Hematologists' state of knowledge on practical aspects of hemophagocytic lymphohistiocytosis (HLH) in adult patients: A Young Hematologists' Club survey

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Abstract

Background. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome with various etiologies. Its treatment is complicated by several important but not immediately obvious issues (e.g., HLH-2004 criteria are the most commonly used for diagnosis, but the recommended therapeutic regimen is HLH-94).

Objectives. The study aimed to assess hematologists' practical knowledge of HLH.

Materials and methods. A survey was conducted among physicians treating adult hematological patients. A 10-question paper questionnaire was distributed to physicians from various hematology centers. A total of 126 questionnaires were analyzed.

Results. Most respondents had little-to-moderate experience in caring for HLH patients: 59% treated 0–2 patients and 36% treated between 3–5 patients. Among the respondents, the preferred diagnostic criteria were HLH-2004, either in its original form (5 out of 8 criteria) for 70 respondents or its modified version (4 out of 6 available criteria when ferritin exceeds 2,000 ng/mL) for 56 respondents. The preferred treatment regimen was HLH-2004, with a full dose of etoposide in 72 responses or reduced in 39 responses. Fifty percent of respondents incorrectly answered that meeting the HLH-2004 criteria necessitates the use of the HLH-94/2004 regimen in full doses and duration. Sixty-four percent of respondents correctly identified that hemophagocytosis is not necessary for the diagnosis.

Conclusions. This survey reveals that the majority of surveyed physicians adhere to international HLH recommendations. However, there are instances where these guidelines are not fully implemented, which underlines the need for further efforts to raise awareness and share clinical experiences about this patient group.

Key words: hemophagocytic lymphohistiocytosis, HLH, questionnaire, hemophagocytic syndrome

Background

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder characterized by extreme inflammation. Its pathogenesis is complex. Familial HLH in children is associated with mutations in *PRF1*, *STX11*, *STXBP2*, *UNC13D*, and other genes causing syndromes.[1] In adults, although some degree of genetic predisposition is required, the main role is attributed to the triggering factor, with the most important being malignancies (especially lymphoma), infections (notably Epstein–Barr virus (EBV)) and autoimmune diseases (in this context, hyperinflammation is often called macrophage activation syndrome).[2] Differential diagnosis can be challenging because HLH shares similarities with other conditions characterized by high inflammation. Symptoms may include fever, hepatosplenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia, which are part of the HLH-2004 criteria.[3] Additional symptoms may include jaundice, rash and hypertransaminasemia. Prognosis depends on multiple factors, such as the triggering factor, patient age and the intensity of hyperinflammation. If HLH is not diagnosed and treated promptly, it can be fatal.

Hemophagocytic lymphohistiocytosis went unrecognized for many years, but efforts were made to raise awareness – first in pediatric and subsequently in adult settings. In Poland, awareness of HLH grew significantly following publications and lectures by Prof. Wiesław Wiktor Jędrzejczak.[4] Today, HLH is well recognized among hematologists and is included in textbooks and articles aimed at specialists in internal medicine.[5,6] In recent years, the Histocyte Society has issued important recommendations, including the use of etoposide,[7] management approaches for adult HLH patients[8] and considerations for HLH in intensive care settings.[9]

Despite these efforts, HLH gained widespread recognition relatively late, particularly over the past decade. Additionally, HLH is heterogeneous, and some aspects may seem counterintuitive; e.g., diagnostic criteria are based on HLH-2004, but the treatment follows HLH-94 guidelines (with reduced etoposide dosing for adults). Understanding these elements is fundamental for optimal patient care, yet the overall experience level among hematologists remains relatively low. Moreover, there is a lack of studies evaluating the current knowledge of HLH among physicians.

Objectives

The objective of this study was to evaluate the knowledge of hematologists regarding the practical aspects of HLH diagnosis and treatment in adult patients.

Materials and methods

Study design

The study was held under the aegis of the Young Hematologists' Club. To assess physicians' knowledge of HLH, a quantitative method was adopted using a paper-based questionnaire. This cross-sectional study utilized a 1-page questionnaire comprising 10 closed questions (with an option to write any chosen answer as "other"). The original questionnaire is available in the Supplementary material (https://doi.org/10.5281/zenodo.11209475). The questionnaire was designed uniquely: Most answers were partially correct but tailored either to pediatric or adult HLH patients. Thus, differences in interpretation were attributed to the physician's patient population rather than the test itself. Given that respondents in this study exclusively treated adult patients, some of their responses were incorrect.

Data collection methods

Questionnaires were distributed during sessions at the 28th Congress of the Polish Society of Hematology and Transfusion Medicine (September 2019), as well as in courses for hematology specialists and various clinical centers (both academic and non-academic) until the end of 2021.

Study preparation and survey administration

The survey was anonymous, with participants instructed to participate only once. Interviewers were instructed to mix the received questionnaires with previously collected ones to ensure anonymity.

A total of 137 questionnaires were obtained, with 126 included in further analyses. Eleven questionnaires were excluded for the following reasons: respondents were from medical professions other than adult hematology physicians, or there was a complete lack of answers regarding HLH. Manual data entry was assisted by a custom-designed color-coded spreadsheet to minimize human error. Moreover, unique numbers were assigned to the anonymous questionnaires during data entry to facilitate reanalysis in potentially ambiguous cases.

Statistical analyses

The questionnaire included questions only about qualitative (not quantitative) parameters; therefore, the results are presented as numbers of answers and percentages of total responses. No imputation methods were used for missing data. Univariate analyses were performed using Fisher's exact test, with significance set at a p-value of less than 0.05. The Bonferroni correction was applied for multiple

comparisons (with a p-value <0.00625 considered significant for 8 comparisons). Analyses were performed using MedCalc v. 22.019 software (MedCalc Software, Ostend, Belgium).

Results

Respondents were categorized based on their overall work experience and expertise in treating HLH patients (Table 1). Thirty-seven (37.3%) physicians reported less than 10 years of experience. Practical involvement in treating HLH patients was generally low, with 73 (57.9%) respondents caring for fewer than 3 such patients and 45 (35.7%) caring for between 3 and 5.

Table 1. Respondents' characteristics (n = 126)

Years working as a physician [n, %]		
<10	47	37.9%
10–20	45	36.3%
21–30	22	17.7%
31–40	6	4.8%
>40	4	3.2%
Number of HLH patients taken care of (total) [n, %]		
0–2	73	58.9%
3–5	45	36.3%
5–10	3	2.4%
11–20	2	1.6%
>20	1	0.8%

HLH – hemophagocytic lymphohisiocytosis.

In the analyzed population, the preferred diagnostic criteria were HLH-2004, either in its original form (5 out of 8 criteria), chosen by 70 respondents, or its modified version (4 out of 6 available criteria when ferritin exceeds 2000 ng/mL), selected by 56 respondents (Fig. 1; multiple answers were possible). The preferred treatment regimen was HLH-2004, with a full dose of etoposide chosen in 72 responses, whereas in 39 responses reduced dosing was chosen. As multiple answers were possible, the result describes number of responses not respondents. One respondent could have chosen more than 1 response (Fig. 2).

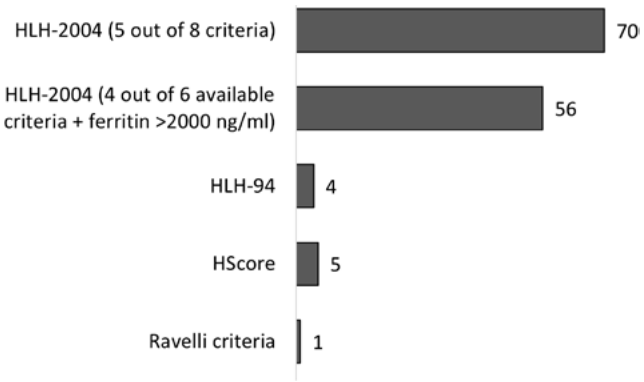

Fig. 1. Preferred diagnostic criteria (more than 1 answer possible)

HLH – hemophagocytic lymphohisiocytosis.

The final part of the questionnaire evaluated responses (yes/no/do not know) to 4 statements that are false for adult HLH patients (Fig. 3). Overall, most of the questions were answered in accordance with guidelines: 54 (42.9%) physicians answered 3 out of 4 questions correctly, and 24 (19.0%) correctly answered all 4 questions in accordance with guideline recommendations. Only 4 participants (3.2%), who had limited experience in treating adult HLH patients, did not answer any questions correctly. The least frequently opposed false statement was that fulfillment of HLH-2004 criteria necessitates the use of the HLH-2004 protocol at full doses and duration (45 physicians, 35.7%). Univariate analysis did not reveal significant differences between physician subgroups based on their work experience (less or more than 10 years) or the number of HLH patients treated (2 or more), as summarized in Table 2.

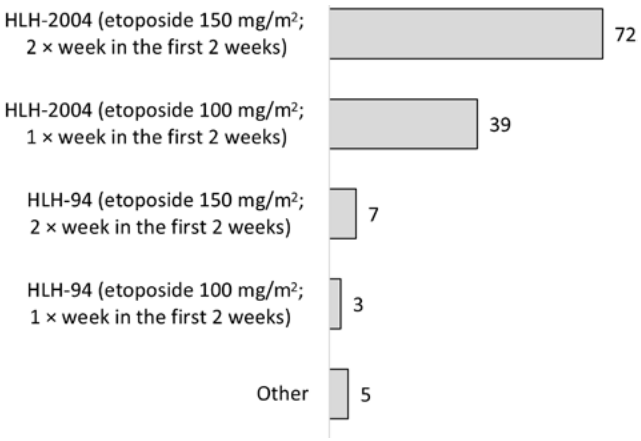

Fig. 2. Preferred treatment regimen

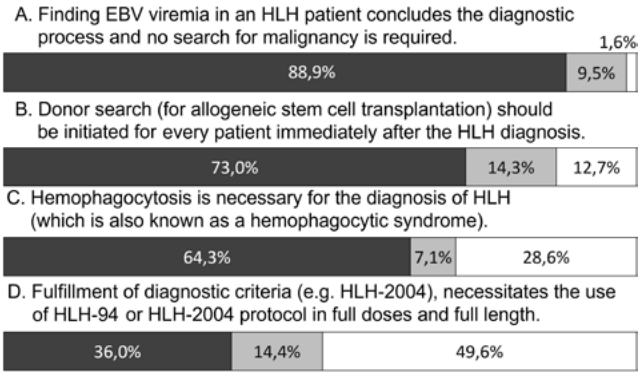

Fig. 3. Opinions about 4 statements that are not true for adult hemophagocytic lymphohistiocytosis (HLM) patients

EBV – Epstein–Barr virus.

Table 2. Number and percentage of correct (negative) opinions about 4 statements from Fig. 3, divided by physicians' work experience and number of HLH patients treated

Statement	Years working as a physician			Number of HLH patients taken care of (total)		
	<10	≥10	p-value (Fisher's exact test)	0–2	>2	p-value (Fisher's exact test)
A. Finding EBV viremia in an HLH patient concludes the diagnostic process and no search for malignancy is required.	45 (96%)	65 (84%)	0.078	63 (86%)	47 (92%)	0.394
B. Donor search (for allogeneic stem cell transplantation) should be initiated for every patient immediately after the HLH diagnosis.	31 (66%)	59 (77%)	0.218	48 (66%)	42 (82%)	0.065
C. Hemophagocytosis is necessary for the diagnosis of HLH (which is also known as a hemophagocytic syndrome).	30 (64%)	49 (64%)	1	45 (62%)	35 (69%)	0.452
D. Fulfillment of diagnostic criteria (e.g., HLH-2004), necessitates the use of HLH-94 or HLH-2004 protocol in full doses and full length.	22 (47%)	23 (30%)	0.083	19 (26%)	26 (51%)	0.0076

HLH – hemophagocytic lymphohisiocytosis; EBV – Epstein–Barr virus; Fisher's exact test, with Bonferroni correction for multiple comparisons, was used ($p < 0.00625$ was considered significant).

Discussion

The questionnaire findings indicate awareness of practical aspects related to HLH diagnosis and treatment; however, there is still considerable potential for improvement.

Results from the question regarding the preferred diagnostic system generally show a consensus that the HLH-2004 criteria are the most popular. However, the main limitation of HLH-2004 is that 2 out of 8 parameters (sCD25 concentration and NK-cell activity) are not widely accessible. Attempts to address this issue include modified criteria proposed by Prof. Wiesław Wiktor Jędrzejczak (requiring 4 out of 5 available criteria, when ferritin exceeds 2,000 ng/mL, with no other identifiable cause) or the HScore, which relies only on commonly used parameters.[10] Using these systems together can improve diagnostic certainty, given that initiating HLH treatment may result in significant toxicity.

Hemophagocytic lymphohistiocytosis treatment depends on the triggering factor. Immunosuppressive treatment, even for patients meeting HLH-2004 criteria, may not be indicated – e.g., in cases of "HLH disease mimics".[11] Many patients may benefit more from direct therapy targeting the underlying trigger, such as chemotherapy appropriate for a diagnosed malignancy, rather than etoposide with dexamethasone. Respondents were asked about their preferred HLH-oriented treatment regimen, with options including a combination of HLH-94 and HLH-2004 protocols with 2 doses of etoposide: full (etoposide 150 mg/m^2; 2 × week in the first 2 weeks) or reduced (etoposide 100 mg/m^2; 1 × week in the first 2 weeks). Full pediatric doses can be excessively high and toxic for adults because children are able to recover form higher doses of chemotherapy than adults. Professor Jan-Inge Henter proposed a regimen with reduced etoposide frequency for treatment of HLH-like severe avian influenza.[12] This reduced, less myelotoxic, regimen was then generally recommended for treating HLH in adults.[6,8]

HLH-94 and HLH-2004 refer to names of pediatric clinical trials.[3] In a single-arm design, these trials tested treatment regimens believed to be optimal. The HLH-2004 regimen is very similar to HLH-94, with the main difference being the timing of initiating cyclosporine A: after 8 weeks in HLH-94 or from the beginning of treatment in HLH-2004. This modification did not significantly affect the comparison of these 2 trials – despite HLH-94 patients being a historical control, HLH-2004 did not demonstrate superiority ($p = 0.064$; proportional hazards model using competing risks methodology, adjusted for age and sex).[13] Therefore, the recommended regimen for adults is HLH-94 with reduced doses of etoposide. It should be noted that diagnostic criteria also take names from these trials. While HLH-94 diagnostic criteria are no longer in use, the HLH-94 treatment regimen remains the basis for treatment, alongside the HLH-2004 diagnostic criteria.

The 4 statements presented in Fig. 3 are false for adult patients, but 2 may be true for the pediatric population. As discussed above, meeting the HLH-2004 criteria does not automatically require initiating the HLH-94 or HLH-2004 protocol at full doses and duration. The treatment regimen should be tailored to the specific triggering factor. If an HLH-oriented protocol is initiated in adults, it does not need to continue for a fixed duration; it can be tapered and stopped once remission is achieved. In children, treatment must be extended as a bridge to allogeneic hematopoietic stem cell transplantation (alloHSCT), which leads to different considerations about donor search between adults and children. For adults, a donor search does not need to begin immediately after diagnosis because only a small fraction of adult HLH patients require alloHSCT (87 patients in EBMT databases from 1995–2018).[14] The alloHSCT is indicated for adults with primary HLH and, on a clinical basis, for some other patients (relapsed/refractory).[8] In most adult patients, HLH is triggered by a significant factor (e.g., malignancy) with a lesser role of genetic predisposition. Therefore,

treatment focuses more on controlling the trigger (e.g., achieving malignancy remission) rather than replacing the immune system with a new one less prone to HLH. In children, a strong genetic predisposition causes HLH when exposed to seemingly minor triggers. Because it is impossible to protect such a child from all potential triggers (e.g., viral infections), alloHSCT is the only option for long-term remission. For asymptomatic siblings with certain predisposing mutations, undergoing upfront alloHSCT before developing HLH can be more beneficial than waiting for HLH to manifest[15]

Two statements that are false for all HLH patients, refer to EBV being accompanied by another trigger and to hemophagocytosis. Finding Epstein–Barr viremia does not conclude the diagnostic process; there remains a risk of underlying malignancy, such as lymphoma. Malignancy is less likely in infants, but teenagers are at higher risk. Hemophagocytosis is not necessary for HLH diagnosis. It is one of the criteria but cannot be considered pathognomonic for HLH. It can occur in various other conditions and may initially be absent, developing in later stages of HLH.[16]

Limitations

The main limitation of this research was due to the COVID-19 pandemic, which made distributing paper questionnaires much more difficult. Switching to an online questionnaire could have affected the homogeneity of the results, so with long intervals, a paper version was used. However, since the beginning of the questionnaire distribution, there was no change in recommendations that would affect the answers.

This is the first (to our knowledge) attempt to assess physicians' adherence to the diagnostic and treatment recommendations for HLH globally, especially among those treating adult patients. In 2019–2021, there were 555–585 hematologists and 235–272 hematologists in training in Poland, making the group of 126 respondents generally representative of this population.

As the first study of its kind, this research was innovative and exploratory. Therefore, it is worth continuing to monitor the state of knowledge regarding HLH. This will enable faster diagnosis of this rare disease in the future and the application of different treatments for children and adults.

Conclusions

The results of the Young Hematologists' Club survey reveal that most surveyed physicians adhere to international HLH recommendations. However, in some cases, these guidelines are still not being adequately implemented, highlighting the need for further actions to raise awareness and share clinical experiences about this patient group.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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