

Table 2. Key investigations in suspected cases of secondary HLH in adults.

Test	Description
Full blood count	<ul style="list-style-type: none"> To evaluate for cytopenias (typically 2 or more cell lines involved; due to cytokine storm-mediated bone marrow suppression and haemophagocytosis) <ul style="list-style-type: none"> Laboratory reference ranges for full blood count in National University Hospital, Singapore: white blood cell 4.3–10.4×10⁹/L (males and females); haemoglobin 13.1–16.8 g/dL (males)/11.5–14.9 g/dL (females); platelets 150–410×10⁹/L (males and females) Cytopenias defined in HLH-2004 criteria²² as such: haemoglobin <9 g/dL, platelets <100×10⁹/L, neutrophils <1×10⁹/L Severe cytopenias defined as such: white blood cell <1.5×10⁹/L, absolute neutrophil count <0.5×10⁹/L, haemoglobin <7 g/dL, platelets <50×10⁹/L To look for eosinophilia (which may suggest DRESS, connective tissue disorder or certain haematological neoplasms)
C-reactive protein/erythrocyte sedimentation rate	<ul style="list-style-type: none"> Typically elevated CRP (but not specific for HLH), may have paradoxically low/normal ESR (due to low fibrinogen)
Renal panel	<ul style="list-style-type: none"> To assess for elevated serum creatinine (acute kidney injury)
Liver panel	<ul style="list-style-type: none"> To assess for hepatocellular pattern of transaminitis (due to cytokine-mediated hepatocellular injury), hypoalbuminaemia (negative acute phase reactant)
Ferritin levels	<ul style="list-style-type: none"> Typically elevated (due to increased liver production and macrophage activation) <ul style="list-style-type: none"> <500 µg/L has a 94% sensitivity in ruling out HLH²⁵ Very high levels (>10,000 µg/L) are highly suggestive of the diagnosis in paediatric HLH²⁶
Fibrinogen	<ul style="list-style-type: none"> Hypofibrinogenaemia is common (due to pro-coagulant processes that consume fibrinogen, and cytokine-mediated fibrinogen breakdown) <ul style="list-style-type: none"> Laboratory reference range in National University Hospital, Singapore: 2.18–4.6 g/L Cut-off <2.5 g/L used in H-score⁸ and ≤1.5 g/L used in HLH-2004 criteria²² Severe hypofibrinogenaemia <0.5 g/L
Lactate dehydrogenase	<ul style="list-style-type: none"> Usually elevated (due to cytotoxic sequelae)⁸
Coagulation panel	<ul style="list-style-type: none"> To assess for coagulopathy (which could be related to liver dysfunction or concurrent disseminated intravascular coagulation; if present, should warrant sending off D-dimer as well)
Triglycerides	<ul style="list-style-type: none"> Usually elevated, cut-off ≥1.5 mmol/L used in H-score⁸, 3 mmol/L used in HLH-2004 criteria²²
Hepatitis B/C/HIV, EBV/CMV/VZV/HSV, HHV-6/8, parvovirus B19, dengue serology, mycoplasma serology, respiratory viral swab, blood cultures, urine cultures	<ul style="list-style-type: none"> Evaluation of common infections that are reported to be associated with HLH/MAS
Autoantibodies (antinuclear antibodies, anti-double-stranded DNA, complement C3/C4, rheumatoid factor, anti-cyclic citrullinated peptide, antineutrophil cytoplasmic antibodies)	<ul style="list-style-type: none"> Evaluation of rheumatic conditions associated with HLH/MAS
CT scan of the neck, thorax, abdomen and pelvis or positron-emission tomography-CT whole body	<ul style="list-style-type: none"> To look for suspicious masses/collections (that may suggest occult malignancy/infections), hepatosplenomegaly, lymphadenopathy (which may be amenable to biopsy), vascular abnormalities (e.g. in vasculitis or intravascular lymphoma)
Magnetic resonance imaging of the brain	<ul style="list-style-type: none"> In patients with neurological symptoms/signs, may reveal white/grey matter inflammation, or leptomeningeal enhancement
Lumbar puncture	<ul style="list-style-type: none"> In patients with neurological symptoms/signs, may reveal cerebrospinal fluid pleocytosis and high protein (suggesting central nervous system inflammation)
Bone marrow aspirate and trephine biopsy	<ul style="list-style-type: none"> To evaluate for histopathological evidence of haemophagocytosis, as well as assess for evidence of myelo/lymphoproliferative disease
Biopsy of affected tissue (e.g. lymph node, liver, spleen, lung, skin)	<ul style="list-style-type: none"> For diagnostic evaluation – both to identify histopathological evidence of haemophagocytosis (in liver, spleen, lymph nodes), and to assess for occult malignancies (e.g. random skin biopsies to detect intravascular large B-cell lymphoma in Asian patients)

CMV: cytomegalovirus; CRP: C-reactive protein; CT: computed tomography; DNA: deoxyribonucleic acid; DRESS: drug reaction with eosinophilia and systemic symptoms; EBV: Epstein-Barr virus; ESR: erythrocyte sedimentation rate; HIV: human immunodeficiency virus; HLH: haemophagocytic lymphohistiocytosis; HLH-2004: HLH-2004 diagnostic and therapeutic guidelines for haemophagocytic lymphohistiocytosis; HSV: herpes simplex virus; MAS: macrophage activation syndrome; VZV: varicella-zoster virus