HLH TREATMENT GUIDELINES

(Updated October 2024)

Dosing for many first- and second-line agents in HLH is complex and should be discussed with the Immune Dysregulation Program Team (DIRT) on weekdays, or with oncology and rheumatology on nights and weekends, as well as with primary care teams.

CATEGORY	OPEN STUDIES	STANDARD THERAPY	NOTES
Presumed or proven genetic HLH, newly diagnosed	Check eligibility for any other open studies.*	Treat the HLH-driver, if known (see **HLH diagnostic guidelines**) Dexamethasone (10mg/m2) +/- emapalumab (1mg/kg with titration of dose). Add etoposide** based on critical illness or if young infant Rituximab*** (375mg/m2 weekly) if EBV-driven (total doses based on response). Consider anakinra (2mg/kg IV or SQ with rapid escalation to 10mg/kg). Consider IVIG (400mg/kg or 1-2gm/kg). Consider IT methotrexate if CNS disease persists.	Calcineurin inhibitors not standard for *de novo* HLH treatment except for maintenance as bridge to stem-cell transplant (SCT). The goal in genetic HLH is often SCT. Thus, treatment is directed at inducing remission, controlling cytokine storm, treating the underlying driver and bridging to SCT. Treatments with some agents can make a patient ineligible for some clinical trials. In general glucocorticoids, IVIG, and anakinra do not impact eligibility. See **HLH infection prevention and surveillance guidelines** for antimicrobial prophylaxis.
Presumed or proven genetic HLH, relapse off therapy	Check eligibility for any other open studies.*	Treat the HLH-driver, if known (see **HLH diagnostic evaluation guidelines**). If initial response to a particular therapy/regimen, may use the same therapy. Dexamethasone (10mg/m2) +/- emapalumab (1mg/kg with titration of dose). Add etoposide** based on critical illness or if young infant. Rituximab*** (375mg/m2 weekly) if EBV-driven (total doses based on response). Consider IVIG (400mg/kg or 1-2gm/kg). Consider IT methotrexate if CNS disease persists.	The goal in relapsed HLH is often SCT. Thus, treatment is directed at inducing remission, controlling cytokine storm, and bridging to SCT. See **HLH infection prevention and surveillance guidelines** for antimicrobial prophylaxis.

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HLH Treatment Guidelines (continued from page 1)

Presumed or proven genetic HLH, relapse on therapy	Check eligibility for any other open studies.*	Treat the HLH-driver, if known (see **HLH diagnostic evaluation guidelines**). Increase glucocorticoid use and discuss with primary team and DIRT. Agents to consider: ruxolitinib, emapalumab, etoposide, alemtuzumab (campath), ATG, calcineurin inhibitors, anakinra. Consider IVIG (400mg/kg or 1-2gm/kg). Consider IT methotrexate if CNS disease persists.	The goal in relapsed HLH is often SCT. Thus, treatment is directed at inducing remission, controlling cytokine storm, and bridging to SCT. See **HLH infection prevention and surveillance guidelines** for antimicrobial prophylaxis.
MAS (typically from sJIA/ Stills), newly diagnosed	Check eligibility for any other open studies.*	Standard therapy: Prednisone (30mg/kg IV daily) and anakinra (2mg/kg with rapid escalation to 10mg/kg). Refractory disease: Add Jak inhibitor (ruxolitinib) and/or consider calcineurin inhibitor.	See **HLH infection prevention and surveillance guidelines** for antimicrobial prophylaxis.
MAS (typically from sJIA/ Stills), relapse	Check eligibility for any other open studies.*	Discuss with Rheum/DIRT. Agents to consider: cyclophosphamide, ruxolitinib, etoposide, corticosteroids, anakinra, calcineurin inhibitors, emapalumab.	See **HLH infection prevention and surveillance guidelines** for antimicrobial prophylaxis.
Infectious-associated HLH, newly diagnosed and relapsed	Check eligibility for any open studies.*	Treat infection and recognize balance between the need for immune modulation and immune protection (see **HLH diagnostic evaluation guidelines**). Glucocorticoids (1-2mg/kg/day) +/- IVIG (400mg/kg or 1-2gm/kg). Anakinra (2mg/kg with escalation to 10mg/kg if needed). Other agents discuss with ID, DIRT	HSV in neonates: Any immune suppression has considerable risk. See **HLH infection prevention and surveillance guidelines** for antimicrobial prophylaxis.

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Secondary HLH (NOS), newly diagnosed	Check eligibility for any open studies.*	Treat the HLH-driver, if known (see **HLH diagnostic evaluation guidelines**). Glucocorticoids (either prednisone 1-2mg/kg/day or dexamethasone 10mg/m2/day or prednisne 30mg/kg/day). Anakinra (2mg/kg/day with escalation to 10mg/kg/day). Consider IVIG (400mg/kg or 1-2gm/kg). Other agents to consider: emapalumab or ruxolitinib are preferred agents. Consider etoposide for critical illness or refractory disease. Consider IT methotrexate if CNS disease persists.	See **HLH infection prevention and surveillance guidelines** for antimicrobial prophylaxis.
Secondary HLH (NOS), relapse off therapy	Check eligibility for any open studies.*	Treat the HLH-driver, if known (see **HLH diagnostic evaluation guidelines**). If initial response to a particular therapy/regimen, may use the same therapy. Glucocorticoids (either prednisone 1-2mg/kg/day or dexamethasone 10mg/m2/day or prednisone 30mg/kg/day). Anakinra (2mg/kg/day with escalation to 1m/kg/day) Consider IVIG (400mg/kg of 1-2gm/kg). Agents to consider: emapalumab or ruxolitinib are preferred agents. Consider etoposide for critical illness or refractory disease. Consider IT methotrexate if CNS disease persists.	Goal in relapsed HLH is often SCT. Thus, treatment is directed at inducing remission, controlling cytokine storm, and bridging to SCT. See **HLH infection prevention and surveillance guidelines** for antimicrobial prophylaxis.

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HLH Treatment Guidelines (continued from page 3)

Secondary HLH (NOS), relapse on therapy	Check eligibility for any open studies.*	Treat the HLH-driver, if known (see **HLH diagnostic evaluation guidelines**). Increase glucocorticoid dose and discuss with primary team and DIRT. Consider IVIG (400mg/kg of 1-2gm/kg). Agents to consider: ruxolitinib, emapalumab, etoposide, alemtuzumab (campath), ATG, calcineurin inhibitors, anakinra. Consider IT methotrexate if CNS disease persists.	Goal in relapsed HLH is often SCT. Thus, treatment is directed at inducing remission, controlling cytokine storm, and bridging to SCT. See **HLH infection prevention and surveillance guidelines** for antimicrobial prophylaxis.
Isolated CNS HLH	Check eligibility for any open studies.*	Treat the HLH-driver, if known (see **HLH diagnostic evaluation guidelines**). Glucocorticoids to stabilize and discuss in DIRT and oncology.	See **HLH infection prevention and surveillance guidelines** for antimicrobial prophylaxis.

Key & Notes

* Updated information about all clinical trials, including eligibility criteria, can be found at **clinicaltrials.gov.**

** Doses of cytotoxic chemotherapy agents are included in the oncology chemotherapy standards and formulary and should be discussed with oncology, primary team and the Immune Dysregulation Program Team (DIRT).

*** If patient is clinically stable — prior to initiating rituximab — consider collecting blood to assess for EBV viral load in sorted lymphocyte populations.

IMPORTANTLY, the Immune Dysregulation Program Team (DIRT) is available Monday-Friday, during business hours, and does not have staff on-call on nights and weekends. **DIRT is a consult-only service that can help manage HLH patients, but cannot be the primary team.** HLH diagnosis and management is ideally multidisciplinary, including DIRT, liquid Oncology, Rheumatology, Immunology and Infectious Disease. Primary HLH, especially in children younger than age 2, often requires cytotoxic chemotherapy which can only be prescribed by Oncology. Thus, Oncology is often the primary service unless the child has a known immune deficiency or rheumatologic disorder. ■