 (1)
Gram-positive bacteria	
Coagulase-negative staphylococci	5 (5)
Staphylococcus aureus	12 (11)
Streptococcus pneumoniae	9 (8)
Group A β-hemolytic streptococcus	3 (3)
Group C streptococci	2 (2)
Non-grouped streptococci	2 (2)
Enterococcus faecium	4 (4)
Enteococcus faecalis	1 (1)
Lactobacillus	1 (1)
Staphylococcus hominis	1 (1)
Corynebacterium propinquum	1 (1)
Mycobacterium tuberculosis	1 (1)
Leptospirosis	3 (3)
Fungi	
Candida	4 (4)
Aspergillus	4 (4)
Pneumocystis	1 (1)
Histoplasma capsulatum	1 (1)
Virus	
Epstein-Barr virus	4 (4)
Hepatitis B	1 (1)
Herpes simplex virus	1 (1)
Cytomegalovirus	1 (1)
HIV	1 (1)
Influenza 1 (H1N1)	1 (1)
Tumoral diseases	
B Cell Lymphoma	2 (2)
Castleman's disease	1 (1)
Kaposi's sarcoma	1 (1)
Chronic myeloid leukemia	1 (1)
Other malignant diseases	5 (5)
Underlying immune disease	
Autoimmune hemolytic anemia	2 (2)
Lupus	1 (1)
Antineutrophil cytoplasmic antibody-associated vasculitis	1 (1)
Rheumatoid arthritis	1 (1)
Autoimmune hepatitis	1 (1)

laboratory results on the day of BMA, including diagnostic criteria for HLH, and patient outcomes. The BMA was performed to evaluate thrombocytopenia, bicytopenia, or pancytopenia in 30%, 53%, and 17% of cases, respectively. Based on the HLH-2004 criteria, 69% of patients had bicytopenia or pancytopenia, 35% had hypertriglyceridemia (> 3 mmol/L), 7% had hypofibrinogenemia, and 80% had hyperferritinemia. The potential precipitating factors are shown in **Table 2**. A bacterial infection was found in 76% of patients, in most cases Gram-negative bacteria (*Escherichia coli* in 30% of cases). A viral infection was present in 8% of patients, which was considered as the HLH trigger in seven patients (four infections with Epstein-Barr virus, one with cytomegalovirus, one with herpes simplex virus, and one with H1N1 virus). The hospitalization time before ICU admission was respectively 5.3, 3.8, 5.1, 4.6, 2.3, and 0.6 days if none, rare, few, normal, many, or numerous megakaryocytes were present on the BMA.

Differences between ICU survivors and nonsurvivors are shown in **Table 3**. Forty-three percentage of patients died in the ICU. The patients who died were significantly older and had a higher SAPS 2 score. An underlying malignancy or autoimmune disease was respectively present in 9% and 6% of patients. Plasma levels of LDH, bilirubin, and serum ferritin were greater, and fibrinogen and the score used for quantifying the megakaryocytes were reduced in the patients who did not survive. Deceased patients had more frequently received renal replacement therapy and/or mechanical ventilation. All these factors significantly predicted death in univariate analysis. However, none of these variables predicted ICU mortality in multivariate analysis. In model 2, hyperferritinemia greater than 4,780 µg/L significantly predicted ICU mortality of HLH patients, with a sensitivity of 46% and a specificity of 95% (**Fig. 3**); Hyperferritinemia greater than 2,000 µg/L had a sensitivity of 71% and a specificity of 76%. There was no difference between

TABLE 3. Comparison of Survivors and Nonsurvivors

Patients' Characteristics, *n* = 106 patients	Nonsurvivors, *n* = 46 (43%)	Survivors, *n* = 60 (57%)	*p*
Age, yr	63 (52–70.8)	49.5 (40–59.3)	0.0004
Male gender	30 (48)	31 (52)	0.23
No. of comorbid conditions[a]	1 (0–2)	1 (0–1)	
Time from hospital to ICU admission, d	1 (0–4)	1 (0–1.25)	0.75
Simplified Acute Physilogy Score II	60 (46.3–82.8)	47 (36.5–60.8)	0.002
Temperature (°C)	38.7 (38.2–39.5)	38.9 (38.4–39.4)	0.15
Platelet count (× 10^9/L)	44 (30–61.8)	40 (22.8–55)	0.35
Hemoglobin (g/dL)	9.3 (8.6–10.4)	9.1 (8.2–10.6)	0.86
Leucocytes (10^9/mm^3)	10.8 (6.6–20.5)	11.9 (7.8–20.5)	0.61
Ferritin (µg/L)	3,665 (1,439–10,825)	901 (581–1,750)	0.0006
Triglycerides (mmol/L)	2.5 (1–4.3)	2.2 (1.5–3.2)	0.41
Lactate deshydrogenase (UI/mL)	1,004 (675–1,679)	706 (483–706)	0.01
Fibrinogen (g/L)	4.2 (2.8–5.1)	5.9 (3.6–7.4)	0.006
Activated partial thromboplastin time (compared to control values)	1.37	1.27	0.09
Prothrombin index (%)	72	64	0.11
Patients with soluble fibrin (%)	6/32 (19)	11/42 (26)	0.45
Soluble fibrin[b]	2 (1–3)	2 (1–3)	0.51
Patients with fibrinogen dégradation products (%)	23/29 (79)	36/42 (86)	0.61
Bilirubin (µmol/L)	40 (21–119)	24 (16–75)	0.07
Serum glutamic oxaloacetic transaminase (UI/L)	94 (49–182)	61 (40–134)	0.09
Creatinine (µmol/L)	160 (115–169)	95 (67–169)	
Proportion of bone marrow megakaryocytes	3 (2–4)	3 (3–4)	0.04
Proportion of bone marrow macrophages	3 (2–4)	3 (2–4)	0.34
Reasons for ICU admission			
Shock	22 (48)	40 (67)	0.08
Acute respiratory failure	12 (26)	8 (13)	0.16
Confusion/coma	7 (15)	6 (10)	0.60
Acute kidney injury	0	2 (3)	
Acute liver failure	3 (7)	0	
Life-sustaining therapies			
Mechanical ventilation	42 (91)	41 (68)	0.004
Vasopressors	41 (89)	49 (82)	0.43
Renal replacement therapy	35 (76)	31 (52)	0.02
Platelets units received	4.9		
Hemophagocytic lymphohistiocytosis etiologies			
Septic	41 (89)	57 (95)	0.44
Other	5 (11)	3 (5)	

[a]Comorbid conditions included hypertension, chronic obstructive pulmonary disease, chronic cardiac or renal insufficiency, diabetes, chronic B or C hepatitis, and cirrhosis. The mentioned score is the sum of all comorbidities.

[b]A semi quantitative score was used to assess the soluble fibrin concentration (1–4).

Results expressed as median (interquartile range) or *n* (%).

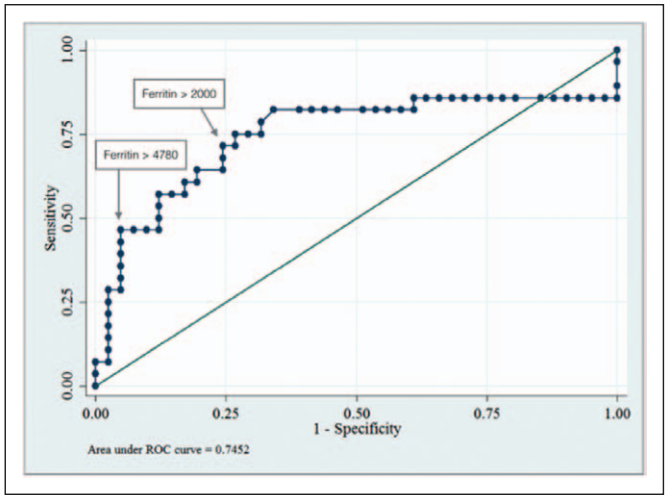

Figure 3. Receiving operating curve (ROC) of ferritin on the day, the day before, or the day after the bone marrow aspiration for predicting mortality. Area under cover: 0.75.

the two groups regarding the semiquantitative assessment of bone marrow macrophages and the biological parameters of disseminated intravascular coagulation (DIC) (activated partial thromboplastin time, prothrombin index, proportion of patients with soluble fibrin). In model 2, a reduced semiquantitative score of megakaryocytes was also marginally predictive of patient death in the ICU ($p = 0.06$).

DISCUSSION

This study describes ICU patients with unexplained thrombocytopenia, bicytopenia, or pancytopenia explored by a bone marrow examination. Hemophagocytosis was the most frequent diagnosis (42%). Our study underlines that hemophagocytosis is an underestimated mechanism for thrombocytopenia in medical ICUs, particularly in patients with septic shock. An alternative cytologic diagnosis explained the thrombocytopenia in 38% of patients. Thus, acute folate deficiency was suspected in 21% of patients because of specific megaloblastic changes, that is, megakaryocytes showing multiple nuclear segments (26, 27). Results from smaller cohorts described diagnosed hemophagocytosis in 44–64% ICU patients analyzed. Risk factors for hemophagocytosis were high macrophage colony stimulating factor levels, multiple organ failure, and septic conditions (16, 17, 23). A German team conducted a retrospective observational study based on autopsy findings in 107 patients who died in ICU (18). HLH was observed in 69 of 107 patients (64.5%). The intensity of hemophagocytosis was positively correlated with T-cell infiltration. Only 50% of patients who had moderate-to-severe HLH had thrombocytopenia, which is consequently not necessary to consider this diagnosis. Another team studied postmortem bone marrow in 28 patients who died of septic shock (28). The hemophagocytosis mainly affected erythroid cells, probably stimulating the macrophage heme oxygenase-1 expression, a protein involved in pathways of anti-inflammatory signalling in sepsis. In another study, soluble cluster of differentiation 163, a marker of macrophage activation, and serum ferritin were increased and predictive of death in 133 ICU patients with pneumococcal bacteremia (29). It is very important for clinicians to be aware that hemophagocytosis may be encountered in patients with sepsis or multiple organ failure. HLH and hemophagocytosis associated with sepsis may overlap and share common characteristics. Usually, the diagnosis of HLH is made with the HLH-2004 diagnostic criteria (**Table 4**), which we did not use for several reasons. These criteria have been established for the diagnosis of primary forms (mainly affecting children, with family history), and are frequently used by analogy in secondary forms, which in our opinion may be inadequate. Two of these criteria are rarely used in routine practice (natural killer-cell activity, soluble interleukin-2 receptor). Fibrinogenemia is not suitable in the context of septic shock, a situation in which it is exceptionally below 1.5 g/L (6% of patients in our series). Similarly, hyperthermia is common in septic patients, and should therefore not be used as a diagnostic criterion for HLH. In addition, all the individual HLH-2004 diagnostic criteria have been reported in situations of severe sepsis/septic shock/multiple organ failure syndrome. Thus, the diagnosis of HLH must be made with caution in a patient with hemophagocytosis and hyperferritinemia, given the overlapping clinical manifestations in these different contexts with significant systemic inflammation. However, because of its severity and possible specific treatment, HLH should be easily evoked in ICU patients presenting some criteria routinely available (fever, organomegaly, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia), especially in the presence of thrombocytopenia/bicytopenia/pancytopenia associated with hemophagocytosis.

Serum ferritin level seems particularly interesting because of its potential diagnostic and prognostic value. In our study, only ferritinemia was significantly associated with death in multivariate analysis. Hyperferritinemia greater than 4,780 µg/L predicted death with a positive predictive value of 93%. However, the sensitivity with this cut-off value is low (46%). In a population of children with severe sepsis/septic shock, Garcia et al (30) showed that hyperferritinemia was associated to a higher risk of death. A retrospective study was performed in 330 children with ferritinemia greater than 500 µg/L. HLH diagnosis was made in 10 of them. Ferritinemia greater than 10,000 µg/L had a sensitivity of 90% and a specificity of 96% for HLH diagnosis (31). A more recent publication describing a larger population found a sensitivity of 70% and a specificity of 68% for a threshold value of 2,000 µg/L (32). The same team demonstrated its prognostic value for mortality in this setting (33). However, these studies were done in pediatric populations, with a majority of primary or virus-induced HLH. Their results can therefore not be generalized in adults with secondary HLH. Nevertheless, our study highlights that hyperferritinemia holds a prognostic value in adults with septic hemophagocytosis and is independently associated with mortality. It is the only factor that independently influenced mortality in our study.

An infectious precipitating factor was identified in 85% of patients. Excluding ICU patients, HLH is often initiated by infectious diseases, predominantly viral (2, 22, 24, 25). In our study, infections were bacterial in most cases. Unexpectedly, we found

TABLE 4. Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis (Histiocyte Society 2004)

The Diagnosis of Hemophagocytic Lymphohistiocytosis May be Established if Five of the Eight Criteria Listed Below Are Fulfilled
Clinical criteria
Fever ≥ 38.5°C
Splenomegaly
Laboratory criteria
Cytopenias (affecting at least two of three lineages in the peripheral blood)
Hemoglobin < 9 g/dL
Platelets < 100×10^9/L
Neutrophils < 1×10^3/mL
Hypertriglyceridemia (fasting > 265 mg/dL or 3 mmol/L) and/or hypofibrinogenemia (< 150 mg/dL)
Low or absent natural killer-cell activity
Ferritin > 500 ng/mL
Elevated soluble cluster of differentiation 25 (α-chain of soluble interleukin-2 receptor)
Histologic criteria
Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver

a large proportion of *E. coli* and *Pseudomonas aeruginosa*, which respectively concerned 30% and 13% of patients. HLH related to these two bacteria have been reported in the literature (33-35).

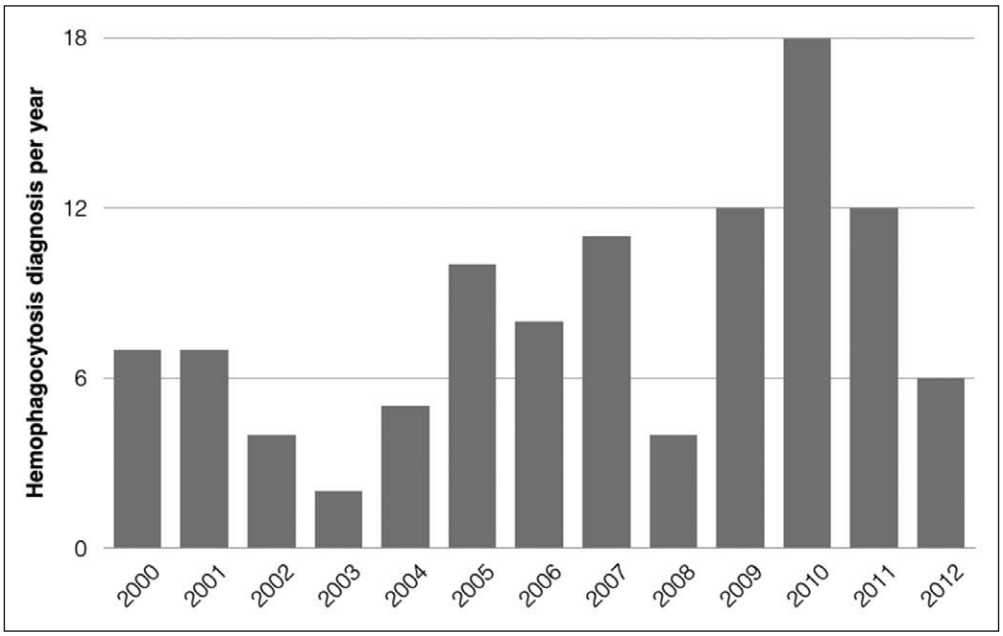

Figure 4. Number of hemophagocytosis diagnoses per year.

Interestingly, the overall prevalence of *E. coli* bacterial infections in our ICU over the 2010–2013 period of time was 18.5%, that is, lower than that found in our study population. An accountability of *E. coli* infections in the hemophagocytosis process can therefore be considered. A significant proportion of our patients had an addiction to alcohol. We cannot prove the existence of a causal link between chronic alcohol consumption and the risk of hemophagocytosis. However, experimental in vitro studies have demonstrated bone marrow toxicity of ethanol (36). We have identified several factors associated with increased mortality in our population. Age, SAPS 2, ferritin, and plasma levels of LDH were significantly increased in patients who died in ICU compared with patients who survived. In contrast, plasma fibrinogen levels were significantly decreased in patients who died compared with nondeceased patients. This result suggests a possible role for HLH in the death of these patients because the opposite result, that is, increased fibrinogenemia, could have been expected in a context of major systemic inflammation. However, a recent study also found a prognostic value for hypofibrinogenemia in patients with septic shock, attributed to hemostasis disorders (DIC) (37). Since only four patients were described as having DIC in our study, HLH was most probably responsible for hypofibrinogenemia in the majority of patients who died. Indeed, regarding the biological parameters of DIC, we did not observe any difference between patients who died and patients who survived. The semiquantitative assessment showed no difference concerning bone marrow macrophages between deceased and surviving patients, but fewer megakaryocytes in deceased patients. This result probably reflects a later diagnosis in deceased patients suspected of having secondary HLH. Indeed, during the initial stage of HLH, hematopoiesis is often preserved with normal bone marrow cellularity. Then, erythroid and granulocyte precursors decrease, with a possible aspect of medullary aplasia.

Currently, the possibility to propose a specific treatment (corticosteroids, etoposide, and cyclosporine) in the context of bacterial infection-associated HLH is not consensual. Thus, may a specific treatment be proposed in the context of septic shock-associated HLH with multiple organ failure and poor prognostic factors, including high ferritin? A recent prospective multicenter study reported 42% mortality at day 28 in 1,495 patients with septic shock (vs 43% in our HLH patients) (38). Whether hemophagocytosis in the context of septic shock is associated with increased mortality and should receive special treatment is unclear. In a recent study, the authors report a cohort of children who received specific

treatment in the context of postinfectious HLH with hyperferritinemia (median serum ferritin, 6,341 µg/dL) and multiple organ failure (median number of organ failures, 5) (10). The 23 children were randomized to receive either the primary HLH protocol (plasma exchange and dexamethasone or cyclosporine and/or etoposide) or a less immunosuppressive therapy (plasma exchange and IV immunoglobulin or methylprednisolone). Survival was significantly improved (n = 17; 100% survival) with the latter protocol versus the HLH protocol (n = 6; 50% survival). IV immunoglobulins have been used successfully in patients with reactive macrophage activation syndromes with hyperferritinemia greater than 10,000 µg/L and/or hemophagocytosis, provided they were administered early in the treatment (39). Randomized controlled trials should be performed to evaluate these treatments in this population. Indications to treat HLH with etoposide in ICU have been proposed: platelets less than 30 G/L, jaundice, DIC, hypofibrinogenemia, presence of organ failure, and failure of corticosteroids (19).

To our knowledge, our study is the largest describing a population of medical ICU patients with hemophagocytosis, although it is difficult to speak rigorously of HLH in the absence of consensus definition applicable to our population. Only one other study evaluated a large cohort of HLH patients in ICU in a center with significant experience in oncohematology (13). This retrospective study described patients meeting the HLH-2004 criteria between 1998 and 2009. Fifty-two percentage of patients died in the hospital. By multivariate analysis, factors associated with increased hospital death were shock at admission and platelet count less than 30 G/L.

Our study presents the particular interest to be focused on non-oncohematologic patients. Nevertheless, it has several limitations. First, it is a single-center study. Given the lack of consensus definition, the lack of specificity of the HLH-2004 diagnostic criteria, and the relative rarity of HLH, this syndrome is presumably underdiagnosed. A team has recently developed a new score, easier to use routinely and probably more suitable than HLH-2004 criteria to improve the diagnosis of HLH (7). Second, we conducted a retrospective study over 12 years, and it is likely that the team was more aware of HLH diagnosis at the end of the study, which may have modified both diagnostic accuracy and management (**Fig. 4**). Third, the predisposing factor of hemophagocytosis/suspected HLH was an infection in more than three of four of our patients. Our data are very difficult to compare with results of other authors. To our knowledge, only one publication has reported the results of an unselected ICU population with hemophagocytosis (13). The inclusion criteria in that study were different because patients had to meet the HLH-2004 criteria to be included, which have been discussed above. The inclusion criteria in our study are also imperfect. Patients were included if they had hemophagocytosis on the bone marrow aspirate, which was performed for exploration of thrombocytopenia/bicytopenia/pancytopenia. However, neither thrombocytopenia nor hemophagocytosis are essential for HLH diagnosis (7.16). The generalization of our results to populations with different characteristics (comorbidities and precipitating factors) is uncertain.

In summary, thrombocytopenia is common and multifactorial in ICU. Hemophagocytosis is a predominant factor in the genesis of thrombocytopenia. It affects more than 1% of patients in ICU and more than 40% of thrombocytopenic septic patients. In this setting, it can be integrated in the context of HLH, the diagnosis of which is particularly difficult in cases of severe sepsis or septic shock. Ferritinemia can be a useful prognostic marker in these patients. In addition, we suggest ferritinemia could be particularly interesting to select patients suitable for a treatment targeting HLH. Prospective studies are needed to define the place, the terms, and the best timing to start these treatments.

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