JOURNAL OF COMMUNITY HOSPITAL INTERNAL MEDICINE PERSPECTIVES
2021, VOL. 11, NO. 5, 639–645
https://doi.org/10.1080/20009666.2021.1954783

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REVIEW ARTICLE

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Hemophagocytic lymph histiocytosis (HLH): etiologies, pathogenesis, treatment, and outcomes in critically ill patients: a review article and literature to review

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ABSTRACT

Hemophagocytic lymph histiocytosis (HLH) is not an independent disease but is instead a clinical syndrome that occurs in many underlying conditions involving all age groups. HLH is the consequence of a severe, uncontrolled hyperinflammatory reaction that in most cases is triggered by an infectious agent. Acquired HLH is much more common than primary HLH syndrome but primary is more fatal, and it does have the worst prognosis with no definitive treatment available to date. This review article mentioned all the latest advancements regarding etiologies, pathogenesis, treatment, and outcomes in critically ill patients who got diagnosed with HLH syndrome in last 15 years.

ARTICLE HISTORY
Received 14 March 2021
Accepted 25 June 2021

KEYWORDS
Hemophagocytic; lymph histiocytosis; etiologies; diagnosis; pathogenesis; treatment; review

1. Introduction

Hemophagocytic lymph histiocytosis (HLH) is a disorder of unregulated immune response in accordance to a predisposing factor. Although rare, mortality rates for HLH have ranged from 20%-75% in hospitals and reached 50%-80% in the ICU [1–5]. Cause of it could be primary or secondary [1,5,6]. Primary HLH is attributed to mutations in genes most common mutation being in the PRF1 gene encoding for perforin [2,7,89]. Acquired HLH is commonly attributed to infection, autoimmune diseases, and malignancy [4,6,7].

2. Objective

The objective of this article is to provide insight on the nuances in diagnostic criteria, laboratory/clinical findings, causative factors, prognostic factors as well as treatment regimens applied in patients with secondary HLH in critical care. Findings correlating to patients with primary HLH in the articles reviewed are also conveyed for completion of review as well as to highlight comparison in etiologies, outcomes, diagnostic criteria, and treatment protocols followed in these critically ill patients.

3. Methods

PubMed, Embase, Cochrane, and Google Scholar search engine were utilized to extract data for this article. As diagnostic criterion for HLH has not been validated as of yet in the critically ill adult population, and treatment protocols as well as laboratory parameters are being challenged and enhanced over time, a time range of the past five years was applied, from 2015–2020, to retrieve recent and comprehensive studies on HLH in the critically ill patients. Keywords such as hemophagocytic lymph histiocytosis, hemophagocytic syndrome, critically ill, ICU, PICU, critical care, intensive care were used as keywords to obtain broad results for all studies incorporating research on this disease in association with critically ill patients. Articles with either adult or pediatric critically ill cohorts were included to be reviewed. Further inclusion of articles was subjected to our objective of primarily discussing secondary HLH. Articles selected incorporated different facets of this rare disease in critical care such as diagnostic criteria, treatment protocol, etiologies, outcomes, and prognostic factors, to encompass an in-depth clinical picture of common management strategies employed by intensivists for the treatment of HLH as well as to convey prospective of recovery, this disease course holds for the critically ill patient.

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4. Literature review

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S. no	Author	Topic	Outcome
1.	Athale J. [1]	Challenges in Identifying Hemophagocytic Lymphohistiocytosis in the ICU	In the ICU, patients with an HLH diagnosis have a 10-fold higher serum ferritin than those with other diagnosis concerning elevated ferritin values, confirms that HLH patients with elevated ferritin levels have poor prognosis
2.	Dao D, et al. [7]	Etiologies and Clinical Outcomes of Patients with Secondary Hemophagocytic Lympho-histiocytosis at a Tertiary PICU	Causative factors for secondary HLH included cytomegalovirus-EBV coinfections (60%), EBV sole infections (20%), cytomegalovirus sole infections (16%) and one unknown cause (4%). 14 (56%) of the 25 patients survived. C Reactive Protein and mean PELOD-2 Score were significantly higher in fatal versus nonfatal cases which confirmed that C Reactive protein if elevated worsen the prognosis.
3.	Gregory J, et al. [13]	Outcomes Analysis of Children Diagnosed with Hemophagocytic Lympho-histiocytosis in the PICU	67% of the 33 patients had secondary HLH, 21% had primary HLH, and 12% had HLH of an unidentified cause. 1-year post hospital discharge survival rate was 58%. This study showed that HLH patients with increase ICU stay or increase length of hospital stay had more probability to die in the first year post discharge from the hospital
4.	Knaak C, et al. [6]	Treatment and Mortality of Hemophagocytic Lympho-histiocytosis in Critically Ill adult Patients: A Systematic Review with Pooled Analysis	Infections were reported most frequently as triggers for secondary HLH across all continents (49.9%), followed by malignancies (28.0%), autoimmune diseases (12.1%) unknown triggers (9.4%), and drugs (0.6%). Highest mortality was seen in the subset with unidentified cause of HLH syndrome. HLH patients treated with IVIG showed improved mortality while those on cyclosporine had increased mortality as it causes suppression of the immune system
5.	Meena NK, et al. [14]	The Performance of Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis in Critically Ill Patients	2 of the 10 patients diagnosed with HLH survived overall. Individually, 5 of the 6 criteria had very high sensitivity values; The fulfilment of any 5 of the 6 criteria had a statistically significant specificity of 97.2%. The criteria of bi-cytopenia had statistically significant sensitivity and specificity. A cut point of ferritin of 1197 ng/mL was a good indicator of HLH with a specificity of 70.0% and a sensitivity of 90.0%. A cutoff of 143.5 of the H-Score with a specificity and sensitivity of 90% was assessed as optimum.
6.	Wohlfarth P, et al. [15]	Interleukin 1 Receptor Antagonist Anakinra, Intravenous Immunoglobulin, and Corticosteroids in the Management of Critically Ill Adult Patients with Hemophagocytic Lympho-histiocytosis	A median decline of 2.5 (1–4) and 3.5 (1–6) points in the SOFA scores of 6 of the 8 patients could be appreciated at 1 and 2 weeks after the initiation of anakinra therapy, respectively, indicating an improvement in organ dysfunction. Among the treatment options, early initiation of Anakinra therapy plays a vital role in decreasing hospital stay of HLH patients
7.	Wohlfarth P, et al. [15]	Prognostic Factors and Long-term Outcome in 52 Turkish Children with Hemophagocytic Lymphohistiocytosis	Of the 52 critically ill pediatric patients, 28 (54%) had primary HLH and 24 (46%) had secondary HLH. Overall, 58% patients survived. Primary HLH correlated with a significantly higher mortality rate of 66% than secondary HLH with a mortality rate of 16%. Which concludes that as secondary HLH usually have a cause, starting early treatment to treat the inciting factor lead to decrease in mortality of HLH patients

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5. Athale J [1]

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8.	Knaak C, et al. [3]	Hemophagocytic Lymphohistiocytosis in Critically Ill Patients	An overall mortality of 60% was seen. The trigger associated with highest mortality was that of malignancy (71.4%) and the trigger associated with lowest mortality was that of autoimmune disease (44.4%). Maximum SOFA score significantly correlated with 30-day mortality. Aspartate aminotransferase levels were also significantly higher in non-survivors.

In this review, Athale J highlights the role of serum ferritin in diagnosing and determining the prognosis in critically ill patients [1]. Lachmann G et al. also studied the identical findings stating that patients with an HLH diagnosis had a 10-fold higher serum ferritin than those with other diagnosis especially including sepsis. Given this finding, Lachmann et al. propose that higher ferritin values in the ICU patients may aid to differentiate HLH from sepsis [10]. Athale J points out that high ferritin levels are more commonly found in patients with renal failure or hepatocellular injury than in HLH, however this study did not specify whether the cohort necessitated ICU stay [11]. In continuation with an elevated ferritin correlating to disease diagnosis, this review further conveyed Lachmann G et al. findings on employing ferritin as a prognostic marker for HLH patients in critically ill patients. The minimum ferritin value in survivors was 2195 ng/L whereas in non survivors it was 9759 ng/L (p= 0.001), proving that ferritin alone can be used to, not only diagnose HLH in the critically ill but also to determine patient prognosis and treatment response.

6. Dao D et al. [7]

This prospective cohort study in Vietnam assessed causative factors and outcomes in terms of mortality and multiple organ dysfunction among pediatric age group patients being diagnosed with secondary HLH [7]. In terms of etiologies, cytomegalovirus-EBV coinfections were most common among patients (60%), followed by EBV sole infections (20%) and cytomegalovirus sole infections (16%). As per outcomes, 14 patients survived (56%). C Reactive Protein was significantly higher in fatal cases (108.2 mg/L) versus nonfatal cases (53.3 mg/L) (p= 0.03). No other clinical or laboratory variables were significantly different between fatal and nonfatal cases. Multiple organ dysfunction was identified in 22 of the 25 cases (88%). The mean PELOD 2 predicted mortality rate for cases with MOD was highest in cytomegalovirus sole infections (14.4%), followed by cytomegalovirus-EBV coinfections (12.2%); although, cases with cytomegalovirus-EBV coinfections had a lower PIM 2 predicted mortality rate at admission than cases with EBV sole infections. Mean age at admission was lowest for cytomegalovirus sole infections (9.8 months) followed by cytomegalovirus-EBV coinfections (21.7 months) followed by EBV sole infections (26.8 months). On univariate analysis, EBV sole infections cases had the lowest platelet levels and the highest fibrinogen levels in comparison to cytomegalovirus-EBV coinfections or cytomegalovirus sole infections [12].

7. Gregory J et al. [13]

In this retrospective study, 21% of the subjects had primary HLH, 67% had secondary HLH while 12% had HLH of an unidentified cause. All seven patients with a primary HLH had mutations present including PRF1 gene (n = 3), MUNC13-4 gene (n = 3), and STXBP2 gene (n = 1). Identifiable infections were attributed as the cause of HLH in eight patients (36%) with secondary HLH. In terms of treatment regimen, most patients received steroids (94%), almost half the patients were treated with anakinra or etoposide, and some were treated with IVIG. 15% of the patients, with most having primary HLH, received stem cell transplant as initial hospital treatment. 26 of the 33 patients survived till hospital discharge, seven patients died between hospital discharge and 1-year post hospital stay resulting in a survival rate of 58% with 19 patients alive at 1-year post discharge. Non-survivors had an over ten-fold higher maximum ferritin level than survivors (119,235 vs 11,700) (p= 0.061). Maximum ferritin levels over 100,000 increased the likelihood of death in patients versus a maximum ferritin level less than 100,000 (50% vs 16%, p= 0.022). There was an improvement in Functional status scale (FSS) of 2 patients from the 26 patients who survived at hospital discharge. Regarding all patients, ICU length of stay had a positive correlation with change in FSS (R = 0.761, p< 0.001) as did hospital length of stay (R = 0.574, p= 0.002). Non-survivors had a longer median PICU length of stay of 21 days than survivors who had a median PICU length of stay of 4.5 days.

8. Knaak C et al. [6]

This systematic review showed that infections were reported most frequently as triggers for HLH across all continents (49.9%), followed by malignancies (28.0%), autoimmune diseases (12.1%) unknown

triggers (9.4%) and drugs (0.6%) [6]. Seventeen different treatment agents were utilized to treat the disorder including corticosteroids, etoposide, cyclosporine, cyclophosphamide, IVIG, rituximab, anakinra, allogenic stem cell transplant, among others. Cumulative mortality was 57.8%, patients with an unknown trigger had the highest mortality of 75.8%. Among infections triggered HLH, 73.7% mortality was seen by fungal infections. On multivariate logistic regression analysis, IV immunoglobulin is correlated with 45.2% reduced mortality; the reduction in mortality is due to its dual anti-inflammatory as well as immune enhancing affect in terms of improving T cell and NK cell function thereby configuring a more modulated immune response. Cyclosporine may have affected mortality adversely in infection-triggered HLH due to immunosuppression interfering with the eradication of the infection itself. The higher mortality with cyclosporine use may reflect its administration in patients with more severe disease as cyclosporine was commonly administered alongside

immunosuppressive/cytostatic drugs as combination therapy. Upon treatment analysis, Knaak C et al suggest incorporating a tailored approach for treating HLH in the critically ill with a simultaneous strive to treat the associated trigger and administer HLH-specific therapy.

9. Meena NK et al. [14]

This retrospective single center study emphasized on ferritin cut-off values that correlate more with an HLH diagnosis [14]. Of the 5652 patients admitted to the ICU,445 patients had their serum ferritin measured out of which 50% had ferritin level > 500 ng/mL, splenomegaly and cytopenia's were less common, found in 10.4% and 26.2% of the patients, respectively. A differential diagnosis of sepsis was made in all patients. Forty one (47%) of the 87 bone marrow biopsies showed hemo-phagocytosis. A median ferritin of 533 ng/dL (IQR: 191

–1445 ng/dL) was identified in all these patients. From the 445 patients with ferritin drawn and criteria applied, an HLH diagnosis was made in ten patients. Upon testing for sensitivity and specificity of HLH criteria, individually, five of the six criteria had very high sensitivity values; 1 criterion with lower sensitivity of 55.6% was that of hypertriglyceridemia or hypofibrinogenemia. Altogether, the fulfilment of any five of the six criteria had a sensitivity of 70% and a statistically significant specificity of 97.2%. On cut point analysis, a cut point of ferritin of 1197 ng/mL was a good indicator of HLH with a specificity of 70.0% and a sensitivity of 90.0%.

10. Wohlfarth P et al. [15]

This study explained treatment outcome in a critically ill adult with secondary HLH, being administered anakinra, intravenous immunoglobulin, and corticosteroids [15]. Three of the eight patients included in this study received prednisone at doses greater than 1 mg/kg prior to initiation of anakinra but didn't respond to this treatment. Overall, all the patients received anakinra, as an absolute dose of 100–200 mg injected subcutaneously three times daily, 1 (0–9) days after an HLH diagnosis was established. Seven of the eight patients simultaneously received IVIG (0.5 to 1 g/kg daily for 3–6 days) and five of the eight patients were treated with corticosteroids (initiated as a high dose pulse of 250–500 mg of prednisone, continued with lower dose maintenance) at the same time as well. All the patients were concomitantly administered broad spectrum antibiotics, three received antiviral while one received antifungals respectively. A median decline of 2.5 (1–4) and

3.5 (1–6) points in the SOFA scores of six of the eight patients could be appreciated at 1 and 2 weeks after the initiation of anakinra therapy, indicating an improvement in organ dysfunction. 5 (63%) of patients who survived till ICU discharge received anakinra therapy for a median of 18 (7–42) days. No adverse outcomes or unscheduled discontinuation of treatment correlating to anakinra administration took place as per the documentation of all cases.

11. Kaya Z et al. [2]

52 critically ill patients were included in this study out of which, 28 (54%) had primary HLH and 24 (46%) had secondary HLH. Genetic analysis performed in 18 of the 28 patients with primary HLH revealed mutations in PRF1, STX11, STXBP2, UNC13D, Rab27a and LYST, with PRF1 and STX11 mutations being the most common. Of the 24 patients with secondary HLH, 21 had an infectious trigger including viral, bacterial, and parasitic infections, while three had lysin uric protein intolerance. With regards to treatment, 2 patients with primary HLH received allogenic stem cell transplant while remaining received steroids, intravenous immunoglobulin, broad spectrum antibiotics, antifungal or antiviral agents and diet regulation. Overall, 30 (58%) of the 52 patients survived. The 22 non-survivors died most due to refractory or relapsed HLH at a median of 6 months from time of initial HLH diagnosis. Primary HLH correlated with a significantly higher mortality rate of 66% than secondary HLH with a mortality rate of 16% ($p< 0.05$). On univariate and

multivariate analysis, poor prognostic factors included: age below 2 years, thrombocytopenia (platelet < 50,000 x 10^3/micro L), high disseminated intravascular coagulation score (≥ 5), and a high ferritin level (> 2,000 mg/dL). No clinical response at 2 weeks of induction treatment was also independently associated with worse prognosis in these patients.

12. Knaak C et al. [3]

This retrospective observational study analyzed risk factors and outcomes of critically ill adult patients with HLH admitted over a period of 13 years from January 2006 to August 2018 with an elevated serum ferritin levels [3]. Of the 2632 patients that were identified as having increased fibrinogen levels, 40 (1.52%) patients were diagnosed with secondary HLH. Triggers included infection (42.5%), lymphoma (20%), HIV (12.5%), and leukemia (10%), as well as autoimmune diseases. An overall mortality of 60% was seen. The trigger associated with highest mortality was that of malignancy (71.4%). A higher ferritin at diagnosis was associated with increase in mortality. On multivariate analysis, a maximum SOFA score significantly correlated with 30-day mortality (p= 0.005). Non-survivors were also more likely to be older, require more vasopressors, mechanical ventilation, and dialysis. Patients received HLH-specific and non-specific therapy including 19 different treatment strategies consisting of treatment agents such as corticosteroids, etoposide, cyclosporine, and anakinra among others.

13. Discussion

An uncontrolled immune response spearheaded by disordered cytotoxic cell activity precipitating cytokine and macrophage over-activation also known as Macrophage activation syndrome (MAS). It's the forefront of the frequent multiple organ damage induced by hemophagocytic lymph histiocytosis [1,6]. In the literature, while genetic mutations are identified as a cause of primary HLH, it is suggested that genetic mutation variants that are yet to be discovered may form the basis of secondary HLH as well [1]. Secondary HLH in the critically ill, which is the primary subject of this review, is identified mostly in the adult population as primary HLH often presents in childhood [6,13]. Secondary HLH is attributed mostly to triggers such as infection, malignancy, autoimmune disease, immunodeficiency, and drug reaction [4,6]. Infections are most commonly identified as causative factors of secondary HLH in the critically ill in both pediatric and adult population, followed by malignancy; Among infectious etiologies, viral infections are most frequently identified with Epstein Barr Virus and cytomegalovirus being the most common of the viruses identified [4,6,7]. Children are more likely to experience the HLH associated manifestation of a primary EBV infection [4]. An EBV reactivation presenting as HLH can occur in older patients with T cell lymphoma or in solid organ transplant recipients [4].

Due to nonspecific clinical and laboratory findings, often progressing to multiple organ dysfunction, it is common for HLH to be misdiagnosed as sepsis or other causes of shock [1,6,14,15]. Diagnosis relies heavily on a strong familiarity of HLH-2004 criteria which may be augmented by the H-Score that numerically conveys the strength of clinical suspicion toward an HLH diagnosis [14,16]. Limitations of applying the HLH-2004 criteria in critically ill adults include not only lack of randomized controlled trials validating criteria for this patient population but also the unavailability of 2 of the 8 criteria, that of soluble CD 25 levels and evaluation of low or absent NK cell activity, in tertiary care and critical care settings [14,16,17]. Nonetheless, fulfilment of any five criteria from the remaining 6 criteria has a statistically significant specificity of 97.2% according to a study by Meena et al. According to this same study, among laboratory findings enlisted in the HLH-2004 criteria, while it is common to identify an elevated ferritin, the criteria of bicytopenia has a statistically significant specificity and sensitivity [14]. Regarding clinical findings, fever and hepatosplenomegaly are common; among systemic signs, respiratory insufficiency, often in the form of acute respiratory failure, is commonly ascertained in HLH patients upon their admission to the ICU [4,13]. Other organ systems likely to yield injury due to this disorder include the cardiovascular (15%), neurological (25%), hematological (60%), renal (8%- 62% according to factors varying in cohorts) and hepatic (60%) system as mentioned earlier in common clinical findings [4].

Patients experiencing multiple organ involvement resulting from HLH may present to the ICU with need for mechanical ventilation, renal replacement therapy, vasopressors, and extracorporeal membrane oxygenation; the need for these supportive modalities is associated with poor prognosis [3,6,13,15]. Factors associated with poor prognosis in solely the pediatric cohorts reviewed include high Sequential Organ Failure Assessment score, Pediatric Risk of Mortality Score III, The mean Pediatric Logistic Organ Dysfunction 2, C reactive protein levels, maximum total bilirubin levels, and maximum ferritin levels [7,13]. Pediatric patients with refractory or relapsed HLH are more likely to experience poor outcome if any of the following factors apply: age below 2 years, thrombocytopenia (platelet < 50,000 x 10^3/microL), high disseminated intravascular coagulation score (≥ 5), and a high ferritin level (> 2,000 mg/dL) [2]. In the adult cohorts reviewed factors including older

age, maximum Sequential Organ Failure Assessment score, aspartate aminotransferase levels, higher ferritin at diagnosis as well as a higher minimum ferritin at diagnosis correlate with poor prognosis [3,14]. Notably, cyclosporine use correlated with higher mortality in infection triggered HLH, causality of this occurrence could include hinderance in immune mediated pathogen clearance. IVIG on the other hand, decreased the likelihood of mortality in the same adult patient population possibly due to its augmentative role in infection eradication [6].

Along with cyclosporine, steroids and etoposide are therapeutic agents incorporated as the epi-center of treatment in both the initial HLH-94 protocol as well as the updated HLH-2004 protocol frequently utilized in management of patients with HLH [2,6,15,18]. In the case of primary HLH or persistent HLH, the protocol is utilized to subdue the cytokine storm and halt its detrimental effects on organ systems until an allogenic stem cell transplant can suitably be conducted [2,4,18]. Elimination of identified triggers stands as cornerstone of therapy in patients diagnosed with secondary HLH in critical care [4,6,18]. Of late, interleukin 1 receptor antagonist, anakinra, is being incorporated into treatment regimens for secondary HLH due to its efficacy, cost effectiveness, good tolerability and lack of interference in trigger identification such as in that of an underlying lymphoma or infection which could otherwise be difficult to detect or treat in a steroid based therapeutic approach [15,19]. Supportive therapy for HLH can include antibacterial, antiviral, and if required, anti-fungal agents [2,4,6,15]. To add, in refractory or persistent cases of HLH, 'salvage therapies' are utilized which may give better treatment response, these include: anti-thymocyte globulin, alemtuzumab as well as other biologic agents including rituximab, (particularly effective in EBV infections) daclizumab, infliximab, tocilizumab, TNF alpha inhibitors, JK inhibitors, IVIG, and the recently FDA approved interferon gamma antibody for the treatment of HLH, Emapalumab [1,6,18,20].

14. Conclusion

Hemo-phagocytosis lympho-histiocytosis is a rapidly deteriorative life-threatening disorder that is commonly encountered in the ICU with involvement of multiple organs. Hallmarked as well as propagated by its cytokine storm, defect in the cytotoxicity of mainly T cells leads to an aberrant immune response in individuals susceptible to the disease or experiencing it due to a trigger. Difficult to diagnose, HLH symptoms are often misinterpreted for that of sepsis or other causes of shock. It is therefore of utmost importance for intensivists as well as other physicians likely to encounter HLH patients in their respective fields to be well familiarized with the HLH diagnostic criteria, therapeutic protocol as well as recent treatment modalities employed to achieve better treatment response rates in these patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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