

**Supplement Table 1. HLH-2004 diagnostic guidelines based on Henter et al. (6).**

<b>HLH-2004 diagnostic criteria: <math>\geq 5</math> must be fulfilled</b>
<ul style="list-style-type: none"><li>- Ferritin <math>\geq 500</math> <math>\mu\text{g/L}</math></li><li>- Fever (<math>\geq 38.3</math> <math>^{\circ}\text{C}</math>)</li><li>- Splenomegaly</li><li>- Cytopenias in <math>\geq 2</math> lines (hb <math>&lt; 9</math> g/dL, plt <math>&lt; 100</math> /nL, neutrophils <math>&lt; 1.0</math> /nL)</li><li>- Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides <math>\geq 265</math> mg/dL, fibrinogen <math>&lt; 1.5</math> g/L)</li><li>- Hemophagocytosis in bone marrow or spleen or lymph nodes</li><li>- Low or absent NK activity</li><li>- Soluble CD25 (soluble IL-2 receptor) <math>\geq 2,400</math> U/mL</li></ul>

Hb, hemoglobin; NK, natural killer cell; plt, platelets; U, Units.

**Supplement Table 2. HScore based on Fardet et al. (16).**

<b>HScore: calculated by scoring criteria of each parameter (<a href="http://saintantoine.aphp.fr/score/">http://saintantoine.aphp.fr/score/</a>)</b>
Known underlying immunosuppression (no   yes)
Temperature (< 38.4°C   38.4-39.4°C   > 39.4°C)
Organomegaly (no   hepato- or splenomegaly   hepatosplenomegaly)
Cytopenias (1   2   3, hb ≤ 9.2 g/dL, leukocytes ≤ 5,000 /μL, plt ≤ 110,000 /μL)
Ferritin (< 2,000 μg/L   2,000-6,000 μg   > 6,000 μg/L)
Triglycerides (< 1.5 mM   1.5-4 mM   > 4 mM)
Fibrinogen (> 2.5 g/L   ≤ 2.5 g/L)
ASAT (< 30 U/L   ≥ 30 U/L)
Hemophagocytosis in bone marrow aspirate (no   yes)

ASAT, *aspartate aminotransferase*; hb, *hemoglobin*; mM, *mmoles/liter*; plt, *platelets*; U, *Units*.

**Supplement Table 3. Patients being clinically judged as unlikely to have suffered from aHLH while fulfilling HLH-2004 criteria  $\geq 4$  or HScore HLH probability  $\geq 80$  %.**

CASE-ID	Age	Sex	Underlying condition	Ferritin ( $\mu\text{g/L}$ )	Max. core body temperature ( $^{\circ}\text{C}$ )	Hb (g/dL) platelets (/ $\mu\text{L}$ ) leuko (/ $\mu\text{L}$ )	Triglycerides (mg/dL) fibrinogen (mg/dL)	sIL-2R (U/mL)	ASAT (U/L)	Hepato- and/or splenomegaly	Hemophagocytosis	ICU/hospital stay (d)	Fulfilled HLH-2004 criteria	HScore probability (%)	Outcome
10	39	female	Complication after aortic valve replacement, septic shock, cardiogenic shock, state by renal transplantation	6,665 (29.04.2006)	38.5 (28.04.2006)	7.9/48/16.1 (29.04.2006)	335/411 (06.05.2006/30.04.2006)	-	170 (29.04.2006)	yes (05.05.2006)	-	46/46	5	92.5	dead
11	34	male	AIDS, EBV, CMV, sepsis	3,410 (15.01.2011)	38.7 (12.01.2011)	11.9/55/4.3 (15.01.2011)	307/155 (15.01.2011/14.01.2011)	-	49 (15.01.2011)	no (16.01.2011)	-	30/30	3	90	dead
12	39	male	ARDS, pneumonia, septic shock	7,186 (23.01.2013)	38.5 (23.01.2013)	8.8/66/9.8 (22.01.2013)	348/334 (31.01.2013/22.01.2013)	1699 (28.11.2012)	142 (23.01.2013)	yes (05.02.2013)	-	140/140	5	92.5	dead

ARDS, acute respiratory distress syndrome; ASAT, aspartate aminotransferase; AIDS, acquired immune deficiency syndrome; EBV, Ebstein-Barr virus; CMV, Cytomegalovirus; sIL-2R, soluble IL-2 receptor.

**Supplement Table 4. Mortality data at specific ferritin cutoffs.**

<b>Ferritin cutoff [<math>\mu\text{g/L}</math>]</b>	<b>Mortality</b>
500	71 (29.1%)
1,000	55 (36.2%)
2,000	31 (51.7%)

*Number of deceased patients with n (%).*