Blood Reviews 30 (2016) 411–420

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

Hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) in adults: A systematic scoping review

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ARTICLE INFO

Keywords:
Hemophagocytic lymphohistiocytosis
Hemophagocytic syndromes
Hematophagic histiocytosis
Macrophage activation syndromes
Hyperferritinemia
Adults

ABSTRACT

Most knowledge of hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) is derived from pediatric studies; literature on adult HPS/HLH predominantly consists of small retrospective studies with clinical and methodological heterogeneity. The aims of this systematic scoping review were to provide an overview of existing literature on adult HPS/HLH, describe current practices in diagnosis and treatment, and propose priorities for future research. Articles from Ovid Medline, Embase and Pubmed (1975–2015) describing 10 or more unique adults (age > 15 years) with HPS/HLH were included. 82 publications were eligible: 10 were prospective and 72 were retrospective. Of the six distinct diagnostic criteria, the HLH-2004 criteria were by far the most commonly used. A minority of studies tested for genetic abnormalities (12), soluble interleukin-2 receptor (11), and/or NK function (11) in a subset of patients. Most centers used steroids and either etoposide-based (HLH-94/HLH-2004) or doxorubicin-based (CHOP) initial therapy regimens. Allogeneic hematopoietic cell therapy for treatment of adult HLH has rarely been reported. Mortality in larger treatment focused studies ranged from 20 to 88%. Developing adult-specific diagnostic criteria based on widely evaluable features of secondary HPS/HLH and establishing standard initial therapies are priorities for future research.

1. Introduction

Hemophagocytic syndromes (HPSs) are rare, life-threatening conditions characterized by overstimulation of the immune system leading to systemic inflammation, hypercytokinemia and multi-organ failure [1]. They are broadly divided into primary hemophagocytic lymphohistiocytosis (HLH) and secondary hemophagocytic syndromes [2]. Primary HLH is caused by genetic mutations impairing the cytotoxic function of natural killer (NK) and cytotoxic T cells and typically present in infancy and childhood. Primary HLH includes familial HLH (fHLH), where patients have autosomal recessive mutations in Perforin (PRF1), MUNC 13-4 (UNC13D), MUNC 19-2 (STXBP2), and Syntaxin 11 (STX11) [3–7]. Primary HLH also includes other inherited immunodeficiency syndromes such as Chédiak–Higashi syndrome, Griscelli syndrome, and type II Hermansky–Pudlak syndrome [8]. Secondary hemophagocytic syndromes generally affect adolescents and adults and are not associated with known genetic defects, although rare cases of fHLH have been reported beyond age 70 [9–11].

In secondary, or reactive, HPS there is often an associated "predisposing condition" causing immune dysregulation, such as malignancy (particularly lymphoma), immunodeficiency, or autoimmune disease, and/or a "trigger", most commonly infection such as Epstein–Barr virus (EBV) [8]. In some cases, an associated disease process is not identified [12]. HPS may also be referred to as macrophage activation syndrome (MAS) when it occurs in patients with autoimmune disease such as juvenile idiopathic arthritis (JIA), adult-onset Still's disease (AOSD) and systemic lupus erythematosus (SLE) [13,14]. The pathologic immune activation that characterizes HPS/HLH can be difficult to distinguish from physiologic macrophage activation. For example, neither the presence [15,16], nor amount of hemophagocytosis on bone marrow biopsies is specific for HPS/HLH [17]. Historical terms used to describe HPS are summarized in Table 1.

The modern conceptualization of adult HPS/HLH is derived largely from observations of familial HLH in children followed by the discovery of causative genetic abnormalities. Diagnostic criteria specific for adult HPS have not been established, and diagnosis is largely based on the Histiocyte Society's HLH-94 or 2004 (Table 2) pediatric diagnostic criteria [12]. A number of described manifestations of adult HPS, such as transaminitis, coagulopathy, elevated LDH, rash, hyponatremia, elevated CRP, and neurologic involvement (which is described in one small study), are not included in these criteria [18–22]. As with

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http://dx.doi.org/10.1016/j.blre.2016.05.001

Table 1
Nomenclature and diagnostic criteria of hemophagocytic syndromes: historical overview.

- 1939 — Histiocytic medullary reticulocytosis [85]
- 1952 — Familial hemophagocytic reticulocytosis [86]
- 1966 — Malignant histiocytosis described; majority of cases subsequently re-classified as anaplastic large cell lymphoma [87]
- 1979 — Virus-associated hemophagocytic syndrome (VAHS) [88]
- 1980 — Cytophagic histiocytic panniculitis [89]
- 1983 — Familial *hemophagocytic lymphohistiocytosis* [90]
- 1991 — Histiocyte Society diagnostic criteria for HLH developed [52]
- 1993 — Macrophage activation syndrome (children with inflammatory joint disease) [91]
- 1999 — Perforin gene mutation identified [3]
- 2004 — Histiocyte Society diagnostic criteria updated [12]

diagnosis, treatment protocols for adult HPS/HLH are often extrapolated from the pediatric HLH-94 and HLH-2004 protocols. These are etoposide-based regimens containing corticosteroids, cyclosporine A, intravenous immunoglobulins (IVIG), intrathecal therapy, and liberal use of allogeneic stem cell transplant in higher risk patients [23]. How well these treatment protocols apply to adults is poorly understood.

To date, the literature on adult HPS/HLH consists largely of retrospective studies, often confined to a single center or geographic region. Most literature reviews are narrative [24–26], although systematic reviews have been done for specific types of HPS/HLH such as HPS associated with zoonotic infections [27–29]. We conducted a systematic search to identify the extent of existing literature on HPS/HLH, an area with considerable clinical and methodological heterogeneity. We analyzed the findings using scoping review methodology. Scoping reviews are similar to systematic reviews in terms of searching the literature in a reproducible manner, but the aim of a scoping review is generally to address a broad area or topic (as opposed to a narrowly defined question) and scoping reviews do not emphasize the quality or methodology of included studies (as opposed to the stringent assessment of clinical heterogeneity, methodology and quality in systematic reviews) [30–32]. The aims of this systematic scoping review were to:

1. provide an overview of existing adult HPS/HLH literature and publication trends over time
2. describe established patterns and emerging trends in diagnosis and treatment of adult HPS/HLH
3. propose priorities for future research

Table 2
Histiocyte Society HLH-2004 diagnostic criteria.

The diagnosis HLH requires that either 1 or 2 below are fulfilled:
(1) A molecular diagnosis consistent with HLH
(2) Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below)
(A) Initial diagnostic criteria
  Fever
  Splenomegaly
  Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):
    Hemoglobin <90 g/L (in infants < 4 weeks: hemoglobin < 100 g/L)
    Platelets < 100 × 109/L
    Neutrophils < 1.0 × 109/L
  Hypertriglyceridemia and/or hypofibrinogenemia:
    Fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥265 mg/dL)
    Fibrinogen ≤ 1.5 g/L
  Hemophagocytosis in bone marrow or spleen or lymph nodes
(B) New diagnostic criteria
  Low or absent NK-cell activity
  Ferritin ≥ 500 mg/L
  Soluble CD25 (i.e., soluble IL-2 receptor) ≥2400 U/mL

2. Methods

2.1. Search strategy

A comprehensive literature search was performed using the databases Ovid Medline, Embase, and PubMed. The aim was to maximize sensitivity for finding published, peer-reviewed studies of adult HPS/HLH. Our search terms and medical subject headings (MeSH) were: *h(a)emophagocytic syndrome(s) OR h(a)emophagocytic lymphohistiocytosis OR h(a)ematophagic histiocytosis OR macrophage activation syndrome(s) OR cytophagic histiocytic panniculitis AND adult(s) AND English (language) AND humans*. We excluded *child(ren)* as a search term and limited results to publication years 1975–2015. As extended search techniques, PubMed and the Web of Science were used to identify more recent articles as well as the most highly cited publications in the field. Final updated searches were performed on September 3, 2015. Results were screened based on titles and abstracts to determine suitability for inclusion in this scoping review. "Gray literature" such as theses were not included; most conference proceedings were excluded except for two abstracts with important information on genetic testing and outcomes after Hematopoetic Cell Transplant (HCT). Details of the search strategy can be found in Supplementary Appendices 1, 2 and 3.

2.2. Study selection and data collection

All articles that addressed the topic of HPS/HLH in adults (defined as age > 15 years) were screened by full text review. English language articles with 10 or more original cases were selected for the scoping review. The minimum of 10 cases was arbitrarily chosen to identify larger studies. Data extraction was done by one investigator, checked by two others, and included: first author, journal, year of publication, country of origin, type and design of study, number of patients included, inclusion/exclusion criteria, demographic features, diagnostic criteria, details on genetic testing, associated conditions, clinicopathologic features, treatment, outcomes, and additional notes on the study.

3. Results

The search strategy gathered 2492 articles and upon manual review and cross-referencing (35) and eliminating duplicates (932), the total number of unique articles on adult HPS/HLH identified was 1590 (Fig. 1). Through the last updated search on Sept. 3, 2015, 552 new articles were identified on Web of Science, some of which overlapped with previously identified articles.

82 articles included 10 or more adults with HPS/HLH and were eligible for this review (see Supplementary Appendix 4 for complete list). 72 articles were retrospective and 10 were prospective [33–42]. Two of these prospective studies were clinical trials [33,34], three examined incidence and natural history of secondary HPS, and five investigated cytokine/biomarker significance. Fig. 2 illustrates the dramatic increase in the number of articles published per year on this subject; 56 of the 82 articles included were published in the past ten years. 44 articles were from Asian institutions (Fig. 3).

Three studies that did not strictly meet the inclusion criteria were still included because they were of special interest:

1) A study of 9 patients with HPS because it was one of the few prospective studies [35].
2) An abstract of 10 patients who underwent allogeneic HCT in Cincinnati because it was one of the few studies reporting genetic abnormalities in adults [43].
3) An abstract of 19 patients from Cincinnati, with overlapping patients from the above study, because it reported outcomes after HCT [44].

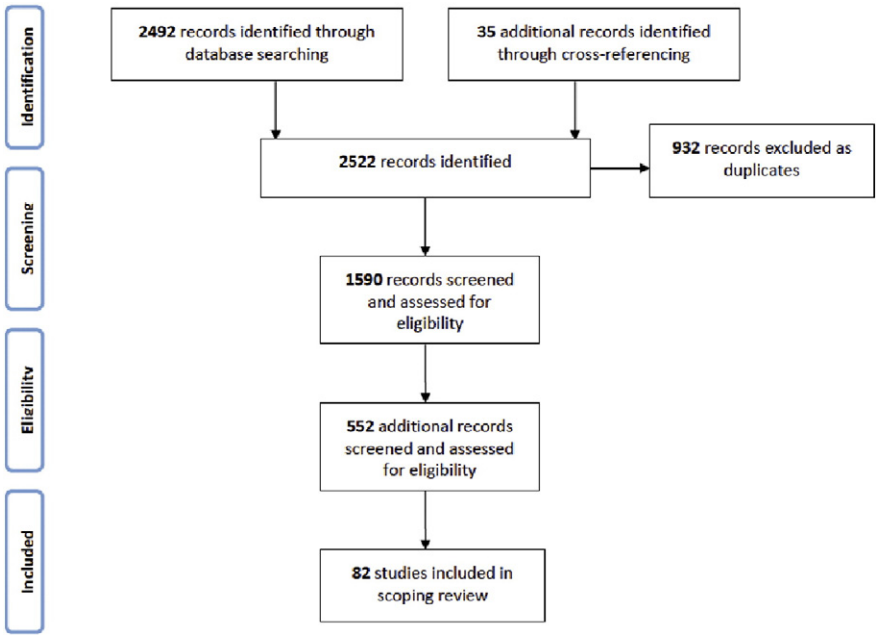

Fig. 1. PRISMA flowchart of study selection process.

3.1. Studies with overlapping patients

A recent systematic review combined results from numerous studies to gather information on the clinical presentation and treatment of HLH in adults [24]. For example, they reported a mortality rate of 41% in 1109 adults pooled from 13 articles. However, it is unlikely that these truly represent 1109 unique patients, as many patient series in the literature have been reported numerous times in different publications. For example, two of the 13 articles cited are from the same French center with overlapping study periods [1,45]. Investigators from this French group have published numerous important articles which describe different aspects of HPS in overlapping cohorts of patients [1,18,39,45–49]. A full list of studies with patients that were definitely or potentially described in more than one study is included in Supplementary Appendix 5.

3.2. Epidemiology

There is limited data on incidence of HPS/HLH, particularly in adult populations. A nationwide survey in Japan evaluating pediatric and adult cases reported annual incidence at 1 per 800,000 [50]. Pediatric HLH diagnosis has been approximated to be 1 case per 3000 inpatient admissions, and incidence per live birth has been estimated to be 1–6/300,000 [25,26]. A single-center retrospective Swedish study reported

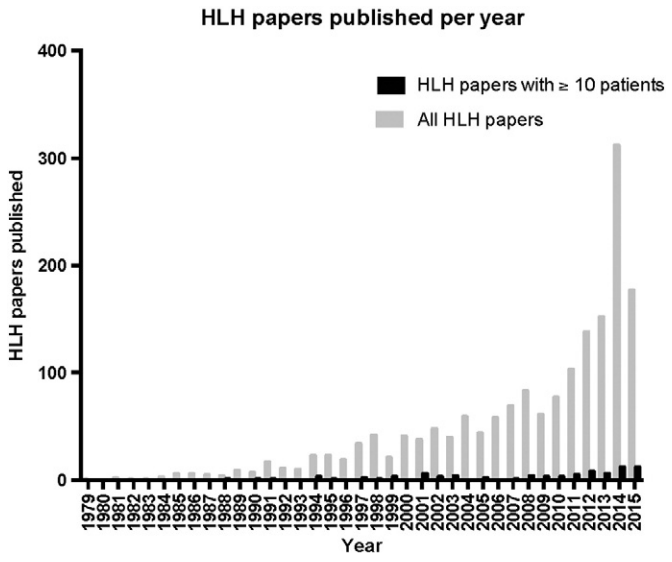

Fig. 2. Number of articles published on HLH in adults 1979–2015.

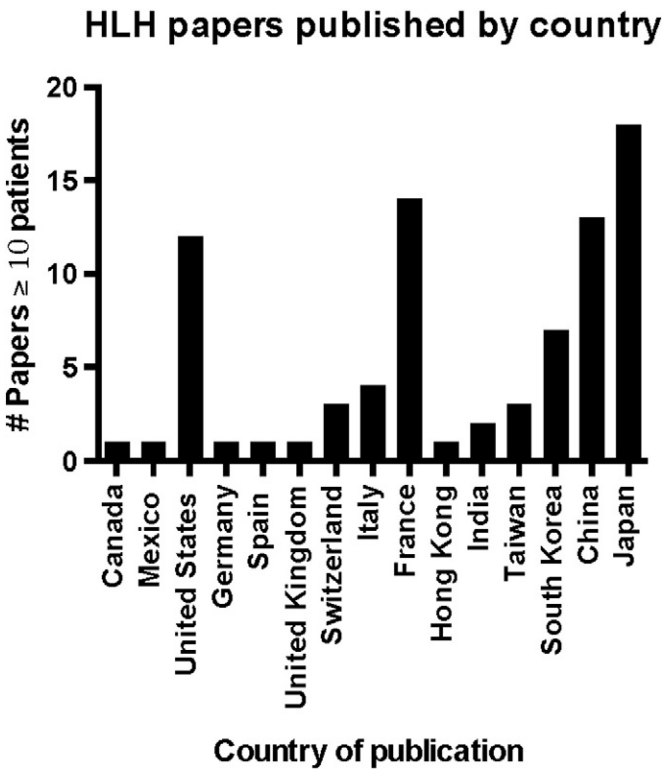

Fig. 3. Countries publishing on HLH with a cohort of ≥10 cases.

an incidence of malignancy-associated HLH in adults of 0.9% (8 of 887) [51]. The majority of articles included in this review originated from Asia and particularly Japan (see Fig. 3). Whether this suggests a higher incidence of HPS/HLH in this region, geographic variations in EBV-associated HPS/HLH, greater academic interest in HPS/HLH, or some combination thereof, is not clear. Three single-center studies prospectively examined the incidence and natural history of HPS associated with specific conditions in consecutive patients: 32 of 343 pts with AML [38], 12 of 20 patients with sepsis and thrombocytopenia on mechanical ventilation [35] and 9 of 25 pts with influenza A [37].

3.3. Diagnostic criteria

We reviewed the diagnostic criteria applied by each of the 82 articles in order to understand the consistency of HPS/HLH diagnosis in the literature and how this has changed over time (Table 1). Six distinct diagnostic criteria have been used (summarized in Table 3); of these, the Histiocyte Society's criteria are by far the most commonly used.

3.3.1. Studies using Histiocyte Society diagnostic criteria

The Histiocyte Society published diagnostic criteria in 1991, which were used for the pediatric HLH-94 trial [52]. 1 survey and 3 other articles used these diagnostic criteria [50,53–55]. Updated criteria, used for the HLH-2004 study, were published in 2007. 36 of the 54 articles (67%) published since 2007 in this review used HLH-2004 and 6 used modified HLH-2004 criteria. Many investigators have recognized the limitations of applying the pediatric HLH-2004 diagnostic criteria to adults [17,18,25,46]. These limitations fall into three categories:

1) Limitations of molecular testing: Only 12 of 54 studies performed genetic testing on at least one patient (Table 4). [10,22,33,34,43,56–62] The largest study of genetic mutations in adults from Cincinnati Children's Hospital Medical Center (CCHMC) reported that 25 of 175 (15%) adults had a mutation in PRF1, MUNC13-4 or STXBP2 [10]. Patient samples in this study were referred from all over North America and so the true denominator of adults with HPS/HLH cannot be ascertained. Moreover, classical familial HLH is caused by homozygous mutations in autosomal recessive genes; heterozygous allele mutations and mutations of unknown functional significance are included in many of these reports, and the significance of these findings is incompletely understood.
2) Accessibility of sIL2r and NK function: Many articles stated that sIL2r and NK function were not readily available at the study center. Only 11 of 54 studies published since 2007 commented on testing for sIL2r [17,19,22,34,37,58,59,61–64], and 11 studies commented on NK function testing [10,17,19,22,43,57–59,62,64,65]. Most of these studies reported testing in a small proportion of patients. sIL2r was elevated in 148 of 161 patients tested (91.9%) and 41 of 72 (56.9%) patients tested had absent or low NK cell activity.
3) Different presenting features in adults: A number of studies comment on how hemophagocytic syndromes, particularly reactive hemophagocytic syndromes, may present in adults with manifestations not included in the HLH-2004 criteria, such as elevated aspartate transaminase (AST) [18] or lactate dehydrogenase (LDH) [66]

3.3.2. Studies using other diagnostic criteria

Prior to 2007, all articles in this review required pathologic evidence of hemophagocytosis on bone marrow biopsy, aspirate, lymph node, spleen or liver, in addition to typical clinical features, which often included but did not require fever, cytopenias and splenomegaly. In total, 14 articles required histologic evidence of hemophagocytosis but no other specific diagnostic criterion. 8 of 11 articles published before 2000 did not use any standardized diagnostic criteria. In 1997, Tsuda et al. and Imashuku et al. each published modified criteria which built on the HLH-94 diagnostic criteria (Table 3) [20,66]. These criteria were employed by 11 articles combined (7 and 4 respectively).

One study developed novel diagnostic criteria for diagnosis of HLH in AML patients [38]. Emmenegger et al. proposed a ferritin value of ≥10,000 μg/L and/or morphologic evidence of hemophagocytosis as a screening strategy [14,67]. Takagi et al. created and applied novel criteria for Hematopoeitic Stem Cell Transplantation-related Hemophagocytic Syndrome (HCT-HPS) comprised of 2 major and 4 minor criteria which excluded cytopenias given the post-HCT context [68].

Fardet et al. proposed a novel set of diagnostic criteria for reactive HPS, the HScore, which is based on data from 162 patients and the first to be validated in an adult population [18]. Nine weighted variables were considered: 3 clinical [known underlying immunosuppression (such as HIV or chronic use of immunosuppressive medications), fever, organomegaly], 5 biologic (triglyceride, ferritin, aspartate transaminase (AST), fibrinogen, cytopenia), and 1 cytologic (HPS features on BM aspirate). sIL2r levels and NK cell activity were not included due to concerns about accessibility.

Table 3
Summary of main HLH diagnostic criteria used in literature.

	HLH diagnostic criteria					
Diagnostic feature	HLH 1994	Tsuda 1997	Imashuku 1997	HLH 2004	Takagi 2009	Fardet 2014
Molecular diagnosis	–	–	–	X	–	–
Fever	X	X	X	X	X	X
Splenomegaly	X	X	X	X	X	X
Cytopenia(s)	X	X	X	X	–	X
Hypertriglyceridemia	X	X	–	X	–	X
Hypofibrinogenemia	X	X	–	X	–	X
Hemophagocytosis	X	X	X	X	X	X
Coagulopathy	–	X	–	–	–	X
Decreased NK activity	–	–	–	X	–	–
Serum ferritin	–	–	X	X	X	X
Increased LDH	–	–	X	–	X	–
Increased sIL2r	–	–	–	X	–	–
Increased AST	–	–	–	–	–	X
Immunosuppression	–	–	–	–	–	X
Engraftment failure post HCT	–	–	–	–	X	–
Number of studies using criteria*	4	7	4	42	1	1
Notes	All required for diagnosis	All required for diagnosis	All required for diagnosis	5/8 or molecular diagnosis	2 major or 1 major and 4 minor criteria	Probability based on HScore

*Not all papers are included as some did not specify details of diagnostic criteria applied.

Table 4
Details of genetic testing done in 12 studies.

Ref.	Center	Period of study	No patients tested	No. genetic defects (%)	Genetic mutations/variants detected
Zhang [10]	CCHMC	ND	175	27 (15%)	18 PRF1, 7 MUNC12-4 and 2 STXBP2 17 monoallelic, 10 biallelic
Chandrakasan [43]	CCHMC	2004–12	10	4 (40)	2 PRF1, 1 MUNC 13-4, 1 XIAP
Otrock [58]	WUMC	2003–14	7	0 (0)	N/A
Otrock [59]	WUMC	2003–14	1	0 (0)	N/A
Huasong [60]	Jinan, China	2004–13	21	0 (0)	N/A
Wang [33]	BFH	2010–11	40	0 (0)	N/A
Wang [62]	BFH	2006–12	195	12 (6.2)	6 PRF1, 2 SH2D1A, 4 STX11, 1 UNCC13D 8 Monoallelic, 4 biallelic or hemizygous
Jing-Shi [61]	BFH	2007–14	19	0 (0)	2 PRF1, 1 MUNC 13-4, 1 XLP-1
Wang [34]	BFH	2013–14	ND	4	ND
Sieni [57]	Italian Registry	ND (6 years)	ND	11 (ND)	6 PRF1, 2 MUNC 13-4, 2 SH2D1A, 1 MUNC 19-9 10/11 biallelic
Kuriyama [56]	Kyushu, Japan	2005–11	ND	1 (ND)	1 PRF1
Gratton [22]	MGUH/WRMC	2011–11	1	0 (0)	N/A

ND, not described; N/A, not applicable; CCHMC, Cincinnati Children's Hospital Medical Center; WUMC, Washington University Medical Center, U.S.A.; BFH, Beijing Friendship Hospital, China; MGUH/WRMC, Medstar Georgetown University Hospital/Walter Reed Medical Center U.S.A.
Numbers reported from studies. There may be overlap in cases reported from the same centers.

Many laboratory tests have been evaluated for adult HLH. Five studies used a prospective method of patient selection to make comparisons with controls or patients with other diseases in laboratory parameters such as glycosylated ferritin [40,48], biologically active free interleukin-18 (IL-18) [36], adenosine deaminase [41] and comparison of cytokine profiles between B-cell and T/NK-cell lymphoma-associated hemophagocytic syndrome [42]. One study reported that the sIL2r/ferritin ratio was significantly higher in 11 patients with lymphoma-associated HPS compared to 10 patients with benign-disease associated HLH [63]. A recent study reported a number of abnormalities in the lymphocyte compartment of 21 patients with HLH. While these abnormalities are too varied and non-specific to assist in diagnosis, they may have prognostic significance [69].

3.4. Treatment

Eighteen studies in this review provided detailed descriptions of treatment and outcomes. Two of these studies were prospective [33,34]. The remainder were retrospective and included a range of ten to 162 patients (Table 5). Unlike diagnosis, where each study applied one set of diagnostic criteria to all study participants, treatment was highly variable both between and within the studies. Among these studies, all except two used an etoposide-based regimen for at least a proportion of patients. CHOP was used widely for lymphoma-associated hemophagocytic syndromes (LAHS); however, 2 studies also used CHOP therapy outside of the LAHS context, predominantly for EBV-HLH patients [55,70]. Hematopoietic cell therapy (HCT) was reported in a small number of patients in seven of these 18 studies [34,44,55,62,65,70,71].

3.4.1. Initial treatment

Initial glucocorticoids were almost always included in adult treatment regimens. Beyond this, there was considerable variation in treatment. The pattern of practice was first and foremost to identify and treat the underlying cause – infection, malignancy, or autoimmune – with disease-appropriate therapy and supportive measures, and if necessary, chemo-immunotherapy. However, there was significant variation both within and among studies in which patients received cytotoxic therapy such as the etoposide-based HLH-94/2004 treatment protocols or CHOP. In many cases, particularly in treating MAS, patients considered corticosteroid-refractory received only a component of the regimen, such as glucocorticoids and another immunosuppressive drug [13].

3.4.2. Etoposide-based Histiocyte Society protocols (HLH-94 and HLH-2004)

In pediatric HLH, which is rarely associated with an underlying malignancy, use of etoposide has shown significant improvement in survival if initiated within the first 4 weeks of symptoms [72]. This finding was replicated in a report of young adults (11 from Kyoto and 9 cases from the literature) with EBV-associated HLH, wherein treatment with etoposide within 4 weeks of presentation was associated with better outcomes (2 of 7 died) than in those who received etoposide after 4 weeks or not at all (12 of 13 died) [55]. In a retrospective study of 162 adults with HLH, Arca et al. described a trend toward better outcomes when etoposide was employed (85% vs. 74% survival, $p = 0.079$) [46]. In contrast, Parikh et al. assessed 62 patients with HLH, of whom 20 received etoposide (9 tumor-associated and 11 non-tumor associated), and found that the overall survival was similar between the cohorts receiving etoposide or non-etoposide based regimens [19]. In a retrospective study of prognostic factors in adult HLH, Li et al. found that etoposide use was not associated with better outcomes [73].

3.4.3. Other initial therapies

Many patients, particularly in Asia, have been treated with doxorubicin-based therapy such as CHOP, often in the context of aggressive lymphoma/LAHS (see Table 5). In a retrospective study examining treatment outcomes with CHOP in 17 adult patients with HLH secondary to lymphoma, EBV, or unknown cause, overall response rate was 58.8% (5/7 with lymphoma, 3/5 with EBV, 2/5 with idiopathic HLH) with 2 year overall survival 43.9% suggesting possible benefit of CHOP in adult HLH of multiple etiologies [70].

3.4.4. Salvage therapy

The only prospective multicenter study in this review investigated the effects of a salvage therapeutic regimen in 63 adults who had not achieved partial response to standard HLH therapy based on the HLH-94 treatment protocol. The regimen was a hybrid of etoposide- and doxorubicin-based regimens, consisting of liposomal doxorubicin, etoposide and pulse methylprednisone (DEP) [34]. Overall response was 76.2%; however, overall mortality was 54% due to either progression of underlying disease or recurrence of HLH.

3.4.5. Special populations

Allogeneic HCT in adults has rarely been reported [25]. Chandrakasan et al. reported on 19 adolescents/adults (age 15–27) with HLH who received alloHCT at CCMHC and reported overall survival 42.1% (8/19).

Table 5
18 Studies with detailed description of treatment and outcomes.

Reference	HPS patients	Country	HLH treatments provided	Prognostic factors and outcomes
Arca Br J Haematol 2015 [46] Riviere Am J Med 2014 [47]	162	France	42 received HLH-94, 39 etoposide only, 19 glucocorticoids only, 1 IVIG, 61 no HLH specific therapy	Etoposide was associated with a better outcome. Poor prognostic factors included age, thrombocytopenia, lymphoma and no etoposide. 42% overall mortality, 20.4% 30-day morality.
Aulagnon Am J Kidney Dis 2015 [49]	95	France	69 received etoposide, 33 other cytotoxic agent, 56 glucocorticoids, 9 IVIG	Early treatment, including etoposide may be associated with improved renal function and survival. Poor prognostic factors included hematologic malignancy and AKI stage ≥2. 56% 6 month mortality.
Buyse Intensive Care Med 2010 [1]	56 ICU patients	France	45 received etoposide, 32 other cytotoxic agent, 31 glucocorticoids, 3 IVIG	Poor prognostic factors included shock, thrombocytopenia. B cell lymphoma, Castleman's disease associated with improved survival. 51.8% mortality.
Chandrakasan Biol Blood Marrow Transplant 2013 [43]	10 young adult who underwent allogeneic HCT	United States	10 received HLH-04 and HCT	Mortality in young adults with HLH is higher than pediatric mortality of 12% at that center. 50% overall mortality (44% with RIC)
Chandrakasan ASH abstract 2013 [44]	19 young adults who underwent allogeneic HCT	United States	19 received HLH-04 and HCT	Mortality in young adults with HLH is higher than pediatric mortality of 25% at the same center. 57.9% overall mortality (43% with RIC)
Emmenegger Am J Hematol 2001 [67]	20 patients with MAS	Switzerland	20 received IVIG	IVIG is effective in MAS if given early in disease process. 25% mortality.
He International Medical J 2012 [75]	21	China	21 received HLH-04; not clear if any patients actually received plasma exchange	The authors speculated that hemodialysis or plasmapheresis should be for patients with ferritin > 1000 ng/mL and LDH > 1000 IU/L to control hypercytokinemia but did not present any data to support this 85.7% mortality.
Imashuku Med Pediatr Onc 2003 [55]	11 patients with EBV-HLH	Japan	4 received HLH-94, 5 etoposide within 4 weeks of diagnosis, 4 CHOP, 1 other cytotoxic agent, 2 HCT	EBV-HLH patients that received etoposide by 4 weeks of diagnosis had a better prognosis than those treated late. 72.7% mortality.
Jing-Shi Ann Hematol 2015 [61]	19 patients with relapsed/ refractory HLH	China	16 received HLH-94, 3 HLH-04, 19 splenectomies	Splenectomy may be effective in treating patients with relapsed HLH. 36.8% mortality.
Li Medicine 2014 [73]	103	China	35 received etoposide, 32/49 LAHS patients received CHOP or other doxorubicin-based regimens, 83 glucocorticoids, 35 IVIG	Treating underlying disease, combined with corticosteroids, immunosuppressive therapy and IVIG may improve prognosis. Poor prognostic factors included age, male sex, splenomegaly, thrombocytopenia. 74.8% mortality,

Table 5 (*continued*)

Reference	HPS patients	Country	HLH treatments provided	Prognostic factors and outcomes
Parikh Mayo Clin Proc 2014 [19]	62	United States	15/32 patients with malignancy 4/6 EBV, 1/3 CMV, 3/5 MAS, 1/7 bacterial/fugal infection, 3/4 idiopathic received etoposide 22 LAHS patients received CHOP	Survival of patients receiving etoposide-based therapy was similar to cohort receiving non-etoposide based treatment. Worse outcomes in tumor (including lymphoma) associated HLH. 30-day mortality 44%, overall mortality 66%.
Park Ann Hematol 2012 [65]	23 patients with non LAHS (16 EBV, 6 idiopathic, 1 HAV)	South Korea	2 received HLH-94, 11 received HLH-04, 11 etoposide, 22 glucocorticoids, 5 HCT	No difference in patient outcomes between group receiving HLH-94/04 protocol or other immunosuppressive regimen. Earlier initiation of treatment and elevated fibrinogen were positive prognostic factors. 73.9% mortality.
Shin J Korean Med Sci 2008 [70]	17 patients with LAHS, EBV-HLH or idiopathic	Japan	17 received CHOP, 2 HCT (1 LAHS, 1 EBV-HLH)	CHOP regimen appears to be effective in both LAHS and non-LAHS with manageable adverse effects. 52.9% mortality.
Takahashi Int J Hematol 2001 [71]	52	Japan	25/26 LAHS patients received CHOP, 3 VAHS patients received vincristine, 44 glucocorticoids, 21 IVIG. Etoposide/HLH-94 not mentioned.	Underlying disease affects prognosis. 88% LAHS mortality compared to 11.5% mortality of non-LAHS patients (VAHS 6%, BAHS 33%, MAS 0).
Wang Ann Hematol 2013 [33]	40	China	40 received HLH-94, all LAHS received ECHOP, All MAS treated with fludarabine + methylprednisone. 20/40 received rhTPO.	rhTPO was associated with improved platelet count, less gastrointestinal, pulmonary and urinary tract bleeding but had no effect on survival. 35% mortality.
Wang PLoS ONE 2014 [62]	18/195 HPS patients with genetic mutations	China	17/18 with mutations received HLH-94, 5/18 HCT	fHLH is more common than expected and should be treated similarly to pediatric HLH. 39% mortality.
Wang Blood 2015 [34]	63 patients with relapsed/ refractory HPS	China	63 received HLH-94 and DEP, 5 received other cytotoxic. 3 EBV patients received rituximab. 13 HCT, 7 splenectomies	DEP is an effective salvage regimen which prolongs survival in refractory HLH. 54% mortality.

HLH-94/04 (a combination of etoposide, dexamethasone with or without cyclosporine A), IVIG, intravenous immunoglobulin; RIC, reduced intensity conditioning; DEP, liposomal doxorubicin, etoposide, methylprednisone; CHOP (a combination of cyclophosphamide, Adriamycin, vincristine, prednisone); LAHS, lymphoma-associated hemophagocytosis;; EBV-HLH, EBV-associated HLH; VAHS, virus-associated HLH; BAHS, bacteria-associated HLH; rhTPO, recombinant human thrombopoeitin; HD, hemodialysis; PE, plasma exchange, fHLH, familial HLH; MAS, macrophage activation syndrome.

In the 15 patients > 15 years who received reduced-intensity alloHCT, survival was 57% compared to 75% in children < 15 years, $p = 0.03$ [44]. Other possible treatment modalities discussed in articles included in this review were IVIG for MAS [67,74], plasma exchange for patients with serum ferritin ≥ 10,000 μg/L and LDH ≥ 1000 IU/L [75], splenectomy for relapsed HLH of unknown cause [61], and recombinant human thrombopoeitin (rhTPO) which improved thrombocytopenia and decreased platelet transfusion requirements in a small randomized controlled trial of 40 adults with HLH [33].

3.5. Prognostic factors and outcomes

Outcomes in adult HLH were heterogeneous; among the 18 studies focusing on treatment and outcomes, mortality ranged from 20.4 to 88% depending on population factors and length of follow up (Table 5). Among these studies, the study with the lowest mortality rate only assessed 30-day mortality in order to limit the impact of underlying disease [46], whereas the highest mortality rate was in patients with underlying lymphoma, which was consistently an adverse prognostic factor [71]. The largest study, describing 162 patients and all associated HLH conditions, reported overall mortality 42% [47]. Mortality was generally lowest in autoimmune disease patients followed by infection-associated and idiopathic HLH patients. Malignancy, particularly lymphoma-associated HPS/HLH, was a prominent adverse prognostic marker correlating with poorer survival in multiple large studies [19,46,47,58,73,76]. Patients with T-cell lymphoma generally had worse outcomes than those with B-cell lymphoma [76–78]. Other common adverse prognostic factors included age > 30 [79], highly elevated ferritin [19,58,79], marked thrombocytopenia [1,46,79], male sex [73], lack of etoposide therapy [46] and low albumin [19].

4. Discussion

The number of adult HPS/HLH publications has risen dramatically from less than ten per year in the 1980s to greater than 100 per year since 2010. Though our inclusion criteria comprises articles from 1975 to current, only one study published prior to 1990 and only 11 articles published between 1990 to 2000 included 10 or more adult patients. The dramatic rise in larger studies of adult HPS/HLH in recent years likely reflects increased recognition; whether it also indicates a rise in incidence of HPS/HLH is not clear.

4.1. Diagnosis: established patterns and emerging trends

The Histiocyte Society's pediatric HLH-2004 diagnostic criteria has been widely extrapolated for use in adults since their publication in 2007. However, these criteria have a number of important shortcomings in the adult population. First, the molecular diagnosis is applicable only to those rare cases of adult-onset fHLH, and testing is available only in specialized centers. Frequency of genetic mutations is inversely correlated with age of disease onset, with 45% of patients < 1 month found to have an fHLH mutation compared to 6% of those over age 2 years [26]. Furthermore, part of the rationale of testing children is to identify patients in whom allogeneic HCT is warranted, but the tolerability and efficacy of HCT in adults, especially older adults is poorly understood. 12 of 82 studies in this review tested a small proportion of patients for genetic mutations, which likely reflects the lack of access, high cost, and ill-defined clinical benefit associated with genetic testing in adults. Thus, the 8 clinical and laboratory features of HLH-2004 are particularly important in adults, and yet these abnormalities are relatively non-specific to HPS/HLH. Extreme hyperferritinemia has historically been described as nearly pathognomonic for HLH [8,26], but recent studies have shown that ferritin > 3000 μg/L and even >50,000 μg/L are very non-specific in acutely ill adults [64,80]. Hemophagocytosis on bone marrow sampling lacks both sensitivity and specificity [17,47,81]. The lack of testing for sIL2r and NK function identified in this review is a major issue in using the HLH-2004 diagnostic criteria in adults. One approach is to simply exclude sIL2r and NK function from adult diagnostic criteria in favor of other more readily available parameters common to HPS in adults. For example, in the HScore for reactive HPS, elevated aspartate transaminase (AST) is included but sIL2r and NK function are not. The exclusion of these two parameters was not on the basis of empiric data. Rather, in the Delphi study which preceded construction of the HScore, it was judged that sIL2r, NK function, and CD163 were "not frequently enough assessed in routine practice" to be included [18,21]. However, HPS is a syndrome of pathologic immune activation occurring typically in immunocompromised patients and ultimately, sIL2r and NK function are important objective markers of increased T-cell activity and impaired cytotoxic function, respectively. sIL2r is a simple, commercially available biochemistry test and most centers with an interest in HPS/HLH should be able to implement this. NK function may be useful in some adults, both for diagnosis and confirmation of disease remission, but is more difficult to implement as the flow cytometry assays require specialized technicians and reagents.

4.2. Treatment: established patterns and emerging trends

Almost all adult studies describing treatment have been small, retrospective and tend to focus on a component of treatment or a subgroup of HPS/HLH. Glucocorticoids are standard, and for patients where cytotoxic therapy is thought to be necessary, the etoposide-based HLH-94 and 2004 protocols and CHOP are commonly used. Optimal initial therapies, as well as duration of treatment in adults, require further investigation. For example, the induction phase of the pediatric HLH-2004 protocol consists of 8 weeks of etoposide-based therapy, and treatment after that, if required, is intended as a bridge to alloHCT. However, adults treated with CHOP would typically receive CHOP every 3–4 weeks for 6–8 cycles (e.g. 18 to 32 weeks of chemotherapy). A recent study evaluating liposomal doxorubicin, etoposide and dexamethasone (DEP) represents a true milestone in being the first prospective, multi center clinical trial in adults [34]. Establishing standards for initial therapy remains a pressing need; unlike fHLH, a uniform protocol may not be feasible given the heterogeneity of the underlying/triggering conditions. Rather, treatment strategies tailored to different associated conditions (malignancy, infection, or autoimmune) may be needed.

In pediatric HPS/HLH, liberal use of allogeneic HCT is indicated to replace defective cytotoxic T cells in familial HLH, and sometimes to treat the underlying disease process, particularly in HPS/HLH associated with hematologic malignancy. However, the liberal use of allogeneic HCT described in the HLH-94 and HLH-2004 protocols may not be as applicable to adults. In the pediatric HLH-94 study, 124/249 patients (50%) underwent HCT, whereas only 7 of the 18 treatment-focused articles in this review report transplanting a small number of adults. The low incidence of fHLH, increased morbidity of allogeneic HCT in adults compared to children, relative scarcity of suitable donors, and the poor performance status and organ function of the relapsed and refractory adult patients are likely all factors in the low rate of HCT use in adults. Moreover, given the high prevalence of secondary HPS/HLH in adults driven by elevated cytokine levels from an underlying trigger, HCT would be unlikely to eradicate the underlying cause. According to some experts, allogeneic HCT should be considered on a case-by-case basis in eligible relapsed or refractory patients as well as the rare adults with late onset familial HLH [25].

5. Areas for future research and conclusions

5.1. Areas for future research

Currently, the paradigm in children is that a largely genetic disease (fHLH) requires allogeneic HCT in a high proportion of patients. This review demonstrates that in adults, the vast majority of reported cases have not been associated with a defined inherited molecular defect. Early diagnosis is essential, as a proportion of these patients will go on to develop critical illness, multi-organ failure, and death, and better diagnostic and prognostic models are needed. Although the HLH-2004 diagnostic criteria are widely used, molecular testing, sIL2r, and NK function are rarely applied in older patients. Diagnostic and prognostic models specific to adults, such as the HScore, have been developed, but exclude these specialized tests more on the basis of availability than whether they are actually helpful in diagnosis. The preponderance of secondary/reactive HPS, combined with the lack of specificity of criteria such as cytopenias and hyperferritinemia in adults, begs the question of whether other widely available markers of pathologic immune activation may be useful in diagnosis. The commercial availability of relatively low-cost sIL2r assays implies that further study of this disease marker should be conducted in adult HPS/HLH. Promising new biomarkers and therapies in children should be promptly evaluated in adults. For example, interferon gamma has been shown to be a key mediator of the cytopenias in HLH [82], and the therapeutic potential of an anti-interferon gamma antibody has shown promise in animal models. A pediatric anti-interferon gamma antibody phase 1 clinical trial is currently underway [83]. Another pediatric study of hybrid immunotherapy (anti-thymocyte globulin, dexamethasone and etoposide, the HIT-HLH trial) [84], is in progress and the results of this trial, along with the long-awaited HLH-2004 study results, should inform future studies in adult HLH.

5.2. Concluding remarks

Hemophagocytic syndromes in adults have received increasing attention in the literature over the past 30 years. However, there remains a paucity of prospectively collected, multi center data, and much of the diagnosis and treatment in adults is extrapolated from pediatric data. In children, the disease paradigm has been based on diagnosis of familial

HLH and aggressive treatment thereof with cytotoxic therapy and liberal use of alloHCT. In adults, the majority of studies describe secondary HPS associated with acquired immune dysregulation, which may present with different clinical and laboratory features, requiring different diagnostic criteria. The optimal initial therapy and role of alloHCT require further investigation in adults. Priorities for future research include development of diagnostic criteria and treatment protocols that accommodate those disease aspects unique to adults and also rapidly evaluate and incorporate novel discoveries in pediatric HPS/HLH.

Practice points

- Publications on adult HPS/HLH have increased dramatically in recent years but the majority are retrospective studies.
- Most studies apply the pediatric Histiocyte Society diagnostic criteria and treatment protocols, or variants thereof, to adult patients.
- Secondary HPS/HLH is much more commonly described than primary HLH, but adults are rarely tested for genetic abnormalities, soluble interleukin-2 receptor, or NK function.
- Survival in HLH is heterogeneous and malignancy/lymphoma- associated HPS/HLH is associated with poor outcomes.

Research Agenda

- Adult-specific diagnostic criteria based on commonly evaluable clinical and laboratory features of secondary HPS/HLH are needed.
- Promising new biomarkers in pediatric HPS/HLH, such as interferon gamma, should be evaluated in adults.
- Prospective multicenter trials to evaluate treatment and outcomes of HPS/HLH in adults are needed.

Conflict of interest

The authors state that they have no interests which might be perceived as posing a conflict or bias.

Acknowledgments

This study was supported by the Hal Kettleson Hematology Research Fund.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.blre.2016.05.001.

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