Prophylaxis and Treatment of Pneumocystis Jirovecii Pneumonia (PJP) for Allogeneic and Autologous Blood and Marrow Transplant (BMT) Recipients

DEFINITION

Pneumocystis jirovecii is a fungal pathogen with a propensity to cause severe pneumonia in immunocompromised patients. Effective prophylaxis should reduce the incidence of infection with pneumocystis jirovecii to <1% but occasional patients will be seen with suspected infection.

Prophylaxis of Pneumocystis Jirovecii Pneumonia

Intravenous Pentamidine

Dose: **4 mg/kg (max dose 300 mg) ONCE MONTHLY** in 100 ml sodium chloride 0.9% via intravenous infusion over 1 hour

Allogeneic recipient Schedule and duration

Start: Day +1 **and** +30 (Day 30 dose is only needed if not on co-trimoxazole)

Continue monthly if:

- patient is intolerant of co-trimoxazole
- has low blood counts i.e. neutrophils < 1.0×10^9/L and / or not platelet independent

Stop: when CD4 count exceeds 0.2×10^9/L

Autologous recipient Schedule and duration

Start: Day +1

Continue monthly if :

- patient is intolerant of co-trimoxazole
- has low blood counts i.e. neutrophils < 1.0×10^9/L and / or not platelet independent

Stop: 3 months post autograft or when peripheral blood lymphocytes > 1×10^9/L

Monitoring:

- U&Es, including creatinine – dose reductions only needed if creatinine clearance < 10 ml/min
- LFTs
- FBC
- Blood glucose before and after infusion
- ECG – before, during and immediately after first dose then as required unless suspect /high risk of arrhythmias
- BP, temperature and pulse - first dose: before, during and immediately after infusion. Further doses: before and after, and if patient symptomatic of hypotension
- Amylase – if pancreatitis suspected (e.g. abdominal pain) or hypoglycaemia

Side effects: IV pentamidine can have many toxic effects, but most of these are cumulative effects in daily treatment dosing. These include:

	nephrotoxicity (about 20% patients), hepatotoxicity (about 5% patients) pancreatitis, electrolyte disturbance, cardiac arrhythmias Adverse effects that can occur in both treatment and prophylaxis include: acute hypoglycaemia, electrolyte disturbance, arrhythmias (rare), QT prolongation, severe hypotension.
Precautions:	Because of potential hypotension, the patient should receive the infusion lying or sitting down

Oral Co-trimoxazole

Dose	**Co-trimoxazole 480 mg OD PO on Mondays, Wednesdays & Fridays only.** **Escalate to 960 mg OD** (Equivalent to approx.150 mg trimethoprim /m^2/day) when counts stable and in the absence of side effects.
Schedule and duration	**Start**: When neutrophils > 1.0 x10^9/L post transplant & platelet transfusion independent **Stop:** **Allogenic Transplant:** Usually 4-8 weeks after immunosuppression is stopped **Autologous Transplant**: 3 months post autologous transplant or when peripheral blood lymphocytes are > 1 x 10^9/L
Side Effects:	Rash, Nausea, Myelosuppression, Stevens-Johnson Syndrome (rare)

Dapsone is an alternative to co-trimoxazole and pentamidine, this should be discussed with a consultant

Dose	Dapsone 100mg PO daily
Side Effects and contraindications	Dapsone causes dose related-haemolytic anaemia and meth-aemoglobinaemia and is **contraindicated for patients with glucose-6-phosphamate dehydrogenase deficiency.** Common side effects include: neutropenia, rash, nausea and a sulfone syndrome (fever, rash, lymphadenopathy, hepatitis and methaemoglobinaemia). It should be noted that a substantial number of patients allergic to co-trimoxazole will also be intolerant of dapsone and the drug should not be used as an alternative for patients with severe or life-threatening co-trimoxazole related toxicities.

Diagnosis of Pneumocystis Jirovecii Pneumonia

- 14-28 day history of breathlessness and cough, which is often non-productive.
- sparse inspiratory crackles in about one third of patients
- tachypnoea and cyanosis may be present
- chest X ray is usually abnormal with bilateral interstitial infiltrates
- blood gases will reveal hypoxia.
- pneumocystis in lower respiratory secretions
- Beta-D glucan levels <80 make PJP unlikely
- Bronchoscopy samples should be sent for PCR. Negative results have a high predictive value. Interpret low level positive results with caution as it can be a normal commensal organism. Advise to discuss with microbiology.

Investigations

- Chest x-ray
- Bronchoscopy
- Arterial blood gases
- Monitoring of oxygen saturation level

Treatment of Pneumocystis Jirovecii Pneumonia

First Line Treatment – Co-trimoxazole (with Prednisolone 40mg od)

Treatment Dose: **120 mg/kg/day in 2-4 divided doses IV infusion over 60-90 minutes** (or PO but only in mild cases and where enteral absorption is not compromised).

Prescribing Notes:
120 mg/kg of co-trimoxazole is equivalent to 20 mg/kg of the trimethoprim component. Dose is usually calculated to the nearest 480 mg vial.

Dosing in renal impairment: Dose reductions are necessary in renal failure:

Creatinine clearance (ml/min)	Co-trimoxazole dose
> 30	Dose as in normal renal function
15-30	60 mg/kg BD for 3 days then 30 mg/kg BD
<15	30 mg/kg BD (This should only be given if haemodialysis facilities are available)

Treatment duration: 14-21 days of Co-trimoxazole prescribed with high-dose steroids e.g. oral prednisolone 40 mg daily or IV equivalent. **The data for corticosteroid use are not clear in non-HIV related pneumocystis infection**

Monitoring: Daily weight with IV administration
U&Es, FBC, Blood glucose
ECG –before, during and immediately after first dose then as required unless suspect /high risk of arrhythmias.
BP, temp and pulse - first dose: before, during and immediately after infusion.

Further doses: before and after, and if patient symptomatic of hypotension

Toxicity/ adverse effects:

- Skin effects: skin rashes with photosensitivity. More severe reactions such as Stevens-Johnson syndrome have occurred rarely (discontinue at the first appearance of a skin rash)
- Allergic reactions: anaphylaxis or less severe asthmatic episodes due to sulphite in injection
- Fluid overload with IV preparation
- Nausea, vomiting, dizziness & confusion are likely symptoms of overdose
- Elevation in serum transaminases and bilirubin
- Bone marrow depression (treat with calcium folinate 15 mg daily)

Second Line Treatments-

There is limited evidence for second line therapy and should only be considered if patient has proven allergy or intolerance to co-trimoxazole.

If patient can take oral medications, and <u>without G6PD deficiency</u>:

Treatment Dose: **Clindamycin 600 mg PO/IV TDS**
Primaquine 30 mg PO OD

Treatment duration: 14 to 21 days

Precautions: **Primaquine is contraindicated in patients with G6PD deficiency**.

Monitoring:

- Daily FBC
- Weekly U&E, Creatinine. No dose reduction is required for renal impairment.
- LFTs – bilirubin, alk phos and AST/ ALT –Baseline, then weekly, unless increased, then twice a week

Side Effects:

- Nausea and vomiting
- Neutropenia
- Clostridium difficile associated diarrhoea
- Haemolysis in patient with G6PD deficiency

If patient can take oral medications, <u>with G6PD deficiency or unable to confirm G6PD</u> status:

Treatment Dose: **Atovaquone 750 mg PO BD**

Treatment duration: 14 to 21 days

Administration: Take with high fat food.

Side Effects:

- Nausea and vomiting
- Rash
- Anaemia and neutropenia
- Hyponatraemia
- Elevated liver enzymes levels

Monitoring:

- Daily FBC
- Weekly U&E, Creatinine. No dose reduction for renal impairment is required but use with caution if CrCl <10 mL/min
- LFTs – bilirubin, alk phos and AST/ ALT –Baseline, then weekly, unless increased, then twice a week

If patient cannot take oral medication: Pentamidine

Treatment Dose: **4 mg/kg/day (300mg max dose)** in 100ml sodium chloride 0.9% IV infusion over 1 hour

Dosing in renal impairment:

Creatinine clearance (ml/min)	Pentamidine dose
>10	Dose as in normal renal function
<10	Depending on severity of infection: 4 mg/kg/day IV for 7-10 days, then on alternate days to complete minimum 14 doses, *or* 4 mg/kg on alternate days to complete minimum of 14 doses

Treatment Duration: 14 to 21 days
Usually co-prescribed with high-dose steroids e.g. oral prednisolone 40mg daily or iv equivalent

Precautions: Because of potential hypotension, the patient should receive the infusion lying or sitting down

Monitoring:

- Daily U&Es, including creatinine – dose reductions only needed if creatinine clearance < 10ml/min
- Weekly serum calcium, magnesium and phosphorus
- Daily FBC
- Blood glucose before and after infusion
- LFTs – bilirubin, alk phos and AST/ ALT –Baseline, then weekly, unless increased, then twice a week
- ECG –before, during and immediately after first dose then twice a week, unless suspect/ high risk of arrhythmias perform daily with each dose
- BP, temp and pulse - first dose: before, during and immediately after infusion. Further doses: before and after, and if patient symptomatic of hypotension
- Amylase – if pancreatitis suspected (e.g. abdo pain) or hypoglycaemia

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Audit

These processes are subject to the OxBMT/IEC audit programme.

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Circulation

NSSG Haematology Website

Review

Name	Revision	Date	Version	Review date
Dr Tim Littlewood	Updating	July 2102	4.0	July 2014
Dr Andy Peniket, Julia Wong Pharmacist	Update Pentamidine dose	Oct 2014	4.1	Oct 2016
Cheuk-Kie Cheung, Specialist Cancer Pharmacist Paolo Polzella, Specialist Haematology Registrar	Minor drug amendments, clarity of instruction, references No changes	Feb 2017	4.2	Feb 2019
Cheuk-Kie Cheung, Specialist Cancer Pharmacist	Addition of atovaquone and clindamycin/ primaquine as alternative treatment agents	June 2017	4.3	Feb 2019
Dr James Davies, BMT consultant Nadjoua Maouche, Lead Haematology pharmacist	Diagnosis information. Reformatting and restructuring of information. New references added	July 2019	5.0	July 2021
Dr James Davies, BMT consultant	Minor changes only	Apr 2022	5.1	Apr 2024