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Antimicrobial prophylaxis for adult patients with haemophagocytic lymphohistiocytosis (HLH)

UCLH Guideline

Trust Wide

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CONTENTS

1. Summary

This guideline advises on the use of antimicrobial prophylaxis for adult and adolescent patients with haemophagocytis lymphohistiocytosis (HLH). It advises clinicians on when and how different antimicrobial agents should be used as prophylaxis for patients with HLH to reduce secondary infections in this group.

2. Equality impact

The author of this guideline has undertaken an Equality Impact Assessment (EIA) and has concluded that there is no negative impact on any of the protected equalities groups. The completed EIA form is available from the Quality and Safety Department.

3. Introduction

Haemophagoyctic lymphohistiocytosis (HLH) is a rare disorder characterised by excessive immune activation. Secondary HLH is the commonest cause in adults and is frequently triggered by haematological malignancies, infections and rheumatological disorders. Patients with HLH often have an increased susceptibility to infection for multiple reasons; the underlying trigger itself, cytopenias associated with HLH and/or the immunosuppressive treatment given to treat HLH.

This guideline aims to set out clear criteria-led guidance for prescribing antimicrobial prophylaxis in patients with HLH at UCLH.

4. Objectives

- To provide clear guidance on antimicrobial prophylaxis prescribing in patients with HLH to reduce the risk of secondary infection
- To improve the quality of antimicrobial prescribing
- To maximise the clinical effectiveness of antimicrobial agents used
- To reduce drug-related toxicity and development of antimicrobial resistance
- To ensure cost-effective use of antimicrobial agents

5. Scope

This guideline applies to all healthcare professionals involved in the treatment and monitoring of adult and adolescent patients with HLH.

6. Definitions

HLH	Haemophagocytic Lymphohistiocytosis
MAS	Macrophage activation syndrome
IFI	Invasive fungal infection
IVIG	Intravenous immunoglobulin
HSV	Herpes Simplex Virus
VZV	Varicella Zoster Virus
PCP	*Pneumocystis jirovecii* Pneumonia
BDG	Beta D Glucan
CMV	Cytomegalovirus
EBV	Epstein-Barr virus
TB	Tuberculosis
ALL	Acute lymphoblastic leukaemia
BMT	Bone marrow transplant

7. Development & Consultation

These guidelines have been developed and produced by members of the clinical teams listed in the consultation section below in conjunction with existing UCLH and national guidance.

The existing evidence base is discussed in the background section.

The following persons and teams were consulted and involved in the production of this guideline:

Dr Strachan Mackenzie	Haematology Registrar
Dr Naina McCann	Infectious Diseases Registrar
Dr Michael Brown	Infectious Diseases Consultant
Dr Neil Stone	Infectious Diseases and Microbiology Consultant
Dr Emilie Sanchez	Virology Consultant
Prof Robert Heyderman	Infectious Diseases Consultant
Dr Ben Carpenter	Haematology Consultant
Dr Kirsty Thomson	Haematology Consultant
Dr Jessica Manson	Rheumatology Consultant

8. HLH background

Haemophagoyctic lymphohistiocytosis (HLH) is a rare disorder characterised by excessive immune activation resulting in excessive pro-inflammatory cytokine production which can lead to a variety of presentations in affected patients including fever, cytopenias and multi-organ dysfunction.

Clinical features can range from moderate to life-threatening including requiring multi-organ support in intensive care. Secondary HLH is the commonest cause in adults and is frequently triggered by haematological malignancies such as lymphoma, infections and rheumatological disorders. When associated with autoimmune and rheumatological disorders, HLH has historically been named macrophage activation syndrome (MAS).

Infection is a major cause of morbidity in some patients with HLH. Increased susceptibility to infection can be caused by

i) Immunosuppression due to the underlying disorders which drive HLH e.g. T cell lymphomas, HIV
ii) Cytopenias associated with HLH e.g. neutropenia, lymphopenia
iii) HLH-targeted immunosuppressive treatments e.g. steroids, ciclosporin, chemotherapy such as etoposide, T cell depleting agents such Alemtuzumab

9. Infection literature in HLH

There are relatively little data directly looking at infection outcomes following or during treatment in adults with HLH.

A retrospective single-centre review of 56 adult patients who fulfilled clinical diagnostic criteria for HLH found that 58% of patients developed at least one infection which included bacterial (80%), viral (21%) and fungal (19%) infections. Proven invasive fungal infections (IFI) were associated with a 55% mortality (n =9). Breakthrough fungal infection with opportunistic moulds was seen in some cases despite prophylaxis (Nelson et al. 2018).

A number of retrospective studies in the intensive care setting have shown high rates of IFI in patients with HLH. The largest series comprising 71 ICU patients with HLH found invasive aspergillosis rates of 25% (Barba et al. 2015); smaller studies have also reported cases of fatal invasive mucormycosis (Kapoor et al. 2018)(Rajagopala et al. 2012).

10. Categorising infectious risk in HLH

Several international HLH guidelines including the HLH-2004 protocol (Henter et al. 2007) and more recent consensus guidelines for HLH treatment in adults (La Rosée et al., 2019) recommend anti-microbial prophylaxis including anti-viral, anti-PCP and anti-fungal cover.

These guidelines do not specify particular antimicrobial drugs, doses or durations of treatment. In addition, these guidelines are based on treating HLH using HLH-2004 treatment protocols (combined high-dose dexamethasone, ciclosporin, etoposide) whereas in clinical practice, many adult patients will not be treated with this regimen and may be treated with other agents, including single agent cytokine-directed therapy such as anakinra or will have treatment directed against the underlying HLH driver.

Since the clinical features of HLH and the subsequent treatment required can vary greatly from patient to patient, a risk-adapted approach for primary antimicrobial prophylaxis is therefore recommended, based on epidemiological risk profiles in particular treatment groups which indicate a high propensity for the development of a particular infection.

The following table is provided as a summary guide based on risk factors. Given the wide variety of underlying conditions which predispose to HLH, recommendations for prophylaxis need to be tailored to specific patients, which take into consideration previous infections and susceptibilities. Where patients with HLH and concomitant haematological malignancies (including bone marrow transplant patients) requiring active systemic chemotherapy, local haematology guidance for patients should be followed.

Table 1 – Summary of immunosuppressive agents and recommended antimicrobial prophylaxis

	Anti-viral (HSV/VZV)	Anti-fungal (mould)	Anti-PCP	Anti-Hepatitis B [1]	TB prophylaxis[2]	Other	Notes
Short-course Corticosteroids (< 7 days)						Exclude Strongyloides if from high prevalence country[5]	No prophylaxis required
Long-course Corticosteroids[3] (≥7 days)	Consider prophylaxis	Prophylaxis recommended	Prophylaxis recommended	Consider prophylaxis or regular monitoring (see section 10)		Exclude Strongyloides if from high prevalence country[5]	
Neutropenia[4]		Prophylaxis recommended					
Rituximab				Prophylaxis recommended			
Etoposide	Prophylaxis recommended	Prophylaxis recommended	Prophylaxis recommended	Consider prophylaxis or regular monitoring (see section 10)	Consider prophylaxis based on TB risk (see section 7)	Exclude Strongyloides if from high prevalence country[5]	
Anakinra							No prophylaxis required
Ciclosporin							No prophylaxis required
Tocilizumab				Consider prophylaxis or regular monitoring (see section 10)			

	Anti-viral (HSV/VZV)	Anti-fungal (mould)	Anti-PCP	Anti-Hepatitis B [1]	TB prophylaxis[2]	Other	Notes
Alemtuzumab (Campath)	Prophylaxis recommended	Prophylaxis recommended	Prophylaxis recommended	Prophylaxis recommended	Consider prophylaxis based on TB risk (see section 7)	Monitor CMV PCR weekly until 2 months after completion of treatment	
Advanced HIV			Prophylaxis recommended		Consider prophylaxis based on TB risk (see section 7)		

[1] If evidence of past hepatitis B (HBsAg negative, HBcAb (Hepatitis B core antibody) positive, negative HBV DNA). This table does not apply to patients who have chronic hepatitis B (**pos HBsAg** and pos HBcore ab) or past hepatitis B with detectable DNA. It also does not apply to patients on combination IST (see section 10).
[2] Patients should be screened for TB risk factors (see section 7). Prophylaxis should only be used in high-risk groups without evidence of active disease and all of these patients should be discussed with ID.
[3] more than 1mg/kg prednisolone equivalent for more than 7 days OR more than 0.5mg/kg prednisolone equivalent for more than 14 days OR more than one course (3 days) of high-dose pulsed steroid OR more than 20mg Prednisolone equivalent for more than 4 weeks.
[4] expected neutropenia (< 0.5 x 10^9/L) for 14 days
[5] Strongyloides serology is usually sufficient but may not be in this immunosuppressed and/or transfused population. If queries please discuss with ID"

11. HSV / VZV prophylaxis

Most patients will not require antiviral prophylaxis. Prevention is aimed at preventing reactivation of herpes viruses such as varicella zoster (VZV) and herpes simplex (HSV). Antiviral prophylaxis should be given when using etoposide or alemtuzumab-containing regimes and should be considered in patients receiving prolonged high-dose steroid.

Table 2 – Anti-HSV/VZV prophylaxis agents

If using etoposide or alemtuzumab-containing regimens or prolonged high-dose corticosteroids	
1st line	**Aciclovir** 200mg PO TDS
If oral intake not possible	**Aciclovir** 250mg IV TDS
Renal impairment	Discuss with pharmacy
Duration	For alemtuzumab-containing regimens continue until CD4 >200 x 10^{12}/L For etoposide and high dose corticosteroids continue for duration of treatment

12. Antifungal prophylaxis

Invasive fungal infection (IFI) is a major cause of morbidity and mortality in patients being treated for HLH. Consider antifungal prophylaxis in all patients. Particularly high-risk HLH groups for IFI include:

- Severe and prolonged neutropenia (< 0.5 x 109/L) for 14 days or longer
- High dose (equivalent to prednisolone >1mg/kg) or prolonged oral corticosteroids for >1 week
- Certain groups of haematology patients including allogeneic HSCT patients (see separate guideline: Antifungal guideline for patients with Haematological malignancies)
  Alemtuzumab-containing regimens

Antifungal prophylaxis is strongly recommended for these patients. The need for antifungal prophylaxis in patients not meeting these criteria should be discussed at the MDT.

All patients with HLH should have a baseline serum beta-D-glucan (BDG) and galactomannan to screen for invasive fungal infection. Any positives should be discussed with Infectious Diseases or Microbiology.

NB: IVIG can lead to false positive BDG, so should be sent **before** IVIG is given.

STARTING prophylaxis:
if a patient is identified as likely to be in a high-risk group that will require anti-fungal prophylaxis (see Table 1) e.g. steroids for > 1 week or anticipated neutropenia > 2 weeks, prophylaxis should be commenced at the **START** of the risk period e.g. when steroids are started or when neutrophils < 1.5 x10^9/L if expected to become neutropenic

STOPPING prophylaxis:
stop when neutrophil count returns to ≥0.5 x 10^9/L or for duration of steroid use

Table 3 – Anti-fungal prophylaxis agents

1st line	**Itraconazole** oral suspension* 2.5mg/kg (max 200mg) PO BD Counselling: Take on empty stomach with acidic pH drink (e.g. coca-cola, fresh orange juice)
If oral intake not possible or reduced GI absorption	**Itraconazole** 200mg IV BD for 48 hours, then 200mg IV OD
Renal impairment	No adjustment
Hepatic impairment (LFTs 3xULN)	**Ambisome** Inpatient setting: 1mg/kg IV OD (*use actual body weight to calculate dose – round to nearest 50mg*) Out-patient setting: 3mg/kg IV 3 times per week *Give initial test dose of 1mg over 10 minutes*

*Oral suspension should be used rather than capsules. Capsules are poorly absorbed, particularly in patients taking proton pump inhibitors.

MONITORING
All patients should have an itraconazole trough drug level performed day 10

13. PCP prophylaxis

Prophylaxis is aimed at the prevention of *Pneumocystis jirovecii* Pneumonia (PCP). High-risk treatment groups include:

- Etoposide-containing regimens
- Prolonged steroids (>7 days)
- Alemtuzumab-containing regimens
- Certain haematology patient groups (including Hodgkin's lymphoma/ALL receiving chemotherapy/allogeneic BMT patients) – Haematology supportive care guidelines should be followed

Table 4 – Anti-PCP prophylaxis agents

1st line	**Co-trimoxazole** 960mg PO OD 3xweek[1]
2nd line agents **(for patients with neutrophils <1x10^9/L or platelets <100x10^9/L)**	**Pentamidine** 300mg nebuliser monthly[1] *OR* **Dapsone** 100mg PO OD **+ Pyrimethamine*** 75mg PO weekly[1,4] **+ Folinic acid** 30mg PO once each week *OR* **Atovaquone** 1500mg PO /day[1] *OR* **Azithromycin** 250mg PO Mon – Fri OR1250mg PO weekly[2] ***** *Test for G6PD before starting*
Renal impairment	No adjustment
Hepatic impairment **(LFTs 3x ULN)**	No adjustment

[1] (Maertens et al. 2016); [2] (Dunne et al. 1999); [3] (Nelson et al. 2011); [4] (Sanford Guide to Antimicrobial therapy, 2020)

STARTING prophylaxis**:** beginning of treatment in high-risk groups
STOPPING prophylaxis**:** continue whilst patient on treatment. For patients on alemtuzumab-containing regimens, continue for 6 months post treatment or until CD4 > 0.2 x 10^9 /L.

14. TB prophylaxis

TB is a rare but well recognised cause of HLH (Zhang et al. 2017) (Padhi S and Sahoo J 2017). In addition, there is a risk of reactivation of latent TB following treatment for HLH with certain immunosuppressive agents.

Whilst routine TB prophylaxis is not routinely recommended, all high-risk patients should be discussed with ID for advice on further investigation and/or treatment of active or latent TB.

High-risk patients include:

- Patients from high prevalence countries or previous residence in a high prevalence country*
- Patients from a high-risk social background; prior/current homelessness, drug miuse or time spent in prison
- History of prior treatment for TB
- Known previous positive Mantoux tuberculin skin test (TST)/IGRA
- History of recent exposure to TB
- HIV positive
- Imaging features compatible with TB

For patients requiring anti-TB medications, drug interactions between rifamycin-containing regimens and HLH-directed treatments (e.g. ciclosporin) should be considered. These cases should be discussed with Infectious Diseases.

*Particularly Africa, South and South-east Asia, the Philippines, Peru and Eastern Europe – see Appendix 1 for a full list

15. Hepatitis B prophylaxis

There is a risk of reactivation of hepatitis B in patients with chronic hepatitis B and with evidence of previous infection (HBsAg negative and HBcAb positive) after administration of some immunosuppressive treatments with B cell depleting therapies such as anti-CD20 agents (rituximab) carrying the highest risk.

All patients with suspected HLH should have hepatitis B serology performed prior to the start of treatment (HBsAg, anti-HBc) as well as HCV and HIV serology. If a patient has started treatment already, serology should be requested urgently.

All patients with chronic hepatitis B infection (positive HBsAg) and patients with evidence of past hepatitis B (negative HBsAg and positive HBcore Ab) should be tested for HBV DNA in the blood. All patients with past hepatitis B should also be tested for anti-HBs antibodies to help stratify the risk of reactivation.

Patients with active hepatitis B infection (e.g. HBsAg (surface antigen) positive and/or HBV DNA positive) should be urgently discussed with Virology.

Patients with evidence of past hepatitis B (neg HBsAg and pos HBcore ab) and undetectable HBV DNA should be risk- stratified according to the immunosuppressive agent being given. For full guidance on this please refer to the trust guidelines (particularly appendix 1 and 2) and discuss with virology if any queries.

A summary table is provided here.

Table 5 – Risk categories of hepatitis B re-activation and associated management

Risk category of hepatitis B re-activation	Examples of immunosuppressive therapy (IST)	Prophylaxis or not	Monitoring
High (>10% risk)	B cell agents e.g.Rituximab, Ofatumumab	Give prophylaxis (see table 6) Continue for 12 months after stopping IST treatment	3 monthly: HBV DNA, HbSAg
Moderate (1-10% risk)	Moderate-dose (10 - 20mg prednisolone daily) or high-dose (>20mg prednisolone daily) corticosteroids daily for ≥4 weeks Most systemic cancer therapy TNFα inhibitors (e.g. etanercept, infliximab)	**Option 1** No prophylaxis – monitor only	1-3 monthly HBV DNA, HbSAg and LFTs*
		Option 2 Give prophylaxis (see table 6) Continue for 6 months after stopping treatment	3-6 monthly HBV DNA and HbSAg (depending on adherence)
Low (<1% risk)	Any dose of corticosteroids daily for ≤1 week Low-dose corticosteroids for ≥4 weeks (10mg prednisolone) Azathioprine, methotrexate	No prophylaxis	No monitoring

*Monitoring should be performed monthly if anti-HBs antibodies < 100 IU/ml or 3 monthly if anti-HBs antibodies > 100 IU/ml.

It should be noted that combination immunosuppressive therapy has an increased risk of hepatitis B re-activation and therefore all patients on combination therapy for HLH with past hepatitis B should be discussed with virology.

Table 6 – Agents for hepatitis B prophylaxis

1st line **for patients with evidence of past infection (HBsAg negative, HBcAb positive) with no active infection requiring prophylaxis**	**Lamivudine** 100mg PO OD
2nd line	**Tenofovir** 245mg PO OD *** *OR* **Entecavir** 500mcg PO OD ***
Renal impairment	No adjustment for lamivudine
Hepatic impairment (LFTs 3x ULN)	No adjustment

*** Clinicians should discuss with Virology before starting treatment

16. Contact details

Virology SpR	ext 78986 / 78975
Microbiology SpR	ext 79515 / 78120
Infectious Diseases SpR	07971010879
Rheumatology SpR	blp 2204
Haematology SpR	blp 7000

17. Guidance implementation

The relevant clinical teams will be notified of the guideline publication at the HLH MDT and on the HLH email distribution list.

Approved antimicrobial guidelines will be housed on the myUCLH intranet page.

18. Review, Monitoring & Compliance

This document will be reviewed and updated regularly by the authors in line with UCLH standard procedure. If new national or international guidance emerges on this topic the guideline will be updated accordingly.

19. References

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