Table 4. Common treatment options for HLH.

Treatment	Mechanism of action	Indication	Common dosage	Important adverse effects/ monitoring required
IV "pulsed" methylprednisolone	Glucocorticoids	MAS	Up to 1 g/day for 3–5 days[1]	Hyperglycaemia/diabetes, metabolic side effects, weight gain, osteoporosis (long-term), avascular necrosis (long-term), cataracts/glaucoma (long-term), adrenal insufficiency (long-term), mood/behaviour changes (e.g. hyperactivity, insomnia), consider PJP (cotrimoxazole) prophylaxis and hepatitis B (entecavir) prophylaxis (anti-HBc positivity) if using equivalent to prednisolone ≥20 mg/day for ≥1 month
IV/PO dexamethasone		Secondary HLH other than MAS	10 mg/m^2 for 2 weeks, 5 mg/m^2 for 2 weeks, 2.5 mg/m^2 for 2 weeks, 1.25 mg/m^2 for 1 week, then taper off by week 8 (HLH-94 regimen)[39]	
Intravenous immunoglobulin (IVIG)	Multimodal immunomodulatory effects	As initial bridging therapy in actively deteriorating/unstable patients	1 g/kg/day for 2 days[27] (can repeat after 14 days)	Allergy, anaphylaxis (IgA-deficient patients may be predisposed to anaphylaxis in older IgA-containing IVIG preparations), or infusion reactions, caution in renal impairment (avoid sucrose-containing IVIG preparations), beware of pseudohyponatraemia, transient cytopenias (rarely haemolysis), fluid overload (in heart failure or renally impaired patients), increased thromboembolic risk, risk of blood-borne infections
SC anakinra (IV route can be used off-label; limited availability in public hospitals)	IL-1 receptor antagonist	MAS	2–6 mg/kg/day, up to 10 mg/kg/day in divided doses[19] (maximum 100 mg per dose[27])	Injection site reaction, infection risk (bacterial)
IV etoposide	DNA topoisomerase II inhibitor	Malignancy-associated HLH, EBV-associated HLH, and for refractory MAS and other secondary HLH	Either 150 mg/m^2 HLH-94 regimen[39] or 100 mg/m^2 when combined with doxorubicin and methylprednisolone in the DEP regimen[40,41] (Renal/liver dose adjustment is required.)	Infusion reactions, gastrointestinal side effects, alopecia, myelosuppression, secondary malignancies (e.g. leukaemia)

IV/PO cyclosporine	Calcineurin inhibitor	MAS	3–7 mg/kg/day in 2 divided doses (IV) or 3–5 mg/kg/day in 2 divided doses (PO)[27]	Hirsutism (cyclosporine), gingival hypertrophy (cyclosporine), gastrointestinal side effects, neurotoxicity (headache/seizures, tremors, neuropathy), acute tubular nephropathy, metabolic side effects (diabetes, hyperlipidaemia, gout), increased infection risk (viral —e.g. CMV, EBV, bacterial, fungal infections); consider checking trough levels (pre-third dose cyclosporine trough 50–100 ng/ml, tacrolimus trough <20 ng/mL[27])
PO tacrolimus	Calcineurin inhibitor	Alternative to cyclosporine for MAS	0.1 mg/kg/day in 2 divided doses[27]	
IV emapalumab (Limited availability in public hospitals)	IFN-γ antagonist	Refractory or recurrent primary HLH, and MAS secondary to AOSD/sJIA	6 mg/kg/day for day 1, then 3 mg/kg/day every 3–4 days (can increase up to 10 mg/kg per 3 days for inadequate response)[27]	Infusion reactions, increased infection risk (especially TB, CMV, VZV, bacterial, PJP), consider antiviral (valacyclovir), PJP (cotrimoxazole), antifungal (fluconazole) prophylaxis[27]; can monitor CXCL9 to confirm functional IFN-γ blockade[27]
IV rituximab	Anti-CD20 monoclonal antibody	Adjunctive treatment in EBV-associated HLH, core component of immunochemotherapy in lymphoma-associated HLH, possible role as salvage therapy in MAS	375 mg/m^2/dose, weekly, for 2–4 weeks[27]	Infusion reactions, gastrointestinal side effects, cytopenias/neutropenia, hypogammaglobulinaemia, increased infection risk (especially hepatitis B virus, CMV, HSV, JC virus, COVID, bacterial, PJP) [consider PJP (cotrimoxazole) prophylaxis and hepatitis B (entecavir) prophylaxis for all anti-HBc positive patients]
PO ruxolitinib	JAK-1/2 inhibitor	Salvage therapy	Start at 10 mg BD, uptitrate to maximum 25 mg BD[27]	Gastrointestinal side effects, flu-like symptoms, hyperlipidaemia, increased risk of venous thromboembolism, increased risk of infections (especially VZV)

AOSD: adult-onset Still's disease; CMV: cytomegalovirus; DNA: deoxyribonucleic acid; EBV: Epstein-Barr virus; HLH: haemophagocytic lymphohistiocytosis; HSV: herpes simplex virus; IFN: interferon; IV: intravenous; IVIG: intravenous immunoglobulin; JAK: Janus kinase; JC: John Cunningham; MAS: macrophage activation syndrome; PO: per os (by mouth); PJP: *Pneumocystis jirovecii*; SC: subcutaneous; sJIA: systemic juvenile idiopathic arthritis; TB: tuberculosis; VZV: varicella-zoster virus

Etoposide requires dose reduction for renal/hepatic impairment and cytopenias (frequently present in HLH) and carries infection and secondary-malignancy risk.