Haematology Neutropenic Prophylaxis Guidelines

Guideline for the Use of Prophylactic Antibiotics in Neutropenic Patients

Guideline Number & Full Title:	1865 - Clinical Guideline for the Use of Prophylactic Antibiotics in Neutropenic Patients
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Explicit definition of patient group to which it applies ***(e.g. inclusion and exclusion criteria, diagnosis):***	All adult in-patients and out-patients within the Clinical Haematology Directorate receiving treatment for haematological malignancies
Changes from previous version ***(not applicable if this is a new guideline, enter below if extensive):***	Reviewed in light of the MHRA alert for Fluoroquinolones, contraindications and cautions added
Summary of evidence base this guideline has been created from:	Microbiology surveillance results on haematology patients NICE CG151: Neutropenic sepsis: prevention and management in people with cancer. September 2012 MHRA Alert Fluroquinolone antibiotics: must now only be prescribed when other commonly recommended antibiotics are inappropriate. Published 22/1/2024 Available via : Fluoroquinolone antibiotics: must now only be prescribed when other commonly recommended antibiotics are inappropriate - GOV.UK (www.gov.uk)
This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date or outside of the Trust.	

Introduction

- Antibiotic prophylaxis refers to the routine administration of oral antibiotic, antiviral and antifungal drugs to neutropenic patients, i.e. those who have an absolute neutrophil count (ANC) of $<0.5x10^9$/L, or those patients who are receiving chemotherapy regimens which are expected to result in this degree of neutropenia within the following 2-3 days. The protocol is in accordance with NICE guidance (September 2012).

- The purpose of antibiotic prophylaxis is to partially sterilise the gut and to prevent the development of potentially severe infections or sepsis during the neutropenic phase. For example, it has been proven that the routine use of quinolone antibiotics reduces the risk of gram negative sepsis during neutropenia. There is however an increased risk of colonisation with resistant organisms and of increasing the risk of MRSA and *C. difficile* infections.

- These antibiotics can usually be discontinued early during the recovery phase from the neutropenia, e.g. when the neutrophil count exceeds $0.5x10^9$/L.

- A number of neutropenic prophylaxis regimens are in use within the Clinical Haematology department; choice of regimen depends on the type of treatment the patient is receiving.

- Despite NICE Guidance (2012) these guidelines have been amended to **ABANDON the use of ciprofloxacin** for all inpatients requiring neutropenic prophylaxis in view of increasing isolation of ciprofloxacin, piperacillin / tazobactam and gentamicin resistant organisms. This includes patients who are admitted for neutropenic care.

- Fluoroquinolones (e.g. ciprofloxacin) can very rarely cause long-lasting (up to months or years), disabling, and potentially irreversible side effects, sometimes affecting multiple systems, organ classes, and senses. Please refer to information regarding important **contraindications and cautions** with ciprofloxacin here. All patients should be counselled on the risks where able and provided with an MHRA patient information leaflet.

- Advice on antifungal prophylaxis and therapeutic drug monitoring of posaconazole can be found in the clinical guideline for the prophylaxis and treatment of fungal infections in haematology patients here.

- The start date of neutropenic prophylaxis varies depending on the chemotherapy regimen, and is detailed as part of each individual protocol on ChemoCare.

- If in doubt, ask a senior colleague for advice.

ORAL PROPHYLAXIS WITH PENICILLIN, CIPROFLOXACIN AND ANTIFUNGALS SHOULD BE DISCONTINUED IF THE PATIENT COMMENCES TREATMENT DOSE IV ANTIBIOTICS/ ANTIFUNGALS

Regimen 1 – Outpatients (Excluding multiple myeloma)

Ciprofloxacin	250mg PO BD**
Aciclovir	400mg PO BD
Antifungal	According to patient's risk category – see Appendix 1
Co-trimoxazole*	960mg PO BD on Mondays and Thursdays# (regimen specific)
Fluoroquinolones (e.g. ciprofloxacin) can very rarely cause long-lasting (up to months or years), disabling, and potentially irreversible side effects, sometimes affecting multiple systems, organ classes, and senses. Please refer to information regarding important **contraindications and cautions** with ciprofloxacin here.	

*In the case of co-trimoxazole allergy or contraindication, use pentamidine nebulisers 300mg monthly. Atovaquone or dapsone may be used as an alternative (third line) – discuss with Consultant before prescribing. # A dose of 480mg once a day can be used in older patients or those with renal impairment

**For multiple myeloma patients follow the guideline "Prophylactic antibiotic therapy for multiple myeloma patients" available on the intranet

- For outpatients who are neutropenic, or likely to become neutropenic post chemotherapy.
- May sometimes be given to patients receiving oral regimens if the risk of severe neutropenia is >50%. Refer to the protocol on ChemoCare.
- Co-trimoxazole may be required depending on the chemotherapy regimen, and this will be indicated by the protocol on ChemoCare. These include:
    - All patients receiving fludarabine, cladribine, clofarabine and alemtuzumab.
    - Oral B-cell depleting agents for CLL (BTK inhibitors, venetoclax)
    - Lymphoma chemotherapy regimens including bispecific antibodies (Glofitamab and Epcoritamab)
    - Patients with ALL except during high dose methotrexate therapy.

Regimen 2 – General Haematology Inpatients

Aciclovir	400mg PO BD
Antifungal	According to patient's risk category – see Appendix 1
Co-trimoxazole*	960mg PO BD on Mondays and Thursdays# (regimen specific)

*In the case of co-trimoxazole allergy or contraindication, use pentamidine nebulisers 300mg monthly. Atovaquone or dapsone may be used as an alternative (third line) –

discuss with Consultant before prescribing. # A dose of 480mg od can be used in older patients as an equivalent alternative

- For general haematology inpatients undergoing myelosuppressive intravenous chemotherapy, eg. for acute leukaemia and some lymphomas.
- CAR-T cell therapy patients will follow this regimen with mandated antifungal prophylaxis as per Appendix 1.
- Co-trimoxazole is contraindicated in patients receiving high dose methotrexate and an alternative should be used as described above.

Regimen 3 – Autologous Transplant Patients

Aciclovir	400mg PO QDS
Antifungal	According to patient's risk category – see Appendix 1
Pentamidine	300mg NEB on Day +1

- For patients undergoing autologous transplant on Fletcher ward.
- To be prescribed on admission. For prophylactics that need to start on engraftment or on discharge, please prescribe them in 'Nerve Centre' and then pause (for example for an autologous patient: prescribe penicillin V / Clarithromycin (for penicillin allergy) and Co-trimoxazole) and write start on engraftment. This will ensure these medications are not missed off the TTO
- Refer to individual transplant conditioning protocols for more information.
- Pentamidine will be prescribed on ChemoCare and ordered by a haematology pharmacist.

TTOs for autologous peripheral blood stem cell transplant

Following engraftment (neutrophils >0.5x10^9/L for 2 days), patients are usually switched to the regimen below. This combination is continued for approximately 12 weeks following an autologous transplant procedure.

- Penicillin V 250mg PO BD (use clarithromycin 250mg PO BD if patient is penicillin-allergic).
- Co-trimoxazole 960mg PO BD on Mondays and Thursdays (use pentamidine 300mg NEB monthly if co-trimoxazole-allergic).
- Aciclovir 400mg PO QDS, duration of QDS acyclovir should be matched to the specific conditioning protocol, after which patient will reduce dose to 400mg BD if clinically appropriate.

For prophylactics that need to start on engraftment or on discharge, please prescribe them in 'Nerve Centre' and then pause. Write start 'on engraftment'. This will ensure these medications are not missed off the TTO.

Ensure a duration of 3 months is added to the TTO for patients who have had an autologous transplant. Please specify 3 months (or other appropriate duration according to patient need in the ‘Duration ‘or ‘Supply’ section of the TTO on the nerve centre.

If patients are readmitted continue their standard prophylactic antibiotics, unless they have been started on IV antibiotics or treatment dose antifungals.

Regimen 4 – Allogeneic Transplant Patients

Penicillin V	500mg PO BD
Aciclovir	800mg PO QDS starting Day -2 (N.B. cords start Day -4) Use 10 mg/kg IV TDS from D-2 for patients having myeloablative conditioning or those unable to tolerate oral aciclovir. For obese patients (>20% above IBW) refer to the antibiotics website for further dosing advice.
Antifungal	According to patient's risk category – see Appendix 1
Pentamidine	300mg NEB as a single dose prior to transplant
Co-trimoxazole	960mg PO BD on Mondays and Thursdays – ONLY if patient is toxo positive
Letermovir	CMV prophylaxis from Day +12 (may be started from day +1 in high risk patients) until Day+100, only for allograft recipients who are CMV IgG seropositive prior to transplant. Refer to BMT guideline for Screening, Pre-emptive Therapy and Treatment of Viral Infections for more information. NB. Requires **Blueteq** approval

- For patients undergoing allogeneic (sibling, unrelated, cord and haploidentical) transplant procedures on Fletcher ward.
- To be prescribed on admission. For prophylactics that need to start on engraftment or on discharge, please prescribe them in 'Nerve Centre' and then pause (e.g. for an allogeneic patient: prescribe Penicillin V / Clarithromycin (for Penicillin allergy) and Co-trimoxazole) and write start 'on engraftment'. This will ensure these medications are not missed off the TTO.
- Refer to individual transplant conditioning protocols for more information.
- Pentamidine will be prescribed on ChemoCare and ordered by a haematology pharmacist
- Eligible patients will receive letermovir as CMV prophylaxis – refer to individual transplant conditioning protocols and the BMT guideline for Screening, Pre-emptive Therapy and Treatment of Viral Infections here for more information. These patients should have their dose of aciclovir reduced to 400mg BD on engraftment.
- In the event of penicillin allergy, use clarithromycin 250mg PO BD
- Repeat pentamidine nebuliser at Day +28 if patient has not engrafted.
- Patients will no longer be discharged with fluconazole.

TTOs for allogeneic transplant patients

Following engraftment, patients are usually switched to the regimen below.

- Penicillin V 250mg PO BD (use clarithromycin 250mg PO BD if patient is penicillin-allergic). Continue indefinitely if patient aged >40 years or if chronic GvHD, otherwise stop at 12 months.
- Co-trimoxazole 960mg PO BD Mondays and Thursdays. Continue for 12 months or longer if on immunosuppression for chronic GvHD.
- Aciclovir 800mg PO QDS (or 400mg PO BD if also on letermovir). After Day +100 dosage can be reduced to 400mg PO BD and should be continued for 1 year or longer if the patient remains on immunosuppression or is lymphopenic.
- Posaconazole tablets 300mg PO OD or voriconazole 200mg PO BD may be used if the patient had a presumed fungal infection during their transplant or if started on steroids for GvHD. Discuss with Consultant). Continue for 3 months.
    - Posaconazole liquid 200 mg tds or gastro-resistant tablet 300 mg od, voriconazole 200 mg or 300mg bd (refer to antifungal treatment guidelines) and isavuconazole 200mg OD may be used if the patient had a presumed fungal infection during their transplant or if started on steroids for GVHD, in these cases there is no need to switch to fluconazole during neutropenic period unless indicated by a consultant.
    - Note, the use of isavuconazole requires micro approval prior to commencing treatment. Refer to antimicrobial website for more information.
    - Patients will no longer be discharged with fluconazole
- Letermovir 480mg PO OD (240mg PO OD if taking ciclosporin). Start on Day +12 and continue until Day +100.

If patients are readmitted continue their standard prophylactic antibiotics, unless they have been started on IV antibiotics or treatment dose antifungals.

Appendix 1

Antifungal Risk Category		
High Risk Patients IV mould active prophylaxis	**High Risk Patients PO mould active prophylaxis**	**Low Risk Patients PO Candida prophylaxis**
• ALL induction chemotherapy including dexamethasone, likely to have prolonged period of neutropenia. Azoles contraindicated due to vincristine interactions – use AmBisome® Liposomal prophylaxis • Previously documented confirmed or highly probable IFI undergoing intensive chemotherapy likely to result in prolonged period of neutropenia (>10 days) eg. AML induction chemotherapy • Allogeneic stem cell transplant (SCT) patients	• Intensive or out-patient AML chemotherapy • NB. Azoles must NOT be given to patients receiving Gemtuzumab ozogamicin (Mylotarg) or quizartinib (AC220) – use AmBisome® Liposomal prophylaxis • Patients receiving >10mg prednisolone for GvHD • Autologous SCT for the following conditioning regimens: Benda-EAM, BEAM, Etop/Melph • CAR-T cell patients until neutrophil recovery	• Autologous SCT EXCLUDING Benda-EAM, BEAM, Etop/Melph • Intensive or out-patient chemotherapy for NHL
Recommended Antifungal Prophylaxis		
ALL induction • AmBisome® Liposomal IV 100mg OD on Mon/Wed/Fri Previous IFI, AML induction or Allogeneic SCT • AmBisome® Liposomal IV 100mg OD on Mon/Wed/Fri • If AmBisome® Liposomal not tolerated discuss with Microbiology • Continue until absolute neutrophil count (ANC) >0.5x10^9/L	• Posaconazole gastro-resistant TABLETS 300mg PO BD on day 1, then 300mg PO OD thereafter • Posaconazole LIQUID may be used for swallowing difficulties – see below for dosing*	Autologous SCT EXCLUDING Benda-EAM, BEAM, Etop/Melph • Fluconazole 100mg PO OD Intensive or OP chemotherapy for NHL • Fluconazole 50mg PO OD • (Patients will no longer be discharged with fluconazole)

*Posaconazole liquid PO 200mg TDS with food (ideally administered with a high fat meal) may be used for patients with swallowing difficulties/NG tube. GvHD patients previously on oral posaconazole should be switched to posaconazole IV 300mg OD if the oral route is no longer available.