NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Pneumocystis Pneumonia (PCP) or Pneumocystis Jirovecii Pneumonia (PJP) Management in Adults

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

PNEUMOCYSTIS PNEUMONIA (PCP) or PNEUMOCYSTIS JIROVECII PNEUMONIA (PJP) Management in Adults

Pneumocystis pneumonia (PCP) is a serious lung infection caused by the fungal organism *Pneumocystis jirovecii* (formerly known as Pneumocystis carinii). Typically, it causes clinical disease in severely immunocompromised patients, such as HIV-positive patients with CD4 cell counts <200 cells/microlitre, haematopoietic cell transplant patients, solid-organ transplant patients, or patients on chronic immunosuppressive therapy. Due to high mortality associated with the disease treatment should be initiated immediately when clinical suspicion is high.

INFECTION PNEUMOCYSTIS PNEUMONIA (PCP) (*Pneumocystis jirovecii*)

Patients with HIV infection should be managed by or in conjunction with an ID consultant. Non-HIV patients, particularly those with severe infection, drug toxicity or when considering [1]Alternative 2nd line therapy, should be discussed with an ID consultant.

All doses stated should be reviewed for each patient and adjusted if they have renal or liver impairment. Discuss with Pharmacy or refer to the British National Formula (BNF), Summary of Product Characteristics (SPC) or Renal Drug Database for further information.

DIAGNOSTIC TESTS

The following diagnostic tests should be performed in patients with suspected PCP to identify other causes or confirm PCP diagnosis:

- Sputum for culture stating atypical infection suspected
- Urinary Legionella antigen
- Bronchoalveolar lavage (BAL) for PCP polymerase chain reaction (PCR), Viral screen and Mycoplasma (if BAL is unavailable other lower respiratory tract samples can be considered including Induced Sputum, Sputum and tracheal aspirate. Please note that upper respiratory tract samples should not be submitted for PCP testing)
- Serum for Beta D glucan testing which can be raised in PCP infection.

TREATMENT		
SEVERITY	**1ST LINE**	**[1]Alternative 2ND LINE**
Mild to Moderate **Arterial blood gas room air PaO_2 ≥70 mmHg (9.3 kPa) or an alveolar-arterial (A-a) gradient ≤35 mmHg**	**Co-trimoxazole ORAL** 90mg/kg/day in 3-4 divided doses (rounded to the nearest 480mg). [2] **Duration: 21 days** **Use actual body weight (ABW) unless BMI > 30 where adjusted body weight (AdjBW) should be used.** AdjBW =Ideal body weight (IBW) +0.4(Total body weight (TBW)-IBW)	**Option 1:** **Clindamycin ORAL** 600mg 8 hourly **and** [3, 4] **Primaquine ORAL** base 30mg once daily **Option2:** **Dapsone ORAL** 100mg once daily **and** **Trimethoprim ORAL** 15mg/kg/day in 3 divided doses rounded to the nearest 50mg **Option3:** [5] **Atovaquone ORAL** liquid 750mg 12 hourly, with food (preferably high fat). [2] **Duration: 21 days**
Moderate to Severe **Arterial blood gas room air PaO_2 <70 mmHg or an alveolar-arterial (A-a) gradient >35 mmHg**	[3,6,8] **Co-trimoxazole IV infusion** 120mg/kg/day in 3-4 divided doses (rounded to the nearest 96mg) **and** [7] **Corticosteroids-** start at the same time as treatment or within 72 hours (see further information box below). Consider dose reduction to 90mg/kg/day in 3-4 divided doses after 3 days or if poorly tolerated. **Use Actual body weight (ABW) unless BMI > 30 where adjusted body weight (AdjBW) should be used.** [8] **Co-trimoxazole oral bioavailability is 100%.** **Switch to oral (IVOST) Co-trimoxazole** at the same dose when appropriate after clinical improvement and patient can tolerate the oral route to complete the course. [2]**Duration: 21 days**	**Option1:** **Clindamycin ORAL** 600mg 8 hourly **or** [8] **Clindamycin IV infusion** 600mg 6 hourly or 900mg 8 hourly **and** [3,4] **Primaquine ORAL** base 30mg once daily **Option2:** [9] **Pentamidine isethionate IV infusion** 4mg/kg once daily Reduce dose to 3mg/kg once daily if toxicity [2] **Duration: 21 days**

FURTHER INFORMATION

[7]**Adjunctive Corticosteroids- start at the same time as treatment or within 72 hours**

The evidence base for steroid treatment is from HIV infected patients but steroids should be considered in all patients with severe disease. Suggest discuss with ID consultant.

For Moderate to Severe PCP based on the Following Criteria :

- Arterial blood gas room air PaO_2 <70 mmHg or
- Alveolar-arterial (A-a) gradient >35 mmHg
- O_2 saturations <92% or PaO_2 ≤9.3 kPa on room air.

Dosing Schedule:

Prednisone oral doses- start at the same time as treatment or within 72 hours

- Days 1–5: 40 mg twice daily
- Days 6–10: 40 mg once daily
- Days 11–21: 20 mg once daily then stop

IV methylprednisolone can be given at 75% of prednisone dose.

[1]**Alternative /2nd line treatments** should only be considered if patients are intolerant to Co-trimoxazole (TMP/SMX) and cannot be managed supportively, or there is evidence of treatment failure. As patients often worsen within the first 3 to 5 days of treatment, treatment failure is considered if the patient has worsening clinical status after at least 4 to 8 days of therapy.

[2] **Duration** of therapy is 21 days (IV and oral) even if the patient has clinically recovered. It is essential the course is completed to ensure the infection does not relapse.

[3] **Check for glucose-6-phosphate dehydrogenase deficiency (G6PD)** in all patients before starting **primaquine, dapsone or high dose co-trimoxazole** if possible but do not delay treatment. G6PD - causes haemolysis and may be triggered by oxidant drugs including Primaquine, Dapsone and high dose of Co-trimoxazole. If an individual develops haemolysis, is G6PD deficient or comes from a population at high risk of significant G6PD deficiency, alternative treatment decisions should be taken in consultation with a haematologist

Co-trimoxazole 480 mg consists of trimethoprim 80mg and sulfamethoxazole 400mg (TMP/SMX).

Co-Trimoxazole 16 mg/80 mg per ml for Infusion is contra-indicated in patients with severe impairment of liver function.

Pneumothorax is a common complication of severe disease and carries a poor prognosis. CXR is required if deterioration and/or chest pain.

Renal impairment

Discuss dose adjustment in reduced renal function with Pharmacy.

[6] Co-**trimoxazole renal dosing in PCP**:

CrCl 30 – 50 mL/min: dose as in normal renal function

CrCl 15-30mL/min: 120mg/kg per day in 2 divided doses for 3 days then 60mg/kg per day in 2 divided doses.

CrCl <15 mL/min: Contact renal/ infection specialist for advice.

For all other medication discuss doses with pharmacy.

Administration and preparation

[8] **Oral Bioavailability- the oral bioavailability of co-trimoxazole is 100% and clindamycin is 90%.**

Switch to oral Co-trimoxazole at the same dose and clindamycin 600mg 8 hourly, when appropriate, after clinical improvement and the patient can tolerate the oral route to complete the course.

Refer to Adult Intravenous monographs for advice on preparing and administering IV medication. Contact Pharmacy if further advice needed.

For IV co-trimoxazole - refer to Co-trimoxazole - Intravenous monograph

Consider alternating the diluent used for each dose (e.g. glucose, saline, glucose, saline) to avoid too much glucose or sodium.

Monitoring/ toxicity/ side effects/ Interactions

Monitoring during therapy should focus on evaluating for response to treatment, drug toxicities, and immune reconstitution inflammatory syndrome (IRIS). This section is not exhaustive- check all interactions, adverse effects and monitoring in the British National Formulary (BNF) at BNF (British National Formulary) | NICE and the products, Summary of Product Characteristics (SPC) at Electronic medicines compendium (eMC)

Check any potential interactions with a pharmacist, the BNF, SPC or Stockley's Drug Interactions.

Check any potential interactions with HIV medicines with a pharmacist or at Liverpool HIV Interactions (hiv-druginteractions.org)

Co-trimoxazole high dose:

- Check for glucose-6-phosphate dehydrogenase (G6PD) deficiency before starting as high dose co-trimoxazole can cause haemolysis in G6PD deficient patients. Specialist advice should be obtained in G6PD deficiency.
- Contra-indicated in patients with acute porphyria, a history of drug-induced immune thrombocytopenia with use of co-trimoxazole, trimethoprim and/or sulphonamides and or severe liver impairment of liver function.
- The dose should be adjusted for renal impairment. See the information in renal impairment above and Discuss with pharmacy.
- Use Actual body weight (ABW) unless BMI > 30 where adjusted body weight (AdjBW) should be used.
- If severe symptoms of severe Stevens-Johnson syndrome, treatment should be discontinued.
- Adverse effects include hypokalaemia, acute kidney injury (AKI), Myelosuppression, drug-induced hepatitis, interstitial nephritis, aseptic meningitis, and pancreatitis. Life-threatening cutaneous reactions -Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia with systemic symptoms (DRESS) have also been reported with the use of co-trimoxazole.
- Monitor FBC, U&Es and LFTs at least twice weekly during treatment.
- CrCl > 15ml/min –BNF/SPC recommends performing sulfamethoxazole serum level monitoring. After 2–3 days, plasma samples collected 12 hours post dose should have levels of sulfamethoxazole not higher than 150 micrograms/mL. If higher, stop treatment until levels fall below 120 micrograms/mL.

Pentamidine, when given intravenously:

- Adverse effects include nephrotoxicity, infusion-related hypotension, arrhythmias (including Torsade de Pointes), pancreatitis, hypoglycaemia or hyperglycaemia, diabetes mellitus, and electrolyte abnormalities.
- Patient should receive the medication lying down.
- Monitoring: It is recommended that patients be on continuous cardiac monitoring and electrocardiograms be monitored for QT prolongation.
  Monitor blood pressure before starting, during administration and a regular intervals until treatment is finished.
  Daily U+Es, FBC, LFTs, urine analysis and fasting blood glucose measurements. Fasting blood glucose measurements should be monitored at regular intervals up to 3 months after stopping treatment.
  Twice weekly: Magnesium
  Weekly: Calcium.

Clindamycin:

- Adverse effects include diarrhoea, pseudomembranous colitis, and severe hypersensitivity and skin reactions.
- Monitor: U+Es, FBC and LFTs at least twice weekly.

Primaquine:

- Adverse effects include abdominal cramps, nausea, and vomiting, methaemoglobinaemia and haemolytic anaemia, especially in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, QT interval prolongation.
- Contraindicated in acutely ill patients with rheumatoid arthritis or systemic lupus erythematosus (SLE) due to increased risk of developing granulocytopenia.
- Before starting blood should be tested for glucose-6-phosphate dehydrogenase (G6PD) activity as primaquine can cause haemolysis in G6PD deficient patients. Specialist advice should be obtained in G6PD deficiency.
- Monitor: QT and FBC at least twice weekly.

Dapsone:

- Adverse effects include methaemoglobinaemia and haemolytic anaemia (especially in patients with G6PD deficiency) as well as neutropenia, rash, fever, hepatitis, hyperkalaemia, peripheral neuropathy, and hepatotoxicity.
- Before starting blood should be tested for glucose-6-phosphate dehydrogenase (G6PD) activity as dapsone can cause haemolysis in G6PD deficient patients. Specialist advice should be obtained in G6PD deficiency.
- Contraindicated in porphyria and severe anaemia.
- Monitor FBC, U+Es and LFTs daily.

Atovaquone:

- Adverse effects include diarrhoea, rash, nausea, vomiting, headache, hyponatraemia, hyperglycaemia, transaminase elevations, and fever.
- Monitor: U+Es, LFTs and FBC daily.

Licence/ Availability

[4] **Primaquine** is not licensed in the UK but can be prescribed on a named patient basis. An unlicensed form (ULM) is not required if this guideline is being followed. Contact pharmacist to order. Primaquine dose refers to primaquine base.

[5] **Atovaquone** is only available as a liquid and has poor oral bioavailability. The presence of food (particularly high fat) increases the absorption 2-3 fold.

[9] **Pentamidine** should be made in the Pharmacy Aseptic Unit- contact pharmacy to order.

Prophylaxis

Prophylaxis against pneumocystis pneumonia (PCP) is recommended for all patients who have been treated for PCP and are HIV positive. Some groups of severely immunocompromised patients are also recommended to have PCP prophylaxis depending on the reason for immunosuppression.

Secondary prophylaxis: is essential after the first infection and should be started after completion of PCP treatment

HIV positive patients-

Co-trimoxazole oral 480mg once daily or 960mg three times a week or Dapsone oral 100mg once daily or [5]Atovaquone oral 750mg twice daily.

For all other patients refer to patient speciality and reason for immunosuppression or seek advice from ID/Microbiology**.**

Primary prophylaxis: Prophylaxis against pneumocystis pneumonia should also be considered for severely immunocompromised patients**.**

HIV-positive patients For all patients with CD4 count ≤200 cells/microlitre or CD4 cell percentage <14%

Treat as per secondary prophylaxis above.

Discontinue secondary and primary prophylaxis when CD4 count >200 cells/microlitre for ≥3months.

Prophylaxis should be continued for life in patients who develop PCP despite CD4 count >200 cells/microlitre.

For all other patients refer to patient speciality and reason for immunosuppression or seek advice from ID/Microbiology**.**

References:

- Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. National Institutes of Health, Centres for Disease Control and Prevention, HIV Medicine Association, and Infectious Diseases Society of America. Available at HIV Clinical Guidelines: Adult and Adolescent Opportunistic Infections Accessed August 2023.
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- British HIV Association and British Infection Association Guidelines for the Treatment of Opportunistic Infection in HIV-seropositive Individuals 2011 HIV Medicine (2011), 15(Suppl. 5), 1–5. Accessed August 2023
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