Peer reviewed article

Haemophagocytic syndromes in adults: current concepts and challenges ahead

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Summary

Haemophagocytic syndrome (HS), also referred to as haemophagocytic lymphohistiocytosis or macrophage activation syndrome, comprises a heterogeneous group of disorders featuring sepsis-like characteristics typically combined with haemophagocytosis, hyperferritinemia, hypercytokinemia and variable cytopenias, often resulting in fatal multiple organ failure. The availability of widely accepted diagnostic and therapeutic guidelines for the hereditary, paediatric forms of HS has improved outcome and lead to a better pathophysiological understanding. Although similar, reactive (secondary) HS in adults are distinct from childhood forms. Limited awareness of this type of disorder and the absence of clinical guidelines are to blame for delayed diagnosis and dire prognosis in many cases of HS in adults. Moreover, the underlying mechanisms of adult HS remain to be unravelled yet.

We summarise general features of HS and discuss particular characteristics of this disorder in adults. Furthermore, we describe a simple screening and diagnostic algorithm based on serum markers of macrophage activation (ferritin, soluble CD163 and soluble CD25) and morphological evidence of haemophagocytosis. Application of this strategy might be instrumental for recruiting patients for clinical studies, early diagnosis and hence improved prognosis. Indeed, there is evidence that a subgroup of patients with systemic inflammatory response syndrome presenting with signs of macrophage activation benefit from early administration of intravenous immunoglobulins. Clinical studies are needed to validate our diagnostic approach and to establish well defined prognostic and therapeutic algorithms. Finally, we will discuss whether similar processes contribute to HS in adults compared to childhood forms.

Key words: haemophagocytic syndrome; macrophage activation syndrome; haemophagocytic lymphohistiocytosis; haemophagocytosis; ferritin; soluble CD163; soluble CD25; intravenous immunoglobulin; cellular cytotoxicity

Introduction

Macrophages are key players in innate immunity and effectors as well as regulators of the adaptive immune system. The term haemophagocytic syndrome (HS; synonyms: macrophage activation syndrome, haemophagocytic lymphohistiocytosis) describes a heterogeneous group of disorders featuring sepsis-like characteristics typically combined with haemophagocytosis and variable cytopenias, dysfunctional cellular cytotoxicity, hyperferritinemia, hypercytokinemia, high fever, coagulation disorders, hepatosplenomegaly and lymphadenopathy. Eventually, multiple organ failure with high mortality ensues. Haemophagocytosis, the ingestion of cellular blood components and their precursors by macrophages, results from poorly controlled macrophage activity. This is the final common pathway of reduced cellular cytotoxic activity and/or decreased numbers of natural killer (NK) and cytotoxic T lymphocytes and is the underlying mechanism in most cases [1–3]. The fatality rate is high and depends on the circumstances under which the HS develops, such as related disorders and triggering events. Diagnostic [4, 5], therapeutic [6, 7] and prognostic [8] guidelines for childhood HS have been established, and their implementation lead to a better outcome compared to historical controls [9]. In addition, many of the underlying genetic defects were unravelled recently [5].

In contrast, HS is less frequently diagnosed in adults [10]. While a considerable level of suspicion regarding the dramatic and rapidly fatal course of

No financial support to declare.

the well-defined hereditary types of HS has evolved within the paediatrician community, many cases of adult HS are missed initially, resulting in a negative impact on outcome. The limited awareness of this type of disorder being one problem, another issue is the lack of well defined and widely accepted diagnostic guidelines for adults, although several authors have published diagnostic criteria (eg [11–13]). Moreover, treatment guidelines established for childhood HS might not necessarily apply to adults, even though many pathophysiological and clinical characteristics are shared.

We summarise basic characteristics of childhood HS as well as recent new findings regarding HS in general, and focus on how these data are applicable to adult HS. Besides a simple screening/diagnostic algorithm based on markers of macrophage activity and the description of general therapeutic concepts, evidence is discussed that HS might represent a subgroup of patients with systemic inflammatory response syndrome (SIRS) amenable to high dose intravenous immunoglobulin (IVIG) treatment on an emergency basis.

Historical remarks and terminology

The histiocytic system consists of a still growing number of phenotypically distinct cell types (monocytes, macrophages, dendritic cells and their subgroups) in various body compartments. Besides elimination of invading pathogens and subsequent antigen presentation, non-inflammatory removal of aging cells or cellular debris represents a central role of macrophages in tissue homeostasis. In 1952, Farquhar and Claireaux described a histiocytic disorder associated with prominent haemophagocytosis, which they called familial haemophagocytic reticulosis, nowadays named familial haemophagocytic lymphohistiocytosis (FHL) [14]. As opposed to the rapidly fatal course of FHL, Chandra et al. realised the potential transient nature of a similar phenomenon in two patients with miliary tuberculosis and a presumed viral infection, respectively [15]. In the years to follow, Risdall et al. described the virus-associated haemophagocytic syndrome [16], Reiner and Spivak the association with various underlying afflictions [17], and Hadchouel et al. the development of haemophagocytic syndromes related to rheumatic disorders [18], later referred to as macrophage activation syndrome by the same group [19]. In the most recent classification of the Histiocyte Society (www.histio.org/society), haemophagocytic syndromes are categorised as primary (corresponding to FHL, including sporadic forms) and secondary (also called reactive, eg. infection-associated) forms [5]. However, it is important to note that clinical manifestation of the primary forms is usually triggered by eg infections [20] and that genetic susceptibility is increasingly recognised as a major determinant in the pathogenesis of reactive HS. Throughout this review, we will use the term HS, which we and others (eg. [8]) consider a synonym for macrophage activation syndrome and haemophagocytic lymphohistiocytosis. HS subgroups are specified as proposed by Athreya, eg rheumatic disease-associated HS [21].

Epidemiology

The incidence of HS in children is in the order of 1 per 1 million children per year in Scandinavia and Italy, corresponding to 1 affected child per 50 000 live births [1, 22]. Similar data for adult HS are not available. Although the disorder is generally believed to be less common in adults than in children, recent evidence suggests that this might not be the case, in particular in patients with SIRS (eg [23]) and rheumatic disorders (eg [10]). In fact, our own experience suggests that clinically significant HS is increasingly diagnosed in patients with suggestive clinical presentation upon implementation of a valid screening strategy. Regarding the various subgroups, EBV-associated HS (including HS associated with EBV-related malignancies, mainly non-Hodgkin lymphomas (NHL)) is more common in Asian populations. Although a publication or "awareness" bias cannot be excluded, virus strain differences and the genetic background might be instrumental [24].

Pathophysiology

Much of the knowledge regarding HS has been obtained by the study of FHL and other hereditary disorders, predisposing to uncontrolled macrophage activation. Although HS arise spontaneously eg. in dogs (in particular Bernese Mountain dogs) and cats, these animals are not very suitable for the study of HS for mostly practical reasons [25, 26]. Published mouse and rabbit models have many limitations [27–32], but they may contribute to refine the pathophysiological under-

Table 1

Conditions associated with HS and triggers of HS.

A. Conditions associated with HS	
Primary immunodeficiencies	familial lymphohistiocytosis (FHL1, FHL2, FHL3)
	X-linked lymphoproliferative syndrome (XLP)
	Chediak-Higashi syndrome
	Griscelli syndrome (GS2 only)
	severe combined immuno- deficiency (IL-2 receptor γ chain)
	ICF (variable immunodeficiency, centromeric instability, facial anomalies) syndrome
	purine nucleoside phosphorylase deficiency
	Wiskott-Aldrich syndrome
	Di George/del (22q11) syndrome
Acquired immunodeficiency	HIV infection/AIDS
	transplantation
	chemotherapy
	immunosuppressive treatment
Infections	in particular Ebstein-Barr virus related disorders
Rheumatic diseases	rheumatoid arthritis, in particular systemic juvenile idiopathic arthritis (juvenile-onset Still's disease) and adult-onset Still's disease
	systemic lupus erythematosus
	sarcoidosis
	systemic sclerosis
	dermatomyositis
	chronic infantility neurologic cutaneous and articular syndrome
Malignancies	hematological malignancies: Non-Hodgkin lymphomas (mostly T and NK-cell type)
	solid tumors
Autoimmune diseases	Kawasaki disease
	glomerulonehpritides
	inflammatory bowel disease
	vasculitides
	Hashimoto thyreoditis
Dermatological disorders	pyoderma gangrenosum
	histiocytic cytophagic panniculitis
Inborn errors of metabolism	lysinuric protein intolerance
	multiple sulphatase deficiency
	methylmalonic aciduria
	hereditary fructose intolerance
	galactosialidosis
	galactosaemia
Varied	other histiocytoses: Langerhans cell histiocytosis, malignant histiocytosis
	Kikuchi's disease
	drug hypersensitivity reactions
B. Triggers of HS	
Infectious agents (for details see [33])	viral, in particular Ebstein-Barr virus
	bacterial, including atypical bacteria such as mycobacteria
	parasitic, in particular visceral leishmaniasis
	fungal
Medications	non-steroidal antiinflammatory drugs, including aspirin
	anti-epileptic drugs (phenytoin, lamotrigine)
	methotrexate
	gold salts
	sulfasalazine
	parental nutrition
	anti-tumor necrosis factor-α treatment [etarnecept/Enbrel™]
	anti-CD52 treatment [alemtuzumab/Campath™]

standing and allow testing new therapeutic approaches.

Disorders and triggers linked to HS

Various disorders have been more or less convincingly associated with HS as outlined in table 1A. In the majority of cases, a trigger can be found (table 1B). The contribution of infectious agents in HS has recently been extensively reviewed [33]. Importantly, iatrogenic manipulations might trigger the pathophysiological cascade as well (table 1B).

Monocyte and macrophage phenotypes in HS

Emminger et al. described the expansion of $CD14^{dim}/CD16^{bright}$ circulating monocytes in a boy with HS, which together with decreased expression of CD35, CD11b and CD64, corresponds to a rather mature monocyte phenotype [34]. Other authors demonstrated activation markers such as OKM1, OKT9, HLA-DR, and the co-expression of the chemokine receptors CCR6 and CCR7 [35, 36]. From spleen preparations, $CD14^{+}$ macrophages in adult HS patients were shown to express MHC class I and II molecules, M-CSF receptors, LFA-1, LFA-3 and ICAM-1 [37]. Though more extensive immunophenotyping is clearly needed, the majority of reports support the concept of mature, activated macrophages as the main effectors in HS. Non-specific phagocytic activity of dendritic cells might constitute a distinct pathway in a subpopulation of HS [38].

Role of NK and cytotoxic T-cells in HS

Defects of the cytotoxic effector pathways of NK and cytotoxic T-cells are fundamental to the current pathophysiological understanding of HS. Based on cytolytic function assessed under various experimental conditions and absolute NK/cytotoxic T-cell numbers, four distinct subgroups of defects in cellular cytotoxicity were described in children with haemophagocytic lymphohistiocytosis [39]. The molecular defects recently identified as leading to the hereditary HS forms FHL, Griscelli syndrome type II (GS) and Chediak-Higashi syndrome (CHS), all disrupt the secretory cytotoxic pathway at different levels (table 2, [40]). Whereas in patients with FHL-2 perforin expression is barely detected in cytotoxic granules [41], defective granule exocytosis as a consequence of hMunc13-4 mutations disrupts cytotoxicity in FHL-3 patients [42]. In GS type II, the granule content is normal but the release is impaired, because Rab27a is an essential effector of granule exocytosis [43]. Similarly, mutations in the CHS gene result in an inability to secrete giant granules containing lytic proteins [44]. X-linked lymphoproliferative syndrome (XLP) is caused by a mutation in the adaptor protein SAP, involved in the regulation of the signal transduction induced by the members of SLAM family receptors expressed at the surface of T-lymphocytes and NK-cells. SAP defective mice reproduce the human pathology with uncontrolled viral infection and HS, dysgammaglobulinemia, but not with lymphoproliferative disorders [28, 45, 46].

The molecular basis and functional consequences of the often transient and more subtle defects of cellular cytotoxic activity observed in some patients with non-hereditary HS have not yet been revealed. Intriguingly, depressed NK cell activity is also found in secondary HS, eg in systemic juvenile idiopathic arthritis (SJIA) [3, 47].

Deficient cytotoxic activity not only precludes the elimination of antigen expressing cellular targets, resulting in continuous immune activation, but also impairs the contraction of the immune response [40]. Hence, sustained activation of the immune system and deficient negative feedback mechanism explain the overwhelming macrophage activation seen in HS (figure 1). This model has recently gained support by studies of perforin knock-out mice, which display an overwhelming inflammatory response characterised by lymphocyte-mediated macrophage activation upon LCMV-infection [27].

Table 2
Hereditary disorders and HS.

Disease	Human phenotype	Gene (location, name)	Function of protein	Animal model
Familial haemophagocytic lymphohistiocytosis (FHL)	HS	9q21.3–22 = FHL-1 (~10%) 10q21–22 = FHL-2 (~20–40%) 17q25 = FHL-3 (? %)	FHL-1 →??? FHL-2 → perforin: lytic enzyme, cytotoxic activity FHL-3 → hMunc13–4: cytolytic granule exocytosis	Perforin KO mice
Griscelli syndrome type 2 (GS)	Partial albinism, recurrent infections, HS (accelerated phase)	15q21–22 = RAB27A	Melanosome transport, cytotoxic granule exocytosis	Ashen mice
Chediak-Higashi syndrome (CHS)	Partial albinism, recurrent infections, bleeding tendency, HS (accelerated phase), enlarged lysosomes	1q42.1–24.2 = CHS1 (human), LYST (mice)	Lysosome transport and/or fission	Beige mice
X-linked lymphoproliferative syndrome (XLP)	Fulminant infectious mononucleosis with HS, lymphomas, dysgammaglobulinemia	Xq25 = SH2D1A/SAP/DSHP (~60–70%)	Modulates signaling through SLAM family members	SAP KO mice

KO: knock-out

Cytokine network in HS

The cytokine network instrumental in HS has recently been described in detail [48] and is outlined in figure 1. In patients with active HS, serum levels of T_H1 cytokines such as IFN-γ [49], IL-12 and IL-18 [50] are significantly higher than in the remission phase of the disease or in healthy controls. IL-18 seems to play a central role in inducing IFN-γ and IL-12 secretion and serum levels of IFN-γ and IL-18 correlate positively with disease activity. IFN-γ and sFasL may both contribute to apoptosis and tissue damage in HS patients [51, 52]. IFN-γ has been demonstrated to be the major mediator of macrophage activation in the before mentioned perforin knock-out mouse model of infection-induced FHL [27]. Reflecting the suggested "cytokine-storm", serum levels of the pro-inflammatory cytokines TNF-α, IL-1β and IL-6, of the anti-inflammatory IL-10 and IL-1ra, but not of the T_H2 cytokine IL-4, are elevated in patients with active HS [48]. Highly increased concentrations of the soluble IL-2 receptor α-chain (sCD25) are frequently detected in active HS and correlate with poor prognosis [53]. Increased plasma levels of sCD25 are one of the three new criteria reported in the recently modified guidelines for childhood HS [5].

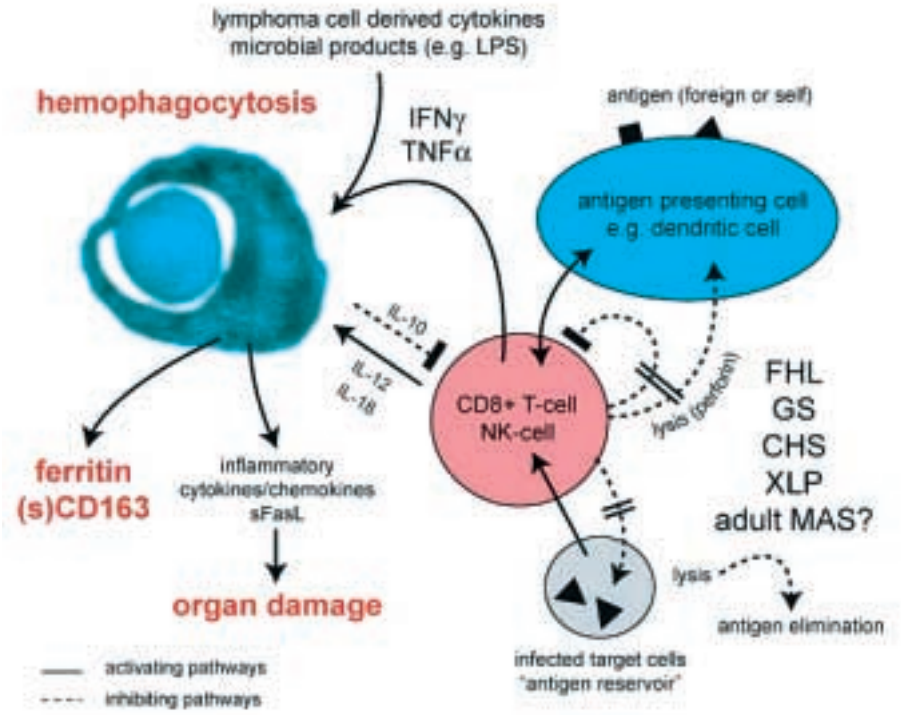

Figure 1

Postulated pathogenetic mechanisms of HS. Deficient cytotoxic activity not only precludes the elimination of antigen expressing cellular targets, resulting in continuous immune activation, but also impairs the contraction of the immune response. FHL: Familial haemophagocytic lymphohistiocytosis; GS: Griscelli syndrome; CHS: Chediak-Higashi syndrome; XLP: X-linked lymphoproliferative syndrome; LPS: lipopolysaccharide.

Clinical presentation

HS patients conform to the characteristics of SIRS. Increased T_H1 helper lymphocyte cytokines and uncontrolled macrophage activation explain many clinical manifestations such as fever, cytopenias and coagulation disorders. Almost every organ system participates in the disease process with liver and skin as particularly common targets beside the organs of the reticuloendothelial system. However, the different underlying disorders and genetic defects are responsible for subgroup-typical features.

Specific features of the main HS subgroups

FHL comprises a group of at least 3 genetically distinct autosomal recessive disorders presenting in early childhood. FHL is rapidly fatal unless allogenic stem cell transplantation is performed. Beside strongly reduced or absent cellular cytotoxic activity, involvement of the central nervous system and hypertriglyceridemia are common features and might direct to the diagnosis [4]. In the absence of a familial history and if triggered by eg infections, the differential diagnosis regarding other HS forms is still very difficult. Arico et al. have recently described an algorithm that aims at distinguishing FHL from other HS subgroups, in particular, HS associated with *GS*, *CHS and XLP*. The differential diagnostic approach is based on the presence or absence of albinism, NK-cell activity, perforin expression, 2B4 receptor activity, microscopic hair analysis and mutation analysis (table 2, [4]).

In the majority of *Ebstein-Barr virus* (EBV) infections, the virus integrates in B-lymphocytes. As such, EBV infection can act as a HS trigger. However, EBV infecting T-lymphocytes or NK-cells

lead to distinct clinical presentations such as chronic active EBV infection, lymphoproliferative (reactive) disorders and bona fide neoplasias (mostly NHL), which all harbour a high risk of ensuing HS [24]. It is reasonable to assume that the oligo/monoclonal nature of these disorders explains why an aggressive approach including the early use of etoposide seems to be indicated [54].

Non-EBV infection-associated HS has been linked to various viral, bacterial and also protozoan infections [33], which must be excluded in patients presenting with HS of unknown etiology. Besides supportive care and effective treatment of the underlying infection whenever possible, the role of immunosuppressive therapies is less well established in these patients compared to other forms of HS. The benefit of controlling inadequate macrophage activity has to be weighted against the potential risk of an infection flare. Less immunosuppressive treatment strategies such as high dose IVIG might be particularly appropriate in these patients.

Although the association of *rheumatologic disorders*, in particular SJIA (also called juvenile-onset Still's disease), with the development of HS was first described in detail almost 20 years ago [18], larger paediatric series were published only recently [55, 56]. The data presented by Sawhney et al. suggest that around 5–10% of children with juvenile idiopathic arthritis will develop HS during the course of their disease [56]. In a recent retrospective study in adults, we showed that the criteria for AOSD were met in 40% of HS patients, and that AOSD might be identical with HS in at least a subgroup of these patients [10]. Patients with rheumatic disorders are often exposed to drugs with triggering potential. Moreover, a disease flare is often difficult to separate from a haemophagocytic episode. Therefore, a (relative) drop of the typically increased white blood cell count or a decreasing sedimentation rate (due to hypofibrinogenemia) should direct the attention to an HS [3]. The recent finding of reduced NK and T-cell function due to low or ineffective perforin expression in patients with SJIA, as described in the pathophysiology section of this review [3], might be a first step towards a unifying concept of HS.

Malignancy-associated HS is most frequently linked to NHL, especially of NK and T-cell origin, and characterised by a very poor prognosis [57]. The HS manifestations may be masked and/or modified by the malignant process or therapeutic measures, and diagnosis is therefore often delayed. In some cases, HS is the first, often dramatic presentation of NHL. In contrast to other types of HS, which are thought to represent an overwhelming immune-response to self or foreign antigens, lymphoma-associated HS is suggested to result from aberrant cytokine secretion by tumour cells [58]. Rapid control of the malignant process is often not easily achieved and cytostatic treatments further increase the risk of infectious complications.

Differences between childhood and adult HS

Several features have to be considered when HS in children are compared with HS in adults. 1) The maturation state of the immune system may partially explain why the threshold for eliciting HS might be lower in children. Intriguingly, perforin expression is age dependent. Rukavina et al. showed that perforin expression is very low at birth and increases thereafter. However, children have a higher percentage of perforin expressing $CD4^+$ lymphocytes compared to adults [59]. 2) The spectrum of underlying disorders is different for several reasons. For instance, children carrying perforin mutations almost exclusively present during early childhood, although late-onset FHL cases have been described and linked to specific mutations [60, 61]. Immunodeficiency is mostly acquired in adults as opposed to inherited in children. Malignancy-associated HS is rather rare in children although there are exceptions [62]. 3) The spectrum of triggering insults differs as well. For example: EBV infection is usually acquired during childhood/adolescence and therefore primary infection is rare in adults. 4) Tsuda described a different frequency of clinical manifestations such as hepatosplenomegaly, rash and neurological involvement, which are all more common in children [13]. With respect to diagnostic parameters, hypertriglyceridemia is frequent in children, but rare in adults [63]. 5) Recently, prognostic factors have been described for high-risk childhood HS and include age <2 years, presence of a hereditary disorder, underlying EBV infection or malignancy, severe neutropenia and disseminated intravascular coagulation (DIC), opportunistic infections, central nervous system involvement, various laboratory markers and initial treatment response [8]. In the adult setting, age >30 years, DIC, hyperferritinemia, increased b2–microglobulin, combined anaemia and thrombocytopenia and jaundice have been described as prognostic by Kaito [64]. In our series, the degree of renal impairment and the development of an acute respiratory distress syndrome were associated with fatal outcome [10]. Because laboratory data are highly variable, the underlying disorder (such as the presence of a neoplastic disorder) is considered prognostically more significant by some authors [57]. 6) Treatment response seems to be generally worse in adults for reasons that are not understood in detail [57, 65]. However, failure to immunomodulatory drugs as single treatment are more common in children [7].

Screening, diagnostic markers and monitoring of disease activity

Given these differences, the diagnostic criteria established by the FHL group of the Histiocyte Society in 1991 [22] and modified recently [5] (comprising the following 8 criteria, of which 5 have to be fulfilled: fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, haemophagocytosis, low/absent NK-cell activity, hyperferritinemia >500 µg/L and increased plasma sCD25 [these criteria are not necessary when mutations as outlined in table 2 can be demonstrated]), and the diagnostic algorithm for childhood HS proposed by Arico [4] cannot be adopted for the adult situation.

Many macrophage activation markers (eg ferritin, β_2-microglobulin, neuron specific enolase, neopterin, transcobalamin II) and cytokines (eg IFN-γ, TNF-α, IL-12 and IL-18) are typically increased during active HS. However, most of these markers are not routinely available and/or lack specificity for the monocyte-macrophage lineage. Moreover, literature regarding the utility for screening and diagnosing HS is scarce. Based on our own experience, we favour a simple, cheap, widely available and reasonably specific screening strategy consisting of serum ferritin measurements in patients presenting in an ominous clinical setting as outlined in figure 2 [10, 66]. In case of serum ferritin levels >10 000 µg/L, confirmatory tests such as the assessment for morphological evidence of haemophagocytosis and quantification of soluble CD163 (sCD163) are indicated [67]. sCD163 is supposedly the most specific monocyte-macrophage lineage marker so far, can be measured by an enzyme-linked immunosorbent assay (ELISA) and is dramatically increased in HS. Only in rare situations of mainly dendritic cell driven HS, sCD163 might not be as increased (Schaer DJ, personal observation). Therefore, in the context of a typical clinical presentation combined with hyperferritinemia but absence of an sCD163 increase, the measurement of sCD25 has to be considered. Bone marrow analyses are indicated in most instances not only for diagnostic but also differential diagnostic purposes regarding underlying pathologies [68]. Moreover, the quantitative analysis of EBV genome in peripheral blood might govern the choice of treatments applied and serial measurements reflect response to therapy [69]. Despite the scientific interest, the diagnostic value of cytotoxicity assays and flow cytometric analysis of perforin expression on various leukocyte subsets, as well as their potential impact on disease management in adults, remain to be proven.

In the absence of an established marker for

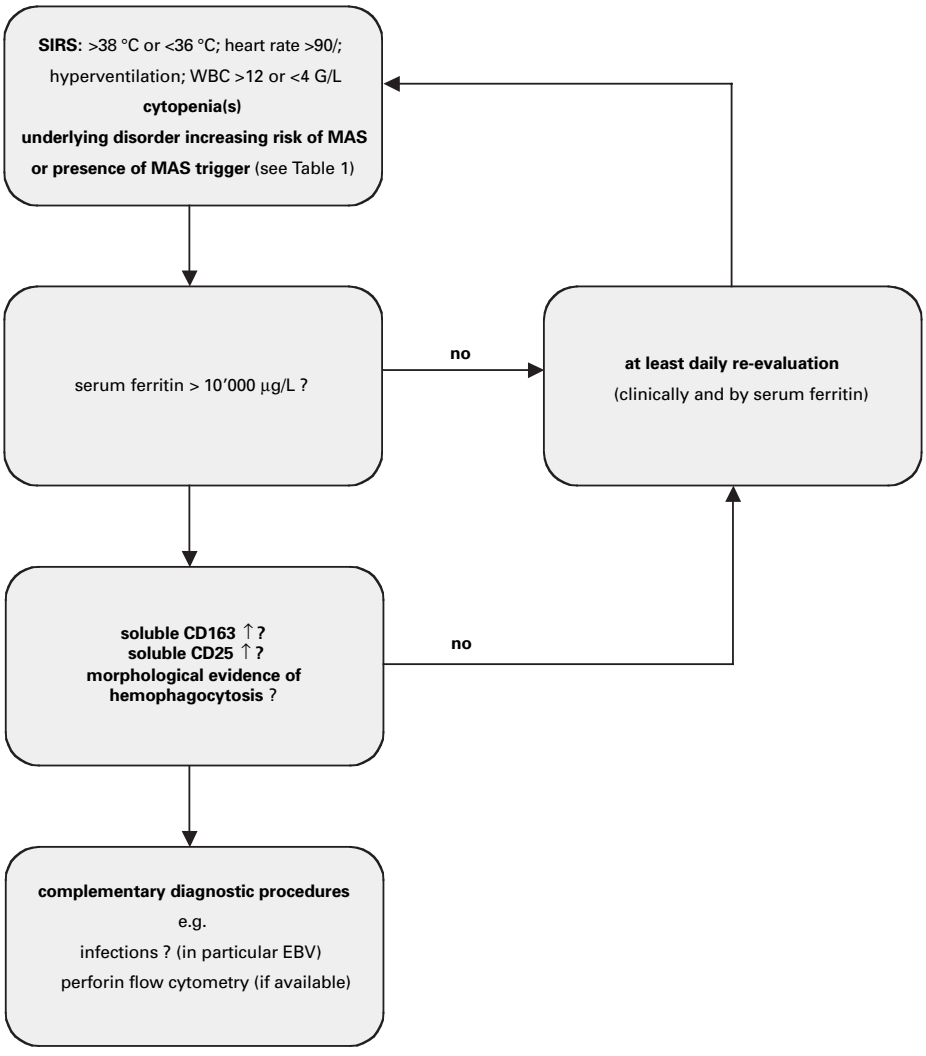

Figure 2

Algorithm for the screening and diagnosis of HS in adults. SIRS: systemic inflammatory response syndrome; WBC: white blood count.

monitoring macrophage activity/treatment response, an individualised approach is proposed. Both assessment of haemophagocytic activity and serum ferritin levels have their limitations [10, 66]. The value of serial sCD163 measurements needs yet to be addressed prospectively.

In the following, some background information and data about the advantages and disadvantages of the main three parameters outlined in figure 2 are summarised.

Haemophagocytosis

Despite the limitations discussed below, morphological evidence of haemophagocytosis is still considered the gold standard in the diagnosis of HS and can be demonstrated in many organs, in particular bone marrow, spleen, liver and lymph nodes, but also in body fluids such as peripheral blood, pleural effusions, cerebrospinal fluid and urine. Haemophagocytosis is a physiological process that might be reinforced in situations such as haemolytic and aplastic anaemia, graft versus host disease, following transfusions and cytotoxic therapies. Whereas haemophagocytosis in the context of HS is normally a systemic event, organ confined haemophagocytosis can be found for instance in regional lymph nodes (after surgery), lung, spleen and skin (cytophagic histiocytic panniculitis) under certain circumstances [70–73]. At least for the case of cytophagic histiocytic panniculitis it is known that the local phenomenon can become generalised. Situations with increased "physiological" haemophagocytosis have to be considered before making the diagnosis of HS. During HS, haemophagocytosis is found rather consistently in organs of the reticuloendothelial system. In contrast, central nervous system (in particular in adults as opposed to children) and lung involvement are rare [70]. Importantly, haemophagocytic activity is not found at any given time in any given organ during the course of HS [74]. Hence, repeated assessment or concomitant analysis of several organs might be necessary. Moreover, one might question the necessity of demonstrating >2% of macrophages showing signs of active haemophagocytosis for the diagnosis of HS, as outlined by Wong et al. [11]. Marked dyserythropoiesis is not an uncommon phenomenon in HS and can mask the phagocytic process [75]. To summarise, haemophagocytosis is not a *sine qua non* for the diagnosis of HS nor should its significance being overestimated in the absence of other clinical and/or biological signs of overwhelming histiocytic activation.

Serum ferritin

Although the presence of ferritin in serum has been described almost 3 decades ago, the biochemical characteristics and biological function(s) remain mostly elusive. Ferritin is composed of 24 units of either heavy chain (H, acidic) or light chain (L, basic) subunits with a molecular weight around 450 kDa. Under physiological conditions, serum ferritin is iron poor, predominantly made up of L chains and >50% glycosylated [76]. The glycosylation and other recent findings suggest active secretion as at least a partial mechanism of serum appearance of this mostly cytosolic protein, as opposed to passive release during tissue damage [77].

Serum ferritin in HS is acidic (H chain rich) [78] and <20% glycosylated [79, 80]. In a prospective study in active adult HS, we have shown that the percentage of glycosylated ferritin is significantly lower in patients hospitalised in intensive care units for at least one organ dysfunction versus conventional hospitalisation with no organ dysfunction. This suggests that low glycosylated ferritin could be a marker of severe HS (Larroche C, unpublished data). The mechanisms leading to the hyperferritinemia seen in HS remain elusive, even more considering that ferritin levels can increase within hours over a range of several 10 000 μg/L [66]. Several hypotheses have been forwarded: a) passive release due to cell damage (yet liver and spleen, ferritin rich target organs of HS, harbour predominantly basic (L chain) isoferritins, and ferritin is disproportionately elevated compared to liver enzymes), b) increased secretion by macrophages (or hepatocytes) and/or release during erythrophagocytosis (erythrocytes are H chain rich), and c) decreased clearing due to lower glycosylation and/or down-regulation of putative ferritin receptors [81]. In a rat in vitro model, Sibille et al. have shown massive release of ferritin in the supernatant after ingestion of erythrocytes by macrophages [82]. Similar findings were reported recently for human macrophages after erythrophagocytosis [83]. Besides iron, IL-1, TNF-α, nitric oxide and reactive oxygen intermediates are important regulators of ferritin H chain synthesis, all of which are implicated in the pathophysiology of HS [84]. In the absence of cytosolic L chains, H chains are secreted in culture media in lens epithelial cells [85]. It remains to be seen whether differential expression of L and H chains in macrophages contributes to the hyperferritinemic state in HS. The reduced glycosylation of serum ferritin in HS might be explained by secretion/release of hypo-glycosylated cytosolic ferritin or differential clearing from the bloodstream. Alternatively, massively increased ferritin expression might exceed the glycosylation capacity of the endoplasmatic reticulum.

The principal role of cytosolic ferritin consists in regulating the intracellular iron pool. However, the H chain exerts also immunomodulatory activity by stimulating the expression of co-stimulatory molecules on antigen presenting cells, followed by increased secretion of IL-10 and decreased secretion of IL-2, IL-4 and IFN-γ by regulatory T-cells [86]. In addition, Pham et al. described recently the inhibition of TNF-α induced apoptosis by NF-κB mediated ferritin H chain up-regulation [87].

It will be interesting to see whether serum hyperferritinemia is part of an (inefficient) anti-inflammatory feedback loop. The recently described

placental immunomodulatory ferritin is not expressed by macrophages (Ch. Moroz, personal communication) and unlikely involved in the pathogenesis of HS.

Serum ferritin values >10 000 µg/L are considered pathognomic for HS, histiocytic malignancies and adult-onset Still's disease [2, 80, 81, 88]. Mostly more moderate hyperferritinemia is a characteristic of 1° and 2° haemochromatosis and also seen in various conditions such as inflammatory syndromes (acute phase reaction or chronic inflammation), due to cytolysis (eg liver necrosis, hematopathies, following cytotoxic treatments, following blood transfusions), related to neoplasias, and as a key manifestation of the hyperferritinemia/cataract syndrome [89]. In our study, we chose a ferritin cut-off of 10 000 µg/L based on the literature available at that time [66]. Interestingly, Ravelli et al. meanwhile found a serum ferritin >10 000 mg/L to be the best marker with respect to specificity and sensitivity in a population of 72 childhood cases of HS [2, 90]. It remains to be demonstrated in prospective studies in adults and more heterogeneous patient populations whether similar specificity and sensitivity is achieved with a ferritin cut-off of 10 000 µg/L, and whether the ferritin threshold can be lowered in order to increase sensitivity but without relevant detrimental effects on specificity. In particular, a lower ferritin threshold might be appropriate if combined with the assessment of more specific markers such as sCD163 and sCD25.

Soluble CD163

The hemoglobin-haptoglobin scavenger receptor CD163 is exclusively expressed on cells of the monocyte-macrophage lineage with increasing expression during terminal macrophage differentiation [91–93] or upon glucocorticoid treatment of monocytes [94]. The tightly restricted expression pattern is even preserved beyond malignant transformation of myeloid progenitor cells as CD163 expression can only be demonstrated on leukaemic cells with a definite monocyte/macrophage differentiation pattern [95]. Like a number of other prominent leukocyte surface antigens such as L-selectin, CD163 is proteolytically cleaved from the cell surface upon monocyte-macrophage stimulation with inflammatory mediators [96]. Thereby, CD163 cleavage seems to be a conserved response, which is induced by a wide range of inflammatory stimuli such as bacterial endotoxins [97], Fc-receptor cross-linking [98] as well as direct activation of protein kinase C by phorbol ester [96]. The cleaved extracellular fragment of CD163 can be detected and quantified in the plasma by a recently developed ELISA [99]. These biologic properties render sCD163 an interesting candidate marker for the specific quantification of overall macrophage activity. In a preliminary study including 18 episodes of adult HS, we found sCD163 levels which were 10 to 40-fold above the levels determined in healthy control subjects [67]. Interestingly, these levels were also clearly above the sCD163 concentrations in patients with severe bacterial sepsis but without clinical or laboratory features compatible with HS. Expansion of the macrophage pool or increased CD163 expression/cleavage during HS may account for these findings. Accordingly, we have found large accumulations of CD163 expressing macrophages with active haemophagocytosis in splenic tissue and bone marrow of our patients. Importantly, sCD163 correlates significantly with other established markers of macrophage activation such as ferritin and sCD25 during the clinical course of HS.

Treatment

General concepts

Compared to historical controls, the HLH-94 treatment protocol has dramatically changed the outcome of children with FHL and other HS [9]. It allows in most instances to stabilise disease activity. This permits performing an allogenic stem cell transplantation, which is the only curative option in the case of FHL and HS associated with hereditary immunodeficiencies. Dexamethasone, etoposide/VP16 and cyclosporin A remain the backbone of the HLH-2004 protocol [5]. Regarding EBV-associated HS, Imashuku stresses the importance of early administration of etoposide combined with immunotherapy, resulting in a high response rate [100]. For the remainder of HS, there are no treatment standards.

Prognostic criteria for childhood HS allow to stratify for treatment aggressivity [8]. For low-risk situations, corticosteroids alone or combined with cyclosporin A and/or intravenous immunoglobulin might be appropriate. For high-risk cases, early etoposide is recommended. In refractory cases or relapse, antithymocyte globulin and polychemotherapy (such as that used for treating Hodgkin's disease or NHL) might be beneficial.

Given the lack of a similar stratification system in adults, treatment is still individualised. Moreover, treatment-related side effects have to be taken into consideration even more because of the potentially transient nature of adult HS, as opposed to genetically defined HS such as FHL, where the underlying defect persists without stem cell transplantation. Critical points of a successful management are: early diagnosis by awareness, in particular in patients at high HS risk (as outlined in table 1A, 1B and figure 2), appropriate screen-

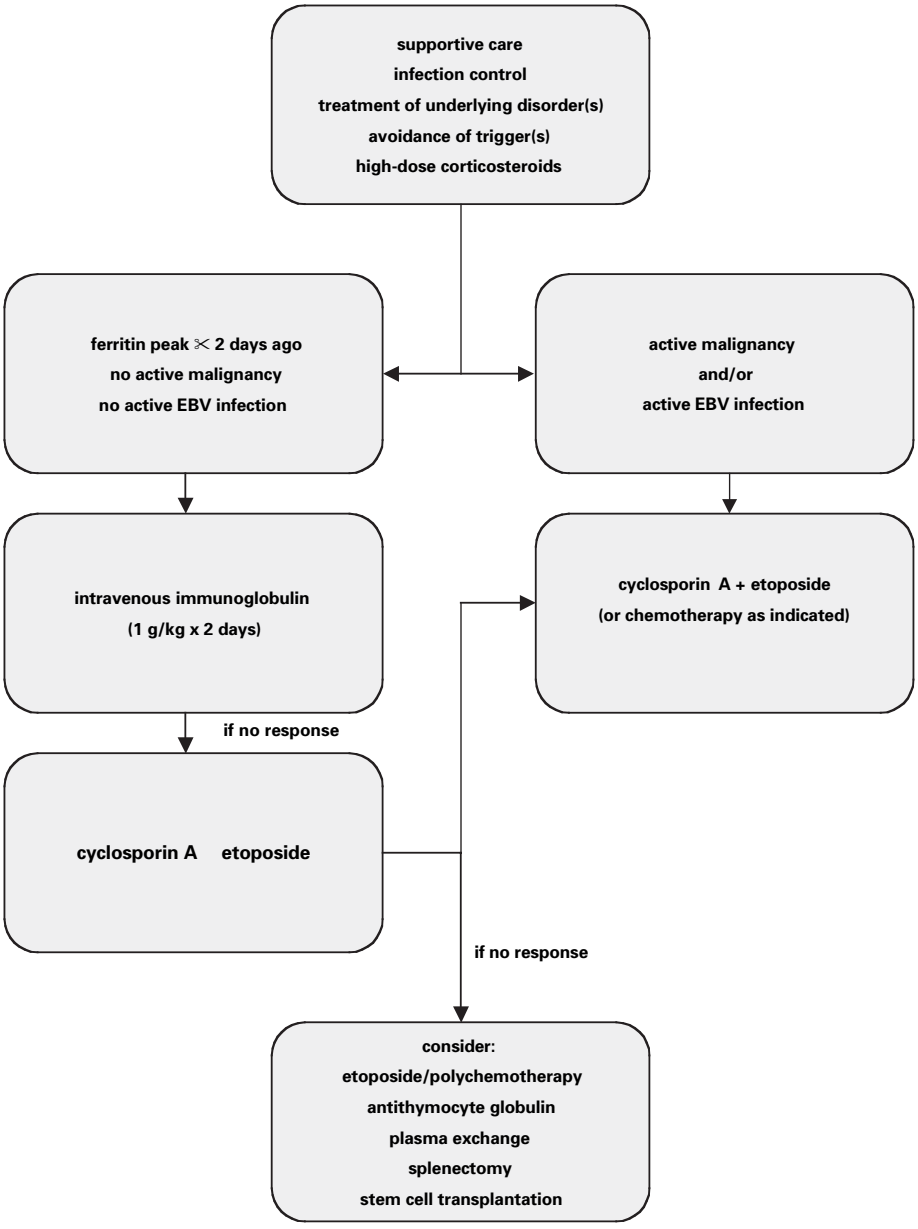

Figure 3
Treatment flow-chart for HS in adults.

ing and causative treatment of the underlying disorder whenever possible, avoidance/removal of triggering drugs/insults, appropriate supportive measures as generally indicated in situations of inflammatory response syndromes and control of NK/T-cell and phagocytic activity and the resulting hypercytokinemia

The essence of these points is summarised in figure 3. In the following, we discuss indications, particularities and limitations of various therapeutic approaches.

Supportive care

Particularly, the risks related to neutropenia, thrombocytopenia and disseminated intravascular coagulation have to be considered. Furthermore, profound depletion of fibrinogen is eventually observed and must be considered even in the absence of DIC [101]. Because of the risk of clinical deterioration, the administration of G-CSF is generally not encouraged [102–104]. However, Tsuda and Shirono present 2 cases of virus-associated HS in young adults responding to G-CSF, albeit administered together with cyclosporine A [105].

Corticosteroids

Corticosteroids are one of the cornerstones of HS treatment. Mostly, water-soluble brain-penetrating corticosteroids such as dexamethasone phosphate (HLH-94 protocol) or methylprednisolone are used. At this point it is unclear whether liposomal preparations (which offer the theoretical advantage of preferential macrophage targeting) are more efficient [106]. Although some authors suggest to decrease immunosuppression in infection-associated HS, at least a short course of corticosteroids seems to be justified in most instances [107].

Intravenous immunoglobulin (IVIG)

In view of the many mechanisms of action described (Fc-receptor blockade, activation of the inhibitory Fcg-receptor IIB, inhibition of complement activation, down-regulation of T/B-cell

functions, anti-idiotypic suppression, neutralisation of superantigens or infectious agents, neutralisation of cytokines, enhanced clearance of pathogenetic antibodies), IVIG are indicated at least theoretically in a broad range of HS [108–111]. The administration of IVIG alone or in combination with other treatment modalities has been described in more than 100 HS case reports and mostly small series. Variable efficacy is demonstrated, which is not astonishing given the heterogeneity of HS, the different IVIG preparations on the market, the inherent batch variability, the different dosing schedules, and administration time points used. However, reports of negative effects on the course of disease are rare [112]. Two larger series of adult HS treated with IVIG show very promising results. Larroche et al. describe a global response rate of 59% in a mixed population of infection, malignancy and systemic lupus erythematosus-associated HS. The mean dose administered was 1.6 g/kg over a mean of 3 days. Infection-associated HS patients seem to benefit most (response rate of 78% versus 39% of the remaining patients). Conversely, IVIG seems to be largely ineffective in lymphoma-associated HS [113]. We found a similar response rate of around two-thirds in a population of rheumatic disease, infection and malignancy-associated HS. The main predictive factor for response was the early administration of IVIG (within 2 days of the ferritin peak). It remains to be seen whether other markers such as sCD163 are of similar value as serum ferritin for early HS diagnosis, enabling emergency IVIG treatment. Many of our patients were administered 2 × 1 g/kg of IVIG over 2 days without overt toxicity. Similarly to Larroche et al., we never observed a sustained improvement in patients with malignancy-associated HS [10, 66]. This coincides with the finding of Imashuku et al. of limited efficacy of IVIG in EBV-related childhood cases with oligo/monoclonal lymphoproliferation, which probably also extends to adult patients [54]. As in our case, IVIG are generally well tolerated. Because of rare reports of renal impairment, renal function has to be monitored and nephrotoxic co-medication avoided.

Cyclosporin A

CSA not only affects early steps of T-cell activation, but also macrophage (decreased expression of IL-6, IL-1, TNF-α, inducible nitric oxide synthetase, cyclooxygenase-2) and dendritic cell functions [114]. It is therefore an obvious choice for targeting the various cellular players implicated in the pathogenesis of HS and reducing the resulting hypercytokinemia. When given in combination with etoposide, CSA might limit the neutropenic period [115]. Moreover, the combination of etoposide and CSA induces apoptosis in a nasal angiocentric natural killer cell lymphoma-derived cell line and CSA single treatment is effective in T-cell lymphoproliferative syndromes [116, 117]. Patients with lymphoproliferative disorders and NHL-associated HS might therefore benefit in particular from CSA. The administration of CSA depends on an appropriate renal function. Hepatic and central nervous side effects might mimic HS manifestations [8]. There is no consensus regarding the moment to start treatment nor for how long CSA should be administered [55]. Regarding the efficacy of other calcineurin inhibitors (eg FK506/tacrolimus) or mTOR inhibitors (eg sirolimus/rapamycin) in the setting of HS no data are available.

Etoposide/VP16

The use of etoposide, a topoisomerase II inhibitor with high, though poorly characterised activity against monocytes, was established as a first line therapy in the context of the HLH-94 protocol and EBV-associated HS [6, 54]. Regarding EBV-associated cases, etoposide might act partially via blocking EBV-DNA and EBNA synthesis [118]. The combination CSA/etoposide might be capable to overcome the apoptotic insufficiency of T-cells implicated in the pathogenesis of FHL [119]. Its use in adult HS unrelated to EBV infection is more rare and mainly considered a second choice in refractory cases (eg [120]). The reluctance to use etoposide results from the risk, albeit small, of secondary malignancies [121]. The resulting neutropenia is attenuated by the concurrent use of CSA [115]. Long-term low dose oral etoposide might be a safe and effective alternative [122].

Antithymocyte globulin (ATG)

Although ATG might be equivalent to etoposide in situations of refractory disease, costs and potential side effects (allergic reactions, severe immunosuppression) limit its use [8].

Plasmapheresis and blood exchange

Plasmapheresis and blood exchange have been described in various case reports and small series with mostly positive results (eg [123]). However, whether clearance of cytokines really takes place and whether this is the key mechanism is questioned [124, 125]. Moreover, Kfoury Baz et al. describe the development of a HS in a patient undergoing plasma exchange for thrombotic thrombocytopenic purpura and procedure-related cytokine release has been suggested [126]. Plasma exchange techniques might be considered in patients needing kidney function replacement procedures for other indications. In most cases reported, the procedure had to be repeated several times.

Anti-TNF-α treatment (anti-TNF-α antibody [infliximab, Remicade™], humanised soluble TNF-α receptor, [etanercept, Enbrel™])

The pathophysiological importance of TNF-α in HS has been outlined above, whereby the only minor impact on T-cell activation is a potential limitation of anti-TNF-α approaches. Aeberli et

al. describe the rapidly beneficial administration of infliximab/etanercept in adult HS associated with AOSD [127]. However, several case reports link the onset of HS with anti-TNF-α blockade (eg [128, 129]. This is a major concern in patients with rheumatic disorders with an increased basal HS risk and where anti-TNF-α treatments are used more commonly. Whether the triggering of HS is indirect via increased susceptibility to infections under anti-TNF-α treatment remains to be seen. Meanwhile, it is reasonable to apply such treatments only when infections are excluded, if at all [3].

Stem cell transplantation (SCT)

Allogenic SCT is the only curative option in FHL and other hereditary forms of HS. However, it is rarely indicated in adults, eg refractory EBV-associated cases or potentially in the context of transplantation for an underlying haematological neoplasia. Of note, autologous SCT has been linked to the development of HS, for instance in children with systemic juvenile idiopathic arthritis, which might result from depletion of regulatory T-cells during the conditioning [130]. HS might worsen if the SCT is performed during active/refractory disease [131].

Varied

The administration of *fludarabine*, a purine antimetabolite, results in profound immunosuppression with particular impairment of T and NK-cells. A case report demonstrates beneficial effects in the setting of FHL [132]. *Methotrexate* was used for intrathecal therapy in the HLH-94 protocol [6] and might be an option in rheumatic disease related HS, given that methotrexate is a standard treatment of rheumatoid arthritis. However, methotrexate potentially can trigger HS [133]. *Daclizumab*, an anti-CD25 antibody, and *interferon-α*, still have to find their place in the treatment of HS, although the rationale for their use is strong [134, 135]. Therapeutic *splenectomy* is very rarely indicated, although successful reports have been published recently in particular in HIV-related cases (eg [37, 136, 137]. Furthermore, in our experience, splenectomy might be of particular value in life-threatening cases of lymphoma-associated HS with significant splenic tumor mass, where secretion of inflammatory cytokines by the malignant cells is supposed to be the major pathogenic mechanism [58]. HIV-associated HS seems to be sensitive to *highly active anti-retroviral therapy* (HAART) alone in some instances [138]. However, a more aggressive approach is probably needed in the majority of cases. To mention that Huang et al. described recently the triggering of a HIV-associated HS with initiation of HAART, which the authors interpreted within the context of treatment related immune reconstitution [139]. Finally, B-cell directed therapy with the anti-CD20 antibody *rituximab* might be a promising approach in some patients with EBV-related HS. Whether the efficacy of B-cell depletion is only related to the exhaustion of the EBV reservoir or whether B-cell cytokine production also contributes to the clinical manifestation of HS, as recently suggested for some rheumatologic diseases, needs to be revealed [140, 141].

Broader implications of the HS concept for SIRS patients?

Many patients admitted to intensive care units present with manifestations defining a SIRS, often combined with acquired immunodeficiences in the presence of potential HS triggers such as infections. There is evidence that HS is not so rare in such populations and probably highly under-diagnosed. Indeed, François et al. found HS in 32/599 patients admitted to an interdisciplinary intensive care unit [23]. More important, haemophagocytosis was demonstrated in a subgroup of 32/50 (64%) patients presenting with a sepsis syndrome and thrombocytopenia <100 000 G/L. A limitation of using thrombocytopenia as a screening parameter is the necessary exclusion of patients with haematological diseases, previous anticancer treatment, major bleeding and/or prior transfusion, DIC and previous administration of heparin. Moreover, thrombocytopenia is not a universal finding in HS. In another study, Stephan et al. found evidence of haemophagocytosis in bone marrow aspirates of 12/20 mechanically ventilated patients with sepsis or septic shock and thrombocytopenia <100 000 G/L with various surgical (n = 15) and medical (n = 5) conditions, but without pre-existing immunodeficiences [142, 143]. Based on two childhood HS cases, Gauvin et al. concluded recently that HS and multiple organ dysfunction syndromes share pathophysiological traits and might be related to each other [144]. Interestingly, $CD14^{dim}$/$CD16^{bright}$ monocytes are not only increased in HS, but also in sepsis patients and have higher phagocytic activity than their $CD14^{dim}$/$CD16^{bright}$ counterpart [142, 145]. Although the presence of bone marrow haemophagocytosis in ICU patients might not necessarily be of clinical relevance in every single case [146], we emphasise the importance of a broad serum ferritin screening in intensive care unit patients, based on our experience. If a HS is diagnosed by following the algorithm outlined in figure 2, rapid administration of IVIG seems to be beneficial in the majority of patients [10, 66].

Only limited progress has been made in the treatment of SIRS patients over the last years despite growing knowledge of the underlying pathophysiological mechanisms [147]. One major obstacle in performing clinical studies is patient heterogeneity. The administration of IVIG has a small

impact on outcome in unselected SIRS patients (http://www.cochrane.org/cochrane/revabstr/ab001090.htm). However, ferritinemia >10 000 µg/L, and thus macrophage hyper-activation, probably defines a SIRS subgroup with particular high response rate to IVIG, a hypothesis which remains to be tested in a prospective, randomised manner.

Conclusions

Although the deciphering of the genetic defects underlying various childhood forms of HS has broadened the pathophysiological understanding of HS in general and contributed to improve prognosis in childhood cases, much needs to be learnt as to whether and to which extent the diagnostic and therapeutic concepts established in children can be adopted for adults. In the absence of diagnostic guidelines, HS diagnosis is still too often missed or delayed in adults. Moreover, therapeutic decisions are mostly based on case reports or small series. We have described a simple screening and diagnostic algorithm, which might become instrumental to recruit patients for clinical studies. Such studies should allow refining the diagnosis of HS in adults and establishing therapeutic guidelines, eg testing the impact of early IVIG administration in SIRS patients presenting with a HS. Finally, it will be interesting to see whether defects of the cytotoxic effector pathways contribute to the pathogenesis of HS in adults as well and how this can be exploited.

The authors would like to thank K. Arn for help with figure 1.

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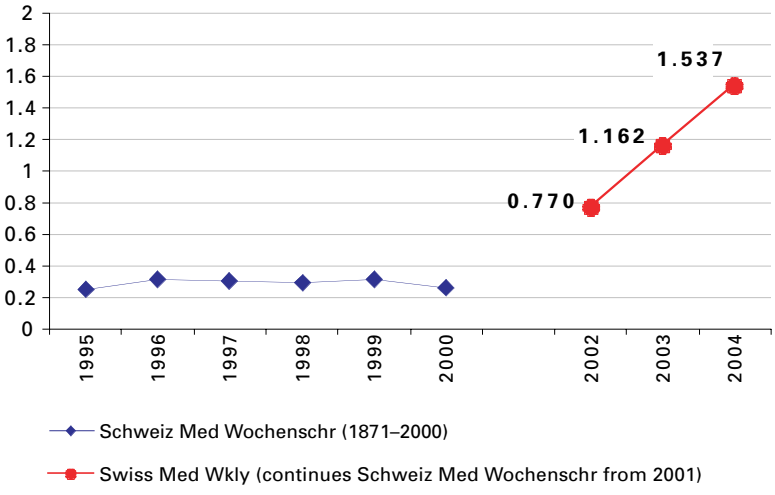

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