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

**Schedule and duration**

- **Allogeneic recipient**
  - 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 x 10⁹/L and/or not platelet independent
  - Stop: when CD4 count exceeds 0.2 x 10⁹/L

- **Autologous recipient**
  - Start: Day +1
  - Continue monthly if:
    - patient is intolerant of co-trimoxazole
    - has low blood counts i.e. neutrophils < 1.0 x 10⁹/L and/or not platelet independent
  - Stop: 3 months post autograft or when peripheral blood lymphocytes > 1 x 10⁹/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:

This is a controlled document and therefore must not be changed
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 /m²/day) when counts stable and in the absence of side effects.

**Schedule and duration**

**Start:** When neutrophils > 1.0 x10⁹/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 10⁹/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-aemoglobinemia 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 methaemoglobinemia). 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:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Co-trimoxazole dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30</td>
<td>Dose as in normal renal function</td>
</tr>
<tr>
<td>15-30</td>
<td>60 mg/kg BD for 3 days then 30 mg/kg BD</td>
</tr>
<tr>
<td>&lt;15</td>
<td>30 mg/kg BD (This should only be given if haemodialysis facilities are available)</td>
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</tbody>
</table>

**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 without G6PD deficiency:

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, with G6PD deficiency or unable to confirm G6PD 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:**

<table>
<thead>
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<th>Creatinine clearance (ml/min)</th>
<th>Pentamidine dose</th>
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<tr>
<td>&gt;10</td>
<td>Dose as in normal renal function</td>
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<tr>
<td>&lt;10</td>
<td>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</td>
</tr>
</tbody>
</table>

**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
REFERENCES
4- Williams KM et al. The incidence, mortality and timing Pneumocystis jiroveci pneumonia after hematopoietic cell transplantation: a CIBMTR analysis, Bone Marrow Transplant 2006; 51 (4): 573-580
7- Oxford University Hospitals NHS Foundation Trust. IV Pentamidine Monograph. Updated August 2016.
8- Oxford University Hospitals NHS Foundation Trust. IV Co-trimoxazole Monograph. Updated November 2014.

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

Author
E. Rawlings, SDU Manager, Version 1 & 2, 2004
D. Wareham, BMT Co-ordinator, Version 3, 2010

Circulation
NSSG Haematology Website
## Review

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