Thesis

Management of Critically Ill Adult Patients With Hemophagocytic Lymphohistiocytosis

submitted by

Johannes Maierhofer

in partial fulfillment of the requirements of the degree of

Doktor der gesamten Heilkunde

(Dr. med. univ.)

at the

Medical University of Graz

executed at the University department of

Internal Medicine - Intensive Care Unit

under the supervision of

Priv.-Doz. Dr. Stefan HATZL

Univ.-Prof. Dr. Robert KRAUSE

Graz, 25.11.2023

Declaration of Academic Integrity

I hereby confirm that the present diploma theses is the result of my own independent scholaly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, disserations and on the internet) is acknowledged, quotations and paraphraes are clearly indicated. No material other than cited in the reference list has been used. I hace read and understood the Medical University´s regulations and procedures concerning plagiarism.

Graz, am 25.11.2023 Johannes Maierhofer m.p.

Acknowledgement

First and foremost, I would like to thank my supervisor,

Priv.-Doz. Dr.med.univ. Dr.sience med. Stefan HATZL

He not only supported me professionally but generally lent his ears.
Dear Stefan, thank you for all these things.

I would like to use these lines to thank the people who have accompanied and supported me throughout my life, throughout my studies, up to here to the point of my graduation. Medicine is for me not only profession but also vocation and so the time of study brought enormously many hardships in form of lack of time and learning stress on these people. So, I thank my parents, siblings, my wonderful partner and the many friends who have supported me at all times, have picked me up when hard times went through an have accompanied me on this path.

In sincere gratitude
Johannes Maierhofer

Zusammenfassung in Deutsch

Die hämophagozytische Lymphohistiozytose ist ein hyperinflammatorisches Syndrom, welches durch unkontrollierte Makrophagen- und T-Zell-Aktivierung charakterisiert ist.
Es existiert eine hereditäre und eine erworbene Form wobei Zweitere meist durch Malignome, Infektionen und Autoimmunerkrankungen ausgelöst wird.
In letzter Zeit wird auch über einen weiteren auslösenden Faktor berichtet, nämlich die Immunsuppresionstherapie.
Auf der Intensivstation ist die HLH nur schwer vom Erscheinungsbild einer Sepsis zu unterscheiden und manchmal treten beide auch gleichzeitig auf.
Entscheidend für den Verlauf und die Prognose einer HLH ist die frühe Diagnosestellung und die raschestmögliche Therapieeinleitung.
Daher muss bei schwerkranken Patienten mit prolongiertem Fieber und entsprechenden Symptomen oder Laborveränderungen an das Vorliegen einer HLH gedacht werden.
Die Diagnosestellung wird anhand der HLH-2004-Kriterien getroffen und kann mit Hilfe des HScore in ihrer Wahrscheinlichkeit gestützt werden.
Eckpfleiler der Therapie sind hochdosierte Kortikosteroide welche je nach auslösendem Trigger um Etoposid, Immunglobuline, Anakinra und andere neue Medikamente ergänzt werden.
Verlaufs- und Prognose hängt vom auslösendem Faktor, von einem frühen Therapiebeginn und dem individuellen Ansprechen auf ebendiese ab.
Insgesamt ist die Prognose einer HLH als ungünstig zu bezeichnen und ist mit einer hohen Sterblichkeitsrate verbunden.
Mit dieser narrativen Übersichtsarbeit wollen wir die relevanteste Literatur zur HLH mit Implikationen für die intensivmedizinische Therapie zusammenfassen.

Abstract

Haemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome caused by unrestrained activation macrophages and T cells. The acquired form is primarily found in adults and differs from the inborn form in early childhood. Frequent triggers unleashing the cytokine storm of HLH are infections, malignancies and autoimmune diseases. Recently, an increasing number of cases have also been reported in which the occurrence was associated with immunotherapies. In the intensive care unit, HLH is often difficult to distinguish from sepsis due to its similar clinical appearance. In some cases, both are present at the same time. Early diagnosis and initiation of adequate immunosuppressive therapy is essential for the further course and prognosis of HLH. Therefore, the presence of HLH must be considered in critically ill patients with persistent fever and corresponding symptoms (e.g. splenomegaly, neurological abnormalities) or laboratory changes (e.g. elevated ferritin, cytopenia of 2 or 3 cell rows, elevated transaminases). The diagnosis is made using the HLH-2004 criteria. The HScore can be used to calculate the probability of the presence of HLH. High-dose corticosteroids are the cornerstone of HLH therapy. Depending on the trigger, etoposide, immunoglobulins, anakinra or other novel drugs are added. The course of the disease depends on the trigger and the response to therapy, as well as the early start of treatment. Overall, the prognosis of HLH is unfavorable despite maximum intensive medical treatment and it is associated with a high mortality rate. With this narrative review, we aim to summarize the most relevant literature for HLH with implication for intensive care therapy.

Table of contents

1 Definition and basic information 1
2 Epidemiology 2
3 Causes and risc factors 3
3.1 Prevention and early detection 8
4 Clinical image 9
4.1 Diagnostic criteria 10
4.2 Diagnostic measures 13
4.3 Therapy 17
4.3.1 Therapy for hereditary HLH 19
4.3.1.1 Immunochemotherapy 19
4.3.1.2 Second-line/salvage therapy 20
4.3.1.3 Allogeneic stem cell transplantation 20
4.3.2 Therapy for acquired HLH 21
4.3.2.1 HLH with infectious trigger 21
4.3.2.2 HLH in autoinflammatory/autoimmunologic disorders (MAS-HLH) 23
4.3.2.3 HLH in malignant diseases 23
4.3.2.4 HLH in immunocompromised patients 24
4.3.2.5 HLH after immunotherapy 24
4.3.3 HLH in intensive care unit and MAS-like sepsis 25
4.3.4 Therapy of refractory/progressive adult HLH 26
4.3.4.1 Supportive therapy 28
4.3.4.2 Infectious complications 28
5 Evaluation of the response to therapy and monitoring of progress 29
6 Discussion 30
7 Summary 32
8 Bibliography XI

Glossary

AOSD: adult-onset Still´s desease

CMV: Cytomegalie-Virus

CSF: Cerebrospinal fluid

EBV: Epstein-Barr-Virus

FACS: Flow cytometry

FHL: familial hemophagocytic lymphohisiocytosis

HIV: Human immunodeficiency virus

HLH: Hemophagocytic Lymphohisiocytosis

MAS-HLH: Hemophagocytic Lymphohisiocytosis and Macrophage activation syndrom

NOD: nucleotide-binding digomerization domain-like Receptor

sJIA: systemic juvenile idiopathic arthritis

XIAP: X-linked inhibitor of apoptosis

XLP: X-linked lymphoproliverative Syndrome

SLE: Systemic lupus erythematosus

CART: Chimeric antigen receptor T-cell therapy

ALL: acute lymphoblastic leukemia

CNS: Central Nervous System

CRP: C-reactive protein

LDH: Lactate dehydrogenase

SAP: SLAM-Associated Protein

NK/T cell: Natural killer cell

MRI: magnetic resonance imaging

PCR: polymerase chain reaction

sIL2-R: soluble interleukin-2 receptor

AML: acute myeloid leukemia

DLBCL: diffuse large B-cell Lymphoma

PET-CT: Positron emission tomography-Computed tomography

SIRS: Systemic Inflammatory Response Syndrome

MDS: Myelodysplastic syndrome

BiTE: Bispecific T-cell engaging

Allo-SCT: Allogeneic Stem cell Transplantation

VP-16: Etoposid

CSA: Cyclosporin A

MODS: multi organ dysfunction syndrome

FDA: Food and Drug Administration

CRS: cytokine release syndrome

IVIG: intravenous immunoglobulins

DGHO: German Society for Hematology and Medical Oncology

OEGHO: Austrian Society for Hematology and Medical Oncology

ICU: Intensive Care Unit

HEPA: High Efficient Particulate Air

BAL: Bronchoalveolar lavage

KRINKO: Commission for Hospital Hygiene and Infection Prevention of the Robert Koch Institute

List of figures

Figure 1: Diagnosis of hemophagocytic lmphohistiocytosis..... 16
Figure 2: Childhood/adolescent HLH therapy (HLH-1994 protocol)..... 18
Figure 3: Etoposid/Dexamethasone adapted for adult acquired HLH..... 22
Figure 4: Treatment algorithm of HLH (adapted from La Rosée et.al.) 27

List of tables

Table 1: Genetic alterations in hereditary (primary) HLH and related disorders with immune dysfunction 6
Table 2: triggers for HLH 7
Table 3: Diagnostic criteria of HLH according to the Pediatric HLH Sudy Group of the Histiocyte Society 12

1 Definition and basic information

Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS-HLH) are hyperferritinemic hyperinflammatory syndromes belonging to the group of histiocytosis [1]. They are characterized by a cytokine storm of abnormally activated macrophages and T cells. The clinical picture often differs little from sepsis, although the clinical expression and course are heterogeneous. In addition to the triad of fever, bi- or pancytopenia, and splenomegaly, pathologic cytokine secretion and tissue infiltration by activated lymphocytes and macrophages leads to cerebral, pulmonary, hepatic, or renal functional impairment with development of multiorgan failure. The eponymous hemophagocytosis in bone marrow, lymph nodes, or spleen is not detectable in all patients, which is neither necessary nor sufficiently sensitive or specific for diagnosis [2]. The primary (genetic) form, which usually occurs in children, is due to gene mutations that result in altered cytotoxic T and NK cell function and impaired immune regulation. Adults almost always have secondary (acquired) HLH triggered by infections, malignancies, or autoinflammatory and autoimmunologic diseases. The therapeutic and diagnostic recommendations that have been systematically developed in pediatrics through prospective studies are also applied in adapted form to the treatment of adult HLH patients. The disease is life-threatening and requires rapid diagnosis and initiation of therapy. Diagnostic delay is among other causes of high mortality.

2 Epidemiology

All ages are affected due to the division into primary and secondary HLH, but no reliable figures regarding incidence are available for Europe. The incidence of hereditary HLH has been estimated to be 0.12/100,000 children <15 years of age in Sweden, corresponding to 1/50,000 live births [3]. However, hereditary cases may still occur in adulthood [4]. A Japanese retrospective registry study estimated the annual incidence to be in the same range for all ages. 44% of patients were over 15 years of age. 19% of patients over 60 years of age [5]. Patients with malignant lymphoma -- also in Japan -- showed HLH as the primary manifestation of lymphoma in about 3% [6]. All ages are affected. With increasing age, the proportion of patients with malignancy-triggered HLH increases.

The first description is a case series from 1939, which named the clinical picture "histiocytic bone marrow reticulosis" [7]. The familial form of the disease was first described in 1952 and is also referred to as Farquhar's disease after the first describer.

3 Causes and risc factors

Causes of HLH are congenital or acquired dysfunctions at various levels of the immune system.
In hereditary "primary" HLH, usually occurring in early childhood, mutations are found in genes important for the provision and function of the cytotoxic granules of the immune synapse. The consequence is impaired cytolysis by NK cells and cytotoxic T cells [8]. In patients without clearly bi-allelic genetic dysfunction, complex acquired and congenital pathomechanisms, often against a background of preexisting immunosuppression or as a paraneoplasia of malignant disease, lead to the dangerous cytokine storm of "secondary" HLH.

Congenital:

- Autosomal recessively inherited immunodeficiencies with predisposition to HLH, also known as Familial Hemophagocytic Lymphohistiocytosis (FHL), see Table 1.

- Autosomal recessive inherited immunodeficiencies with partial albinism and predisposition to various disease manifestations including HLH and association with other symptoms, see Table 1.

- Immunodeficiencies with disorders of inflammasome activity. These include diseases with mutations in NLRC4 or XIAP [9,10].

- Immunodeficiencies with clustering of EBV-associated HLH. These mainly include XLP1, XLP2, itk deficiency and CD27 deficiency.

- Immunodeficiencies with occasional association of HLH. These mainly include septic granulomatosis and combined immunodeficiencies [11].

- Immunodeficiency with TIM3-mutated HLH associated with panniculitic T-cell lymphoma [12].

- Inborn errors of metabolism (including lysinuric protein intolerance, Wolman's disease).

Acquired:

In contrast to hereditary HLH, the causes of acquired HLH are multifactorial. They include preexisting autoinflammation as in Still's disease, immune incompetence after immunosuppressive or cytostatic therapy, and cytokine release e.g. by tumors. In immunocompetent patients, several factors could interact such as polymorphisms in genes important for the immune response, heterozygous mutations in HLH-associated genes, inhibition of cytotoxic function by viruses or cytokines, disruption of pro-apoptotic signaling pathways by tumors and viruses, and a mismatch between pathogen load and immune cells [8].

Immunodeficiency	gene* (locus)	Syndrome	Clinical picture	Laboratory findings
Cytotoxic granules	PRF1 (10q21-22)	FHL2		Decreased/absent perforin expression (FACS)
Regulation of cytotoxic exocytosis	UNC13D (17q2)	FHL3		low CD107a expression (Degranulation Assay, FACS)
Regulation of cytotoxic exocytosis	STX11 (6q24)	FHL4		low CD107a expression (Degranulation Assay, FACS)
Regulation of cytotoxic exocytosis	STXBP2 (19p13)	FHL5	Colitis, sensorineural hearing loss	low CD107a expression (Degranulation Assay, FACS)
Regulation of cytotoxic exocytosis	RAB27A (15q21)	Griscelli Type 2	Hypopigmentation	Abnormal granulation in neutrophils and pigmentary disturbance in hair, low CD107a expression (FACS).
Regulation of cytotoxic exocytosis	LYST (1q42-43)	Chediak-Higashi	Hypopigmentation	Abnormal granulation in neutrophils and pigmentary disturbance in hair, low CD107a expression (FACS).

Table 1: Genetic alterations in hereditary (primary) HLH and related disorders with immune dysfunction

Disease	Comment
Infections	• Viruses: most frequently herpes viruses, especially EBV and CMV; but also other viruses such as HIV, influenza, adeno, parvo B19, etc. • bacteria, especially intracellular pathogens (e.g. mycobacteria) • Protozoa, especially Leishmania, • Fungi (Aspergillus, Histoplasma, etc.)
Autoinflammatory and autoimmunological diseases (MAS-HLH)	• Systemic juvenile and adult idiopathic arthritis (Still's disease) • Systemic Lupus Erythematosus (SLE) • Kawasaki syndrome • Rheumatoid arthritis • Dermatomyositis • Other
Malignancies	• Malignant lymphoma, more common in • γδ-T lymphoma • NK/T cell lymphoma • Anaplastic large cell lymphoma • Peripheral T-cell lymphoma NOS • Hodgkin's lymphoma • Diffuse large B-cell lymphoma • Acute lymphoblastic leukemia (B- and T-lines ALL) • Germ cell tumor • Myelodysplastic syndrome • Other
Immunosuppression	• medicinal (e.g. cytostatics) • condition after stem cell transplantation • condition after organ transplantation • AIDS
Immune-activating therapy	• Chimeric antigen receptor T-cell therapy (CART) • checkpoint inhibitors • bispecific antibodies • stem cell transplantation
Metabolic diseases	• e.g. Lysinuric protein intolerance • M. Wolman (lysosomal storage disease)

Table 2: triggers for HLH

3.1 Prevention and early detection

Genetic counseling is recommended for individuals with a known genetic defect or with evidence of hereditary burden, and prenatal diagnosis is possible for all patients with a proven genetic defect. In asymptomatic carriers of disease-causing mutations, allogeneic stem cell transplantation should be sought immediately and a donor search initiated. For mutations with complete loss of function in the Prf1 or UNC13D gene, there is always an indication for transplantation. For certain gene defects with partial loss of function, it is known from sibling studies that genetically detectable HLH predisposition does not obligatorily penetrate to the clinical phenotype and wait-and-see behavior is warranted [13]. Here, the decision to transplant must be made on an individual basis depending on the course of the disease in the family member and the availability of an optimal matching donor. The most common mutation found in adults in an HLH-associated gene is the heterozygous perforin A91V mutation, which has a detection probability of 8-9% in the healthy Caucasian population [14]. It is functionally relevant, but its detection has no prognostic or therapeutic consequence even in the homozygous state [8].

4 Clinical image

The clinical picture is highly variable, showing overlap with symptoms of the underlying disease in acquired HLH. As a hyperinflammatory syndrome, HLH and MAS-HLH present like sepsis [15]; however, in contrast to infections or inflammatory processes without HLH, the symptoms and laboratory values are much more pronounced and progressive in the course of HLH.

Characteristic is the symptom triad:

- prolonged fever
- Hepatosplenomegaly
- bi- or pancytopenia

Other possible signs of the disease include neurological symptoms up to coma, lymphadenopathy, hepatitis, coagulation disorders, skin changes, pulmonary infiltrates, pleural effusion and ascites, diarrhea, and others.

In childhood, about one-third of patients have neurologic symptoms such as seizures, meningitic signs, or cranial nerve deficits [16]. Isolated CNS presentation without any peripheral inflammatory signs has also been described in primary HLH.

4.1 Diagnostic criteria

In 2007, the HLH Study Group of the Histiocyte Society revised its diagnostic criteria first published in 1991 [17], see Table 3.

The pediatric diagnostic HLH-2004 criteria also prove useful for the identification of predominantly secondarily acquired adult HLH, with certain limitations [19]. However, they are not suitable for patients with MAS-HLH in the juvenile or adult form of Still's disease (sJIA, AOSD), because the underlying disease already leads to high inflammatory signs and the dynamic decrease of certain values is more important as a warning symptom for MAS [20]. Only in the severe form of MAS-HLH cytopenia and hypofibrinogenemia also occur, whereas initially leukocytosis and high CRP are accompanied by hyperfibrinogenemia and hyperferritinemia.

The diagnosis of HLH using the HLH-2004 criteria requires consideration of the entire spectrum of clinical manifestations in each case. The boundary between a normally progressing severe infection and inadequate hyperinflammation of HLH is fluid. Special reference should be made to the following points:

- The temporal association between infection and HLH does not exclude a predisposing genetic defect; rather, genetic HLH is also likely to be triggered by infection in most cases.

- Secondary infections in treated HLH may mimic HLH recurrence. Consistent infection diagnosis and use of CRP, procalcitonin, microbiological and molecular pathogen diagnostics are essential.

- The French HLH group has developed HScore as a complementary diagnostic tool that can be used as an online calculator (http://saintantoine.aphp.fr/score/). Here, in contrast to the pediatric HLH-2004 criteria, the diagnostic value of the severity of pathologic laboratory parameters is taken into account and a probability for the presence of HLH is given [21].

- Above-average ferritin elevation and/or strong dynamics of serum ferritin in the febrile and cytopenic patient should always trigger the diagnostic HLH algorithm. It should be kept in mind that hyperferritinemia is not sufficiently specific by itself. Hemolysis, polytransfusion, chronic dialysis, or liver failure, among other conditions, can cause extreme values of ferritin [22].

	Criterion	Comment
Clinical symptoms / laboratory changes (5/8 criteria should be fulfilled).**	• Fever • Splenomegaly	
	Cytopenia ≥2 cell series	• Hemoglobin <90g/l (<100g/l in neonates less than 4 weeks of age). • Platelets <100x109/l • Neutrophil granulocytes < 1x109/l
	Hypertriglyceridemia and/or hypofibrinogenemia	• Triglycerides (fasting) • ≥3 mmol/l (265mg/dl) • Fibrinogen <1.5g/l
	Ferritin elevated*	• Ferritin ≥500 µg/l
	Soluble CD25§ increased	• sCD25 ≥2,400 U/ml
	• NK cell activity decreased or undetectable • Hemophagocytosis*** in bone marrow, CSF or lymph nodes	

Table 3: Diagnostic criteria of HLH according to the Pediatric HLH Sudy Group of the Histiocyte Society

*Legend: in case of underlying disease with per se inflammatory activation, the dynamic decrease in cell counts in the blood count and not an absolute value is decisive. Here, significantly higher ferritin values are found and a higher fibrinogen limit (<2,5g/l) applies [20]. * A ferritin value >10.000 mcg/l has a specificity of 96% for the diagnosis of HLH [18]. § soluble IL-2 receptor (sIL-2R); ** Other clues to support the diagnosis include moderately increased cell count and/or increased protein in CSF and increased transaminases, increased bilirubin or increased LDH in the serum. *** Hemophagocytosis is not per se probative of the presence of HLH. Also, evidence of hemophagocytosis is not necessary for diagnosis if sufficient criteria are already met.*

4.2 Diagnostic measures

The criteria listed in Table 3 allow the diagnosis of HLH to be made. In patients with confirmed underlying disease such as malignancy, autoinflammatory or autoimmunologic disease, known immunosuppression, or in adults without EBV infection, no HLH-specific functional diagnosis is initially necessary. In all other patients, familial HLH, or other genetic defects with HLH predisposition (Table 1, Figure 1) must be differentiated from acquired forms to establish the indication for curative consolidation therapy (allogeneic stem cell transplantation) at an early stage. Functional immunological investigations are available for this purpose. In flow cytometry, the degranulation test can detect all known gene defects of familial HLH except the perforin defect as well as mutations in Griscelli syndrome 2, Chédiak-Higashi syndrome and Hermansky-Pudlak syndrome 2. Perforin as well as XIAP and SAP expression can also be detected by flow cytometry. Measurement of NK/T cell function can be added as a supplement; however, it may also be decreased in acquired forms, but then it is not persistent. Interpretation of functional immunologic findings requires experience and meaningful placement in the clinical context. Confirmation of a genetic form of HLH is done by mutation analysis, but functional testing with results in 48 hours already allows a rapid adjustment of the therapy strategy even before the genetic findings are available. The indication for flow cytometric examination in the context of screening of possible genetic defects should primarily be discussed with a reference center.

Late-onset familial HLH should also be considered in adulthood, so genetic defects should not be overlooked [4,23]. For targeted genetic diagnosis, prior flow cytometry is recommended as part of the screening process. Systematic analyses on this have been collected in pediatrics in primary HLH [24].

Diagnostics also include measurement of immunoglobulins, as hypogammaglobulinemia is possible in familial HLH or XLP, and secondary hypogammaglobulinemia may be directional in malignant lymphoma. Lumbar puncture and MRI examination of the brain should always be performed in hereditary HLH and in other forms of HLH if CNS symptoms are present (see Figure 1).

Morphologic diagnosis of the bone marrow is standard. Exclusion/diagnosis of hematologic systemic diseases, additional infectious diagnostics (PCR tuberculosis, Leishmania) if necessary, and assessment of hemophagocytosis are key questions. The assessment of whether significant hemophagocytosis activity is present requires careful microscopy and, because of the low specificity, the classification of the findings in the overall clinical picture [2]. Gars & colleagues have proposed and retrospectively validated a quantitative score to increase the specificity of hemophagocytosis. Cell borders clearly delineated by intact cytoplasm of phagocytes and, in addition to phagocytosis of mature erythrocytes, detection of nucleated cells of hematopoiesis (granulocytes, erythoblasts, lymphocytes) in the cytoplasm significantly increase specificity. Activated macrophages with nonspecific intracellular debris are nonspecific and cannot be used for HLH-2004 criteria.

In patients after chemotherapy with infection-triggered HLH, diagnosis is complicated because of therapy-related cytopenia, often transfusion-dependent hyperferritinemia, and infection-dependent fever. Antibiotic-resistant fever should be screened for HLH by bone marrow aspiration, determination of ferritin, sIL2-R, and extended coagulation analysis. Bacteremia, fungal and viral infections caused a 9% rate of HLH in a French monocentric series of 343 consecutive AML patients after standard induction therapy [25]. Here, a sudden ferritin increase with a threshold of >8000 µg/L could support diagnostic accuracy.

With advancing age, lymphoma diagnosis is at the forefront of the trigger search. Entities such as diffuse large B-cell lymphoma (DLBCL) with the subentities of T-cell-rich DLBCL, histiocyte-rich DLBCL, intravascular DLBCL, Hodgkin's disease, lymphoblastic and non-lymphoblastic T-cell lymphomas, and NK-cell lymphomas are often difficult to identify because of the distinct accompanying inflammatory component. Early involvement of reference pathologists is recommended. To minimize the risk of diagnostic carryover under the often vital need for rapid immunosuppression with corticosteroids, an aggressive diagnostic approach with biopsy of skin, liver, spleen if necessary, bone marrow, preferably PET-CT guided, is recommended. This may require substantial use of coagulolytic plasma products in the presence of hypofibrinogenemia and disseminated intravascular coagulopathy. In cases of significant splenomegaly and suspected lymphoma (B symptoms, weight loss, prolonged HLH course), diagnostic therapeutic splenectomy should also be

considered. The Chinese HLH group demonstrated that in patients with refractory HLH, histopathologic lymphoma detection from the spleen can succeed despite PET negativity (a.e., because of the need for immunosuppression) [26]. Similar casuistics are documented in the German HLH registry [27]. This radical diagnostic measure is well justifiable against the background of the extremely poor prognosis of lymphoma-associated HLH [6]

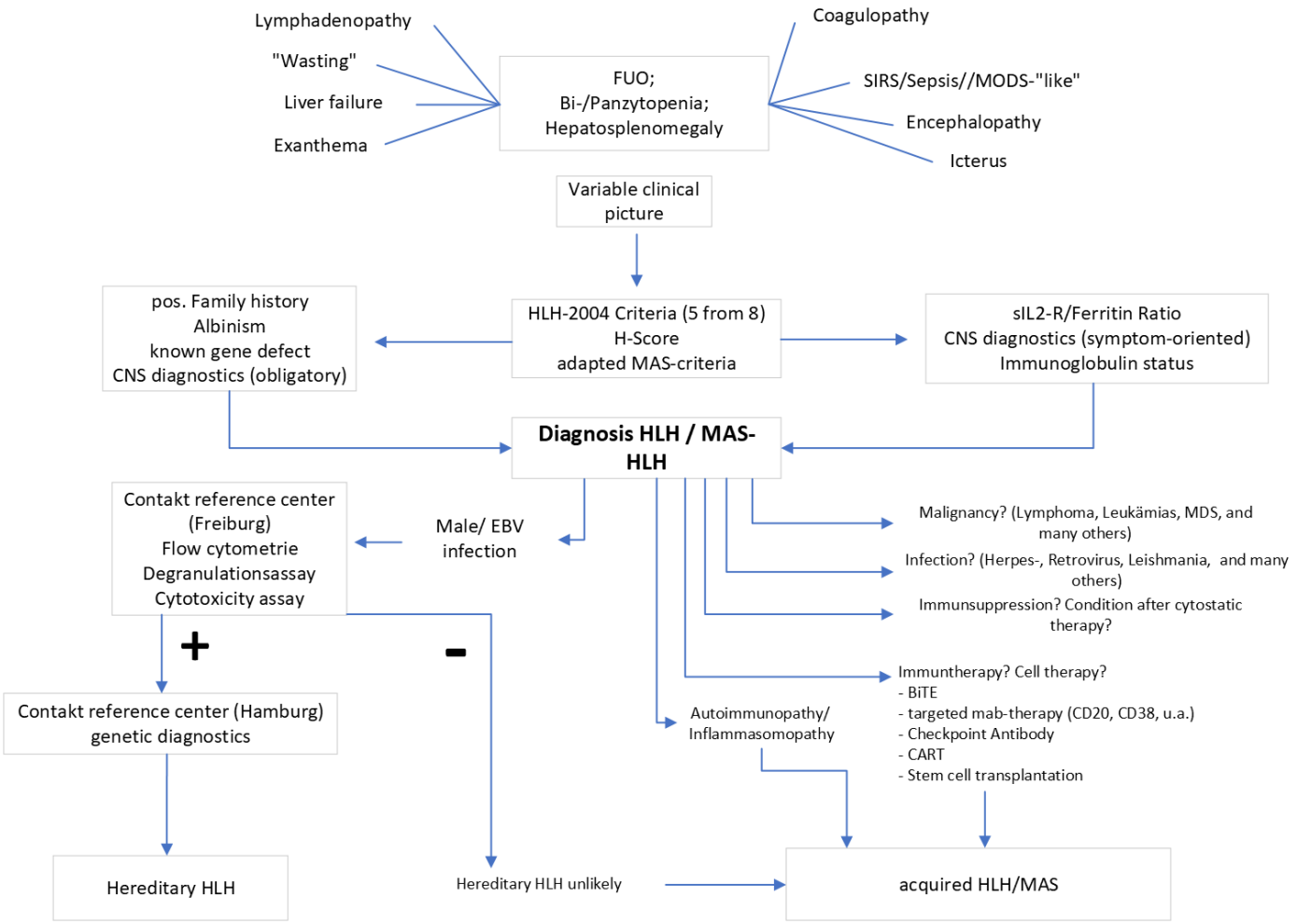

Figure 1: Diagnosis of hemophagocytic lmphohistiocytosis

4.3 Therapy

Therapy for childhood/adolescent HLH has been systematically developed in the HLH Study Group of the Histiocyte Society in the prospective HLH-1994 and HLH-2004 studies [28,29]. Figure 2 shows the HLH-1994 treatment protocol, which is currently the recommended treatment algorithm for hereditary HLH [30].

Depending on the severity and clinical manifestations, the duration of therapy and dose intensity must also be individually adjusted in pediatric/adolescent HLH [31]. With the exception of the rare hereditary form and EBV-associated HLH, uncritical adoption of the pediatric protocol should be cautioned in adulthood. Protracted iatrogenic immunodeficiency leads to sequelae infections and is usually incapable of curative treatment of the underlying disease causing HLH [19,30].

It is recommended that HLH therapy be performed in centers with sufficient experience in HLH therapy.

A crucial factor for the success of therapy is to start treatment as early as possible [32]. For the therapy of adult patients with HLH it is important to point out that in most cases the epiphenomenon of HLH can be successfully treated by therapy of the underlying infectious, autoimmunological or malignant disease, if necessary supported by short-term immunosuppression.

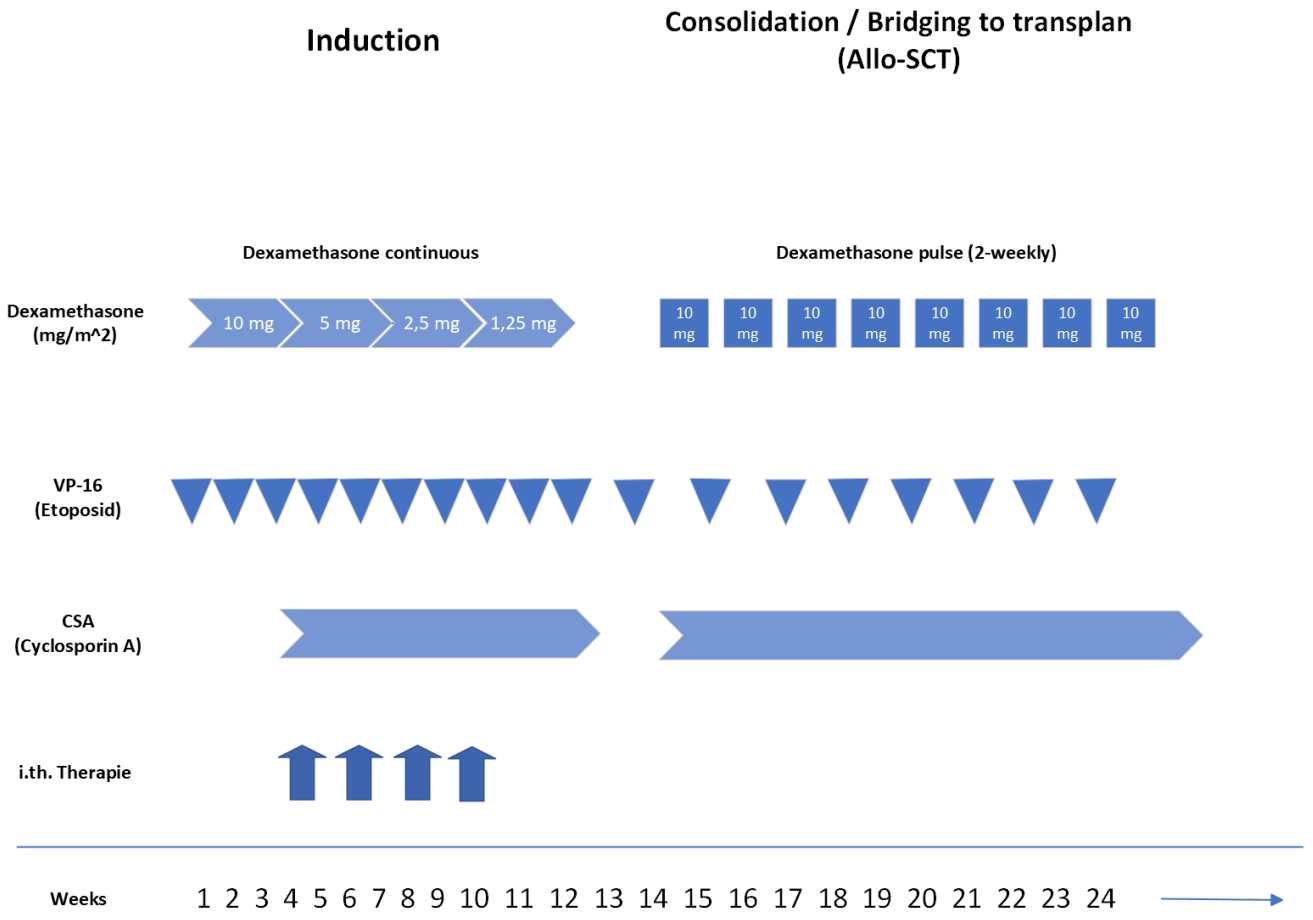

Figure 2: Childhood/adolescent HLH therapy (HLH-1994 protocol)

4.3.1 Therapy for hereditary HLH

Untreated, the median survival time of patients with hereditary HLH is about 2 months. Most patients die of multiple organ failure, neutropenia-related infectious complications, or sequelae of the neurological manifestations.

The first goal of HLH treatment is suppression of the excessive, uncontrolled immune response. If known and possible, the infectious trigger of HLH must also be treated. Therefore, an intensive pathogen search is indicated. Patients with genetic defects must be followed by allogeneic hematopoietic stem cell transplantation to replace the non-functioning immune system.

4.3.1.1 Immunochemotherapy

The aim of therapy is to suppress the excessive immune response that is dangerous for the patient. The standard of care developed in pediatrics for familial HLH is intensive immunosuppressive therapy with high-dose dexamethasone and intravenous etoposide, followed by maintenance therapy with ciclosporin A and stem cell transplantation (Figure 3). Patients with persistent neurologic symptoms also receive methotrexate and prednisone intrathecally. The HLH-94 trial enrolled 249 patients aged <15 years. Survival at 5 years was 54% [28].

In the follow-up HLH-2004 study, ciclosporin A was used as early as induction therapy to avoid the risk of early disease reactivation during dexamethasone tapering [29]. 369 children were included, and the 5-year survival probability was 62%, although the changed conditions of supportive therapy and improved transplantation outcomes must also be considered here due to the long recruitment period. Therefore, due to increased CSA-dependent toxicity in the induction phase of the HLH-2004 protocol, the HLH-1994 approach is considered the recommended standard [31].

4.3.1.2 Second-line/salvage therapy

The central pro-inflammatory cytokine in murine models of hereditary HLH is interferon-γ [33]. With the IFN-γ monoclonal antibody emapalumab, a substance developed specifically for hereditary HLH for the first time is available as a salvage option [34]. European approval is expected in 2020. In the pivotal pediatric study, children with median age of 1 year with predominantly hereditary HLH were treated with emapalumab combined with dexamethasone for 3 to 4 days. A median response was seen after 8 days. The duration of treatment was 8 weeks or until allogeneic SCT. 26% of patients achieved complete remission, and the overall response rate was 64.7%. FDA approval ranges from children to adults with refractory, relapsed, or progressive primary HLH. Patients' intolerant to standard immunochemotherapy can also be treated. Careful infection prophylaxis and pretherapeutic tuberculosis screening are mandatory. See also 6.4. for therapy of refractory/progressive adult HLH.

4.3.1.3 Allogeneic stem cell transplantation

Allogeneic stem cell transplantation is a curative option in patients with hereditary HLH. The introduction of conditioning regimens with reduced intensity and thus toxicity have increased survival rates, especially due to a significant reduction in therapy-associated mortality to about 90% recently. Long-term outcomes are comparable in related and unrelated donors [35].

In patients with genetic HLH, the donor search should be initiated immediately after the diagnosis is confirmed. Allogeneic stem cell transplantation is also indicated in patients with relapse or failure to respond to immunosuppressive therapy, when immunologic testing indicates a probable genetic defect, or in individual cases of acquired HLH.

4.3.2 Therapy for acquired HLH

Therapy for acquired HLH must be based on the very diverse underlying diseases (Table 3) [19]. In childhood, acquired HLH is usually triggered by infectious agents or autoinflammatory/autoimmunologic diseases. Especially in adults with HLH, malignant disease, particularly malignant lymphoma, must always be considered as an initiating cause, which is rather rare in children [36].

4.3.2.1 HLH with infectious trigger

Both congenital and acquired forms of HLH can be triggered by infectious triggers, so that the detection of an infectious agent does not allow a clear assignment. However, genetic forms are much rarer in adolescents and adults. However, a so-called late-onset hereditary HLH in adolescence/adulthood is to be expected, so that depending on the overall constellation (indication of family history, young male with EBV-HLH, albinism) a functional diagnosis should be performed because of the stem cell transplantation to be planned at an early stage (see Table 1).

An intensive search for pathogens is important because if the cause is treatable, the trigger can be eliminated, thereby reducing immune stimulation. HIV, EBV, CMV, and intracellular infections with rickettsiae, leishmaniae, or fungi are prominent infectious diseases with associated HLH [37,38]. However, anti-infective therapy alone is only sufficient in exceptional cases, such as leishmaniasis, which should always be considered even without a relevant travel history, as a stay abroad is not necessarily a prerequisite. Depending on the severity of HLH, immunomodulatory therapy with immunoglobulins and/or glucocorticoids may be sufficient, or combined therapy with etoposide analogous to HLH-1994 protocol is indicated. Here, an individualized dose decision has to be made, especially in adult therapy, to avoid excessive toxicity. A proposal for the adapted use of etoposide/dexamethasone was made for the therapy of H5N1-induced acquired adult HLH, which propagates dose-reduced etoposide (50-100mg/m2 weekly with consistent dexamethasone-tapering [30] (Figure 4).

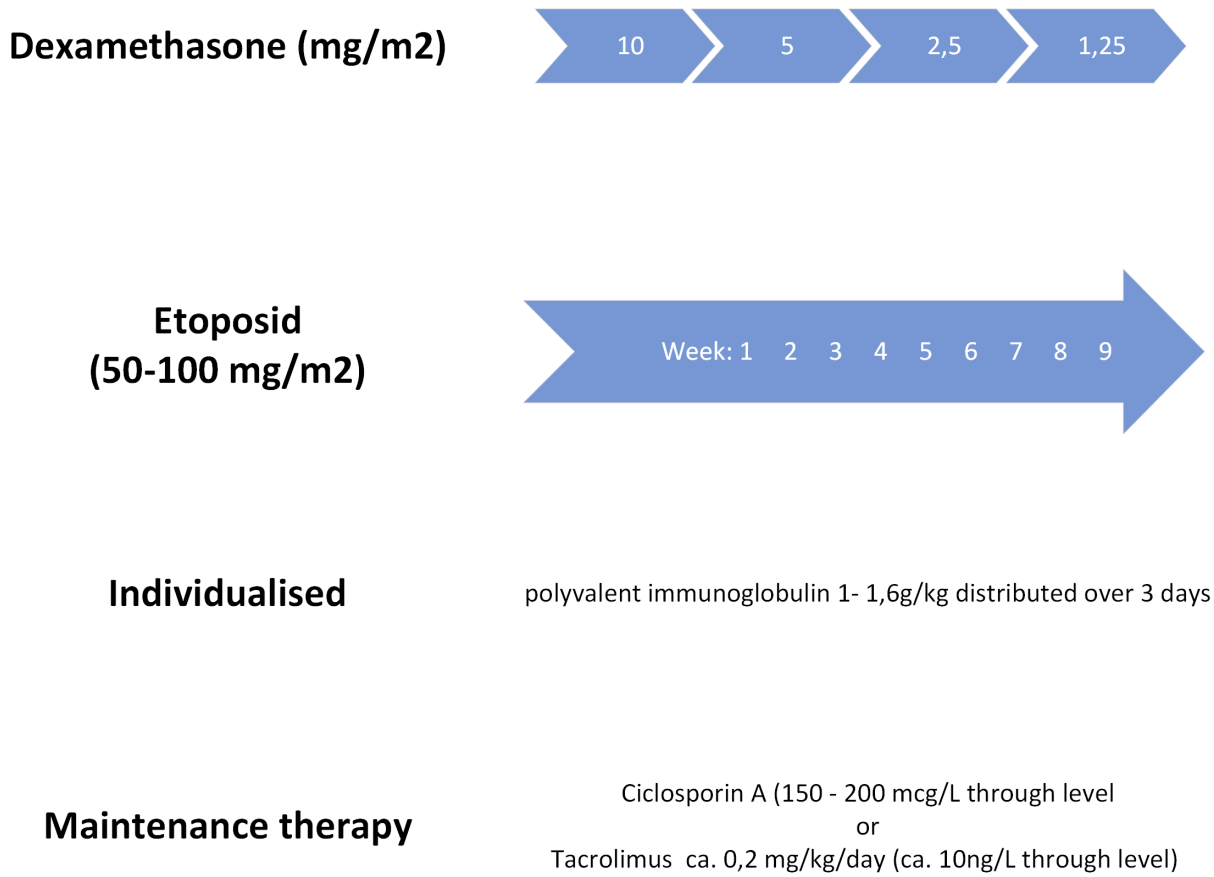

Figure 3: Etoposid/Dexamethasone adapted for adult acquired HLH

4.3.2.2 HLH in autoinflammatory/autoimmunologic disorders (MAS-HLH)

In the current classification of histiocytoses, the terminology has been changed to MAS-HLH to reflect the unified end route of HLH and MAS with end-organ damaging cytokine storm [1]. Also on this terminal track are patients with inflammasome disorders such as adult onset Still's disease (AOSD) [39]. High dose methylprednisolone at an initial dose of 1 g/d for 3 to 5 days, in case of failure ciclosporin A or with increasing evidence anakinra at a modified dose of 2 to 6mg/kg, escalated to 10 mg/kg distributed over 2 single doses, show the different approach. Ultimately, however, etoposide at a dosage of 50 - 100mg/m2 is also considered a highly effective salvage option [19].

4.3.2.3 HLH in malignant diseases

In the initial manifestation of a malignancy with HLH as paraneoplasia, the therapy of the underlying malignant disease is of primary importance. Glucocorticoids usually allow partial remission of the cytokine storm and open a window of opportunity for necessary (invasive) diagnostics. When indicated, etoposide can be incorporated into the therapeutic concept as part of pre-phase therapy, especially in malignant lymphomas.

Patients who develop HLH while receiving cytostatic therapy for malignant disease are already immunocompromised by this treatment and usually have severe neutropenia; HLH here is often an expression of unmanaged infection, although differentiation from the underlying malignant disease as a trigger of HLH can be difficult in individual cases [25]. Consistent infection monitoring, especially the search for fungal infection, is very important here. If threatening HLH symptoms such as incipient organ failure exist, short-term high-dose corticosteroid administration may be attempted. In patients in post-cytostatic neutropenia, the use of etoposide must be critically evaluated and the indication very carefully weighed against the background of the high risk of infection with prolonged aplasia duration. The ability of the bone marrow to recover is decisive for the course. The prognosis in adult patients with malignancy is unfavorable [36].

4.3.2.4 HLH in immunocompromised patients

In this patient group, it can be assumed that HLH is usually triggered by an infectious agent. The same considerations and guidelines as described in Chapter 1.8.2.1 apply. In patients with hematologic diseases and Z. n. stem cell transplantation with only partial immune reconstitution, it is often difficult to differentiate HLH from an "engraftment syndrome." Several cases of HLH have also been reported after organ transplantation [40].

4.3.2.5 HLH after immunotherapy

Immunotherapies, such as bispecific T cell activating antibodies (BiTE, e.g., Blinatumumab), antigen-specific antibodies stimulating a T cell response (e.g., Rituximab, Daratumumab), checkpoint antibodies against CTLA-4 or PD1/PDL1 (e.g. Ipilimumab, Durvalumab, Pembrolizumab, Nivolumab), chimeric antigen receptor T cells (CART, e.g., Tisagenlecleucel, Axicabtagene, Ciloleucel), or even stem cell transplantation have acquired cytokine storm (CRS) in the toxicity profile with development of iatrogenic HLH [41–43]. In BiTE or CART therapy, prompt cytokine-directed therapy with 8 mg/kg Tocilizumab (+/- Corticosteroid) up to 4 times at 8-hour intervals is standard repertoire; after checkpoint blockade or tumor-specific antibody therapy, the use of corticosteroids is considered standard as first-line therapy. If severe HLH develops, treatment with Tocilizumab (off label) can also be attempted, or etoposide if it fails.

4.3.3 HLH in intensive care unit and MAS-like sepsis

The clinical overlap of HLH/MAS-HLH and sepsis leads to HLH patients in intensive care units with the diagnosis "sepsis" remaining unrecognized [44]. Therefore, the Working Group on Intensive Care Medicine of the DGHO/OEGHO has also recommended in its consensus paper on intensive care of oncological patients to add ferritin, triglycerides, fibrinogen and sIL2-R to the routine laboratory in oncological and immunosuppressed patients [45]. Depending on the overall situation, a bone marrow biopsy should also be performed.

Rapid immunosuppression, administration of IVIG in therapeutic doses and, if necessary, emergency therapy with etoposide require close coordination between the intensive care physician and the hematologist. A special case is the still vaguely defined entity of MAS-like sepsis. A post-hoc analysis of an interventional sepsis study on the efficacy of IL-1-targeted therapy with anakinra (interleukin-1 receptor antagonist) showed that a subgroup of sepsis patients with hepatobiliary dysfunction and disseminated intravascular coagulopathy as a grouping marker for MAS-like cytokine storm achieved a survival benefit by IL-1 receptor blockade with Anakinra [46]. If there is uncertainty regarding the diagnostic assignment of sepsis-like cytokine storm disease, a treatment trial with Anakinra, possibly combined with Corticosteroids and polyvalent Immunoglobulins, is certainly warranted. ICU patients in multiorgan failure also benefit from mechanical cytokine elimination by adsorption column or plasmapheresis [47].

4.3.4 Therapy of refractory/progressive adult HLH

Approximately 20% of patients with familial HLH respond inadequately to HLH-1994-based therapy. In chapter 6.1.2, the IFN-γ antibody Emapalumab was already described as a bridging option to allogeneic stem cell transplantation for this predominantly pediatric patient group [34].

Salvage chemotherapy with liposomal doxorubicin, dose-escalated methylprednisolone, and Etoposide (DEP) was able to achieve an overall response rate of 76% in the Chinese HLH study group [48].

The tyrosine kinase Jak1/2 inhibitor Ruxolitinib at doses ranging from 2 x 5 mg to 2 x 15 mg is considered a broadly effective cytokine-blocking off-label therapy [49]. In case reports and initial studies, it shows disease control with only low toxicity.

The T-cell-depleting CD52 antibody Alemtuzumab is another treatment option in the refractory setting [35]. Sporadic responses to antagonists against CD25 (Basiliximab), tumor necrosis factor α (Etanercept), or to various cytostatic drugs have been reported. A standardized protocol does not exist.

In patients with Still syndrome and refractory HLH symptoms, the use of the antibody against interleukin 6 (Tocilizumab) may be considered after failure of interleukin-1 antagonists if the HLH is due to the refractory underlying disease. Again, Etoposide is considered a valid salvage option. In addition, cytokine elimination with cytokine adsorption column should be considered in cases of multiorgan failure [19].

The complex therapeutic options for HLH are summarized in Figure 4

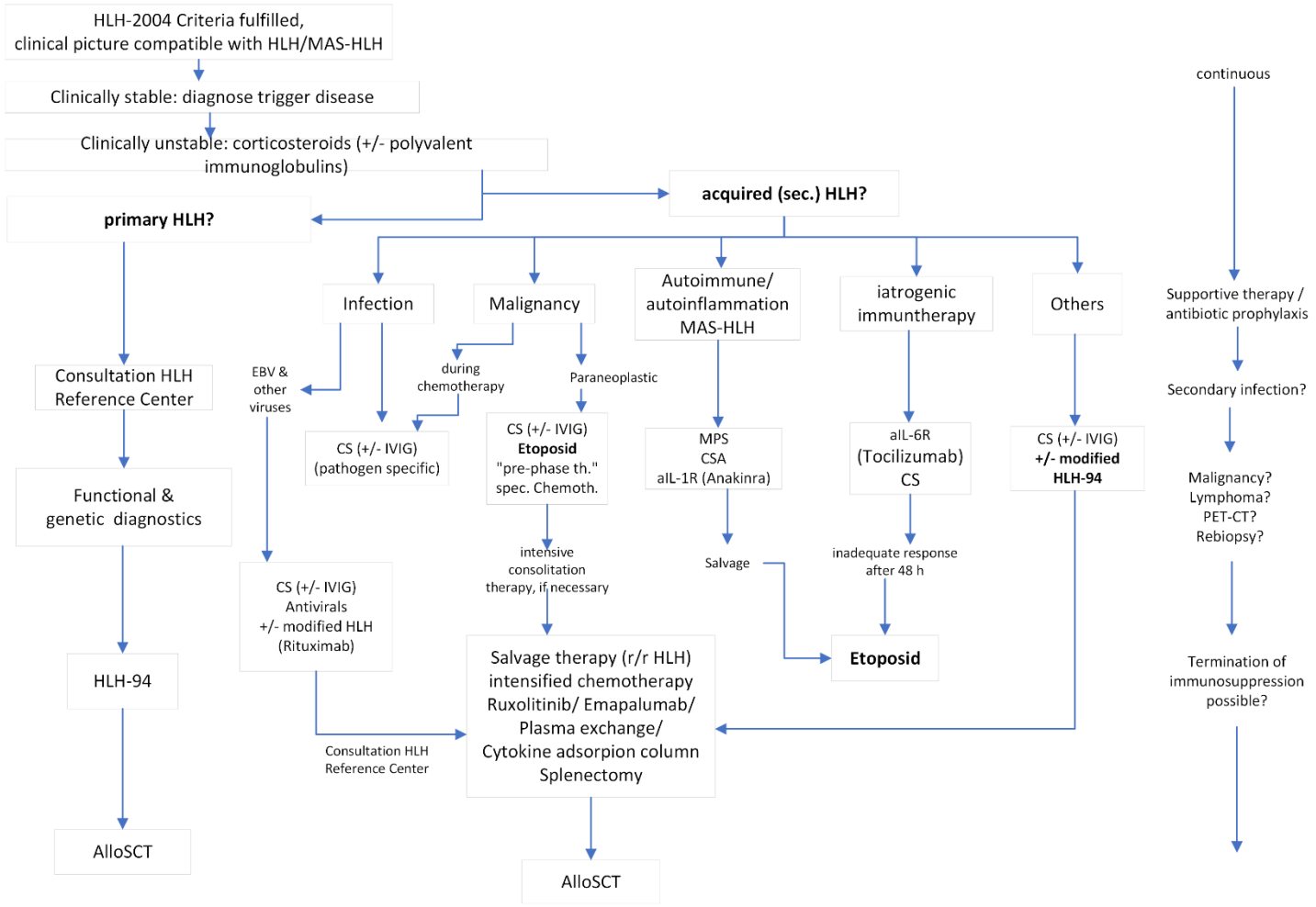

Figure 4: Treatment algorithm of HLH (adapted from La Rosée et.al.)

4.3.4.1 Supportive therapy

The KRINKO recommendations of the Robert Koch Institute groups HLH patients into infection risk class 2 (such as patients with very severe aplastic anemia or after allogeneic/autologous stem cell transplantation). Class 2 indicates high level of immunosuppression. Therefore patients should be treated in air-filtered units (HEPA), careful antimicrobial prophylaxis (antiviral, antifungal, Peumocystis-targeted according to local guidelines) and regular diagnostics regarding atypical infections (CMV, EBV, mycoses) are recommended in this class. If initially no immunoglobulins were used therapeutically, 4-weekly doses are recommended in case of prolonged corticosteroid therapy. [50]

4.3.4.2 Infectious complications

Neutropenia is often present in active HLH. If fever recurs, it must be considered that an infection of bacterial, fungal or viral origin may be present. Interpretation of elevated C-reactive protein (CRP) is limited because HLH leads to increased CRP itself. Patients should be adequately monitored on an ongoing basis (screening for fungal diseases with serologic biomarkers and by imaging, bronchoscopy with BAL if necessary, repetitive blood cultures, CMV diagnostics, etc.). Not every ferritin increase with fever is a HLH recurrence. [45]
An unique problem in classical HLH therapy including IVIG is the masquerade of 1-3 β-D-Glucan which makes serological screening for invasive fungal infections difficult. [51]

5 Evaluation of the response to therapy and monitoring of progress

One of the most difficult questions in the course of HLH is response evaluation end initiation of salvage therapies especially when clinical signs an bookmarks increase subtly. After improvement of fever, organomegaly and recovery of any organ dysfunction, ferritin and sIL2-R decrease indicate response to therapy. Relapse often presents with recurrence of fever, cytopenias, and steadily increasing ferritin, and secondary infections should be sought in each case.. In patients with acquired HLH, outpatient monitoring should continue for several months (ferritin and sIL2-R monitoring). If symptoms occur that indicate a new HLH relapse, extensive diagnostics as at the beginning of the disease and should be performed especilally for infectious pathogens, bearing in mind the immunosuppression applied in each individual with HLH. However stringent criteria when to start relapse therapy are lacking and is upon the experience of the treating physician .

6 Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening hyperinflammation syndrome. A distinction is made between primary, genetically determined HLH, which usually manifests in childhood, and secondary, acquired HLH, which can affect patients of all age groups [19]. In secondary HLH, infections, malignancies and autoimmune diseases are common triggers [27]. However, it is not always possible to identify a trigger. Due to the unspecific clinical presentation, which is often difficult to distinguish from sepsis, the diagnosis of HLH is often not made or is made late, which leads to a delay in the start of treatment and thus to a worsening of the prognosis. This is particularly true for critically ill patients in the intensive care unit, where mortality rates of between 50 % and 80 % have been described [44, 52].

Depending on the trigger, a distinction is made between HLH (e.g. in infections and malignancies) and macrophage activation syndrome (MAS-HLH). MAS-HLH represents the final stage of HLH in underlying rheumatologic diseases. Pathophysiologically, the subtypes of HLH are based on complex dysregulations of T-cell response, macrophage activation and inflammasome. The result is an excessive inflammatory reaction with cytokine storm and pronounced hyperferritinemia. The eponymous phagocytosis of hematopoietic cells by macrophages, together with the often aberrantly proliferative cytotoxic T-cell compartment, can lead to multi-organ failure [53].

Malignoma-associated HLH most frequently occurs in patients with hematologic neoplasms. Various lymphoma subtypes in particular appear to be frequently associated with HLH. Most prominent type of lymphoma are T-cell lymphoma and Hodgkin´s lymphoma HLH associated with a solid tumor is rare [27, 36]. The treatment of malignoma-associated HLH poses a challenge, as the general condition of a relevant proportion of patients does not permit the chemotherapeutic treatment of the malignoma causing HLH that is actually indicated. In this case, pre-phase therapy with corticosteroids and etoposide can precede malignoma-specific therapy with the aim of maintaining and improving organ function. It should also be noted that in the presence of HLH-associated neutropenia, unlike chemotherapy-induced neutropenia, there should be no delay in starting chemotherapy, as it is an expression of the HLH-related inhibitory cytokine storm and is not toxically mediated. HLH following chemotherapy, which is usually triggered by infections, must be

distinguished from malignancy-triggered HLH. In this case, corticosteroids and, if necessary, immunoglobulins should be administered, and too rapid continuation of chemotherapy should be avoided [36].

Patients with autoimmunological or rheumatological underlying diseases as triggers represent the third large group of patients with HLH in the intensive care unit. Patients with MAS-HLH initially receive high doses of corticosteroids, followed by cytokine-directed biologics depending on the trigger disease. For example, there is increasing evidence for the efficacy of the IL-1 receptor antagonist anakinra in MAS-HLH [54].

The prognosis of terminologically and pathophysiologically vaguely defined MAS-like sepsis, which is characterized by the presence of hepatobiliary dysfunction and disseminated intravascular coagulation, can also be improved by the administration of anakinra according to the subgroup analysis of a randomized sepsis study. [46]

Hyperinflammatory events in connection with cellular and antibody-based immunotherapies have been increasingly reported in recently. However, the stage of HLH is rarely reached. Depending on the trigger, treatment is with corticosteroids and tocilizumab, an antibody directed against IL-6 [55]. In severe cases, the administration of etoposide should be discussed.

Despite maximum intensive care treatment, the prognosis of critically ill patients with HLH is poor. According to a recently published systematic review, mortality among HLH patients treated in an intensive care unit was almost 60 % but differed between different patient groups depending on the trigger. The prognosis was most unfavorable in patients with malignoma-associated HLH [56]

7 Summary

- HLH is underdiagnosed in critically ill patients in the intensive care unit due to the unspecific symptoms.

- The presence of HLH should be considered in the differential diagnosis of patients with protracted fever, cytopenias and enlargement of the spleen and/or liver if there is no response to anti-infective therapy.

- In terms of laboratory chemistry, extreme ferritin values in particular support the suspected diagnosis of HLH and should be included into routine work-up of critically ill patients with signs of inflammation.

- The cornerstone of HLH treatment is immunosuppressive therapy with high doses of corticosteroids.

- In addition to drug immunosuppression, the trigger must be treated if identified.

- Despite immunosuppressive therapy, the mortality rate in critically ill HLH patients is still very high.

8 Bibliography

1. Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, u. a. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood. 2. Juni 2016;127(22):2672–81.

2. Gars E, Purington N, Scott G, Chisholm K, Gratzinger D, Martin BA, u. a. Bone marrow histomorphological criteria can accurately diagnose hemophagocytic lymphohistiocytosis. Haematologica. Oktober 2018;103(10):1635–41.

3. Henter JI, Elinder G, Söder O, Öst Å. Incidence in Sweden and Clinical Features of Familial Hemophagocytic Lymphohistiocytosis. Acta Paediatrica. April 1991;80(4):428–35.

4. Zhang K, Jordan MB, Marsh RA, Johnson JA, Kissell D, Meller J, u. a. Hypomorphic mutations in PRF1, MUNC13-4, and STXBP2 are associated with adult-onset familial HLH. Blood. 24. November 2011;118(22):5794–8.

5. Ishii E, Ohga S, Imashuku S, Yasukawa M, Tsuda H, Miura I, u. a. Nationwide Survey of Hemophagocytic Lymphohistiocytosis in Japan. International Journal of Hematology. 1. Juli 2007;86(1):58–65.

6. Sano H, Kobayashi R, Tanaka J, Hashino S, Ota S, Torimoto Y, u. a. Risk factor analysis of non-Hodgkin lymphoma-associated haemophagocytic syndromes: a multicentre study. Br J Haematol. Juni 2014;165(6):786–92.

7. Farquhar JW, Claireaux AE. Familial Haemophagocytic Reticulosis. Archives of Disease in Childhood. 1. Dezember 1952;27(136):519–25.

8. Janka GE, Lehmberg K. Hemophagocytic syndromes — An update. Blood Reviews. Juli 2014;28(4):135–42.

9. Canna SW, De Jesus AA, Gouni S, Brooks SR, Marrero B, Liu Y, u. a. An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. Nat Genet. Oktober 2014;46(10):1140–6.

10. Wada T, Kanegane H, Ohta K, Katoh F, Imamura T, Nakazawa Y, u. a. Sustained elevation of serum interleukin-18 and its association with hemophagocytic lymphohistiocytosis in XIAP deficiency. Cytokine. Januar 2014;65(1):74–8.

11. Bode SF, Ammann S, Al-Herz W, Bataneant M, Dvorak CC, Gehring S, u. a. The syndrome of hemophagocytic lymphohistiocytosis in primary immunodeficiencies: implications for differential diagnosis and pathogenesis. Haematologica. 1. Juli 2015;100(7):978–88.

12. Gayden T, Sepulveda FE, Khuong-Quang DA, Pratt J, Valera ET, Garrigue A, u. a. Germline HAVCR2 mutations altering TIM-3 characterize subcutaneous panniculitis-like T cell lymphomas with hemophagocytic lymphohistiocytic syndrome. Nat Genet. Dezember 2018;50(12):1650–7.

13. Cetica V, Sieni E, Pende D, Danesino C, De Fusco C, Locatelli F, u. a. Genetic predisposition to hemophagocytic lymphohistiocytosis: Report on 500 patients from the Italian registry. Journal of Allergy and Clinical Immunology. Januar 2016;137(1):188-196.e4.

14. House IG, Thia K, Brennan AJ, Tothill R, Dobrovic A, Yeh WZ, u. a. Heterozygosity for the common perforin mutation, p.A91V, impairs the cytotoxicity of primary natural killer cells from healthy individuals. Immunol Cell Biol. Juli 2015;93(6):575–80.

15. Machowicz R, Janka G, Wiktor-Jedrzejczak W. Similar but not the same: Differential diagnosis of HLH and sepsis. Critical Reviews in Oncology/Hematology. Juni 2017;114:1–12.

16. Horne A, Trottestam H, Aricò M, Egeler RM, Filipovich AH, Gadner H, u. a. Frequency and spectrum of central nervous system involvement in 193 children with haemophagocytic lymphohistiocytosis. Br J Haematol. Februar 2008;140(3):327–35.

17. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, u. a. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. Februar 2007;48(2):124–31.

18. Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis: Highly Elevated Ferritin Levels and HLH. Pediatr Blood Cancer. Juni 2008;50(6):1227–35.

19. La Rosée P, Horne A, Hines M, Von Bahr Greenwood T, Machowicz R, Berliner N, u. a. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 6. Juni 2019;133(23):2465–77.

20. Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A, u. a. 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis. März 2016;75(3):481–9.

21. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, u. a. Development and Validation of the HScore, a Score for the Diagnosis of Reactive Hemophagocytic Syndrome: Score for Reactive Hemophagocytic Syndrome. Arthritis & Rheumatology. September 2014;66(9):2613–20.

22. Schram AM, Campigotto F, Mullally A, Fogerty A, Massarotti E, Neuberg D, u. a. Marked hyperferritinemia does not predict for HLH in the adult population. Blood. 5. März 2015;125(10):1548–52.

23. Henkes M, Finke J, Warnatz K, Ammann S, Stadt UZ, Janka G, u. a. Late-onset hemophagocytic lymphohistiocytosis (HLH) in an adult female with Griscelli syndrome type 2 (GS2). Ann Hematol. Juni 2015;94(6):1057–60.

24. Ammann S, Lehmberg K, Zur Stadt U, Klemann C, Bode SFN, Speckmann C, u. a. Effective Immunological Guidance of Genetic Analyses Including Exome Sequencing in Patients Evaluated for Hemophagocytic Lymphohistiocytosis. J Clin Immunol. November 2017;37(8):770–80.

25. Delavigne K, Berard E, Bertoli S, Corre J, Duchayne E, Demur C, u. a. Hemophagocytic syndrome in patients with acute myeloid leukemia undergoing intensive chemotherapy. Haematologica. 1. März 2014;99(3):474–80.

26. Jing-Shi W, Yi-Ni W, Lin W, Zhao W. Splenectomy as a treatment for adults with relapsed hemophagocytic lymphohistiocytosis of unknown cause. Ann Hematol. Mai 2015;94(5):753–60.

27. Birndt S, Schenk T, Heinevetter B, Brunkhorst FM, Maschmeyer G, Rothmann F, u. a. Hemophagocytic lymphohistiocytosis in adults: collaborative analysis of 137 cases of a nationwide German registry. J Cancer Res Clin Oncol. April 2020;146(4):1065–77.

28. Trottestam H, Horne A, Aricò M, Egeler RM, Filipovich AH, Gadner H, u. a. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood. 27. Oktober 2011;118(17):4577–84.

29. Bergsten E, Horne A, Aricó M, Astigarraga I, Egeler RM, Filipovich AH, u. a. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood. 21. Dezember 2017;130(25):2728–38.

30. Henter JI, Chow CB, Leung CW, Lau YL. Cytotoxic therapy for severe avian influenza A (H5N1) infection. The Lancet. März 2006;367(9513):870–3.

31. Ehl S, Astigarraga I, Von Bahr Greenwood T, Hines M, Horne A, Ishii E, u. a. Recommendations for the Use of Etoposide-Based Therapy and Bone Marrow Transplantation for the Treatment of HLH: Consensus Statements by the HLH Steering Committee of the Histiocyte Society. The Journal of Allergy and Clinical Immunology: In Practice. September 2018;6(5):1508–17.

32. Imashuku S, Kuriyama K, Sakai R, Nakao Y, Masuda S ichi, Yasuda N, u. a. Treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) in young adults: A report from the HLH studyl center. Med Pediatr Oncol. August 2003;41(2):103–9.

33. Jordan MB, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. Blood. 1. August 2004;104(3):735–43.

34. Locatelli F, Jordan MB, Allen CE, Cesaro S, Rizzari C, Rao A, u. a. Safety and Efficacy of Emapalumab in Pediatric Patients with Primary Hemophagocytic Lymphohistiocytosis. Blood. 29. November 2018;132(Supplement 1):LBA-6-LBA-6.

35. Marsh RA, Jordan MB, Filipovich AH. Reduced-intensity conditioning haematopoietic cell transplantation for haemophagocytic lymphohistiocytosis: an important step forward. Br J Haematol. September 2011;154(5):556–63.

36. Lehmberg K, Nichols KE, Henter JI, Girschikofsky M, Greenwood T, Jordan M, u. a. Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. Haematologica. August 2015;100(8):997–1004.

37. Rouphael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. The Lancet Infectious Diseases. Dezember 2007;7(12):814–22.

38. Gagnaire MH, Galambrun C, Stéphan JL. Hemophagocytic syndrome: A misleading complication of visceral leishmaniasis in children--a series of 12 cases. Pediatrics. Oktober 2000;106(4):E58.

39. Schulert GS, Canna SW. Convergent pathways of the hyperferritinemic syndromes. International Immunology. 25. April 2018;30(5):195–203.

40. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. The Lancet. April 2014;383(9927):1503–16.

41. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, u. a. Chimeric antigen receptor T-cell therapy — assessment and management of toxicities. Nat Rev Clin Oncol. Januar 2018;15(1):47–62.

42. Teachey D, Rheingold S, Maude S. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. Blood. Blood. 8. September 2016;128(10):1441–1441.

43. Woods A, Wooten M, Thompson Heffner L, Waller E. Daratumumab-associated hemophagocytic lymphohistiocytosis. Ann Hematol. Januar 2020;99(1):181–2.

44. Lachmann G, Spies C, Schenk T, Brunkhorst FM, Balzer F, La Rosée P. Hemophagocytic Lymphohistiocytosis: Potentially Underdiagnosed in Intensive Care Units. Shock. August 2018;50(2):149–55.

45. Consensus of the German Society of Hematology and Medical Oncology (DGHO), Austrian Society of Hematology and Oncology (OeGHO), German Society for Medical Intensive Care Medicine and Emergency Medicine (DGIIN), and Austrian Society of Medical and General Intensive Care and Emergency Medicine (ÖGIAIN), Kiehl MG, Beutel G, Böll B, Buchheidt D, Forkert R, u. a. Consensus statement for cancer patients requiring intensive care support. Ann Hematol. Juli 2018;97(7):1271–82.

46. Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, u. a. Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial*. Critical Care Medicine. Februar 2016;44(2):275–81.

47. Greil C, Roether F, La Rosée P, Grimbacher B, Duerschmied D, Warnatz K. Rescue of Cytokine Storm Due to HLH by Hemoadsorption in a CTLA4-Deficient Patient. J Clin Immunol. April 2017;37(3):273–6.

48. Wang Y, Huang W, Hu L, Cen X, Li L, Wang J, u. a. Multicenter study of combination DEP regimen as a salvage therapy for adult refractory hemophagocytic lymphohistiocytosis. Blood. 5. November 2015;126(19):2186–92.

49. Ahmed A, Merrill SA, Alsawah F, Bockenstedt P, Campagnaro E, Devata S, u. a. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial. The Lancet Haematology. Dezember 2019;6(12):e630–7.

50. Robert-Koch-Institut. Robert-Koch-Institut [Internet]. Robert-Koch-Institut. 2023. Verfügbar unter: https://www.rki.de

51. Egger M, Prüller F, Raggam R, Divjak MK, Kurath-Koller S, Lackner H, u. a. False positive serum levels of (1–3)-ß-D-Glucan after infusion of intravenous immunoglobulins and time to normalisation. Journal of Infection. Februar 2018;76(2):206–10.

52. Kapoor S, Morgan CK, Siddique MA, Guntupalli KK. Intensive care unit complications and outcomes of adult patients with hemophagocytic lymphohistiocytosis: A retrospective study of 16 cases. WJCCM. 30. November 2018;7(6):73–83.

53. Brisse E, Wouters CH, Matthys P. Advances in the pathogenesis of primary and secondary haemophagocytic lymphohistiocytosis: differences and similarities. Br J Haematol. Juli 2016;174(2):203–17.

54. Zhou S, Qiao J, Bai J, Wu Y, Fang H. Biological therapy of traditional therapy-resistant adult-onset Still’s disease: an evidence-based review. TCRM. Januar 2018;Volume 14:167–71.

55. Fishman JA, Hogan JI, Maus MV. Inflammatory and Infectious Syndromes Associated With Cancer Immunotherapies. Clinical Infectious Diseases. 30. August 2019;69(6):909–20.

56. Knaak C, Schuster FS, Nyvlt P, Spies C, Feinkohl I, Beutel G, u. a. Treatment and Mortality of Hemophagocytic Lymphohistiocytosis in Adult Critically Ill Patients: A Systematic Review With Pooled Analysis. Critical Care Medicine. November 2020;48(11):e1137–46.