Title of Guideline (must include the word “Guideline” (not protocol, policy, procedure etc)) | Guideline for the Treatment of Pneumocystis jirovecii pneumonia (PCP) in Adults
---|---
Contact Name and Job Title (author) | Dr P Venkatesan (Consultant in Infectious diseases)
Division & Speciality | All
Date of submission | February 2017
Version | 2
Explicit definition of patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis) | Adult patients with a likely or confirmed diagnosis of Pneumocystis jirovecii pneumonia
Changes from previous guideline | Haematology and Infectious Diseases guidelines have been merged, with sections added about presentation in non HIV patients.

If this version supersedes another clinical guideline please be explicit about which guideline it replaces including version

Statement of the evidence base of the guideline – has the guideline been peer reviewed by colleagues?

Evidence base: (1-5)

| 1a | meta analysis of randomised controlled trials |
| 1b | at least one randomised controlled trial |
| 2a | at least one well-designed controlled study without randomisation |
| 2b | at least one other type of well-designed quasi-experimental study |
| 3 | well–designed non-experimental descriptive studies (ie comparative / correlation and case studies) |
| 4 | expert committee reports or opinions and / or clinical experiences of respected authorities |
| 5 | recommended best practise based on the clinical experience of the guideline developer |


Also
Further recent references on [www.medadvocates.org](http://www.medadvocates.org)
[www.bhiva.org/](http://www.bhiva.org/)
US Opportunistic Infection Guidelines (via

Consultation Process

Infectious Diseases Consultants
NUH Antimicrobial Guidelines Committee
Mid-trent HIV Clinical Network
Haematology
Renal Medicine

Ratified by
Date
NUH Antimicrobial Guidelines Committee
22/02/2017

Target audience

All Drs
Pharmacists
Available on the Trust Intranet – Clinical Guidelines and the Trust Antibiotic Website

Review date:
January 2020

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.
B. **INTRODUCTION**
Pneumocystis pneumonia is due to a fungus, *Pneumocystis jirovecii* (formerly *P. carinii* and still referred to as PCP). It remains a common presenting opportunistic infection for patients with undiagnosed HIV infection and AIDS and therefore may be seen in Acute Medical Admissions. It is also seen in other immunocompromised groups as in Renal Medicine, Haematology and Oncology, and in the latter groups is mainly seen in patients on steroids.

Patients with suspected PCP and HIV should always be discussed with an HIV specialist. Advice is available at any hour seven days a week from an Infectious Diseases consultant or registrar, contactable via switchboard.

C. **ASSESSMENT AND DIAGNOSIS**

1. **Suspicion**
PCP is associated with immunosuppression, in particular HIV, Haematology (especially ALL and post bone marrow transplant), Oncology and Renal Transplant patients. The latter groups are aware of their immunosuppression by disease or drugs, but in patients unaware that they are infected with HIV, features such as oral candidiasis, generalised lymphadenopathy, weight loss, persistent diarrhoea and troublesome, dry skin may indicate an underlying problem.

2. **Clinical features**
PCP usually has an insidious onset over weeks, with progressive tiredness, dyspnoea and later fever. However in the extreme immunosuppression associated with bone marrow transplantation PCP may involve rapidly over a few days. Cough is often dry and there are few chest signs.

3. **Investigation**
In addition to conventional investigations special mention is required for the following -

   **Chest Radiology**
   Various CXR patterns are possible, but classically a ‘bat’s wing’ interstitial pneumonitis is seen. On CT scan there is a ground glass appearance. Other causes of ground glass change include viral pneumonitis, interstitial lung disease and pulmonary oedema and may need to be borne in mind.

   **Pulse Oximetry**
   In the outpatient setting up to 40% of patients may present before any apparent CXR changes. In the early stages of infection a fall on pulse oximetry after exercise indicates that there is a pulmonary problem in an unwell patient. Patients with an oxygen saturation of <92% require arterial blood gases.
Arterial blood gases
Determining whether the pO$_2$ is $<$9.3 affects whether steroids are indicated in HIV patients.

Expectorated sputum
If PCP is suspected any expectorated sputum should still be sent for standard M,C&S and AFB. About one sixth of patients with PCP may also have superadded bacterial infection with purulent sputum.

Induced sputum
A deep lung sample is required for diagnosis. Visualisation of intact fungi by immunofluorescence of induced sputum has reported sensitivities between 50-90%. However these days immunofluorescence is no longer available and instead PCR is performed.

Induced sputum collection should not be routinely requested and only decided by senior staff. This requires physiotherapy and the use of 3.5% hypertonic nebulised saline. A total of 28 mls is nebulised. Pharmacy stocks 7% hypertonic saline. Therefore 14 mls of 7% hypertonic saline is mixed with 14 mls of sterile water. (7% hypertonic saline is required in CF patients, but not other patient groups.) Physiotherapists will usually require nebulised salbutamol written on the drug card as well.

Bronchoscopy
Patient’s coughs are often dry and a deep respiratory sample may also be obtained by bronchoscopy, if safe to undertake. The procedure may be hazardous in thrombocytopaenic Haematology patients. Samples are usually obtained by lavage at bronchoscopy. Lavage has a ~90% sensitivity for detecting PCP. Trans-bronchial biopsies are not routinely performed as pneumothoraces are commoner in PCP. However biopsy may be required if other diagnoses are being entertained or lavage is negative. About 15% of HIV patients with suspected PCP turn out to have another diagnosis. Ideally a bronchoscopy should be performed within 10 days of starting treatment.

PCR
The laboratory will now perform PCP PCR on respiratory samples, and no longer performs immunofluorescence. Quoted sensitivity for immunofluorescence is 97-98% and specificity is 68-96%. PCR is as sensitive but may be positive in the absence of PCP disease. To improve on the latter specificity a quantitative PCR is performed and the laboratory PCR ct value indicates the significance of a result (lower values being more significant).

For those unable to expectorate, senior staff may advise collection of oral washings or blood (purple top, EDTA bottle) for PCR. Oral washings are obtained by gargling 10 mls normal saline for 10-30 seconds and spitting into a universal container. The sensitivity of blood PCR is not clearly established, but will have a high specificity.
**Beta-D-Glucan (BDG)**
This is assayed from a blood sample (yellow or red top bottle). In a meta-analysis of fourteen studies on the diagnosis of PCP in immunocompromised patients, not purely HIV patients, the sensitivity of BDG was 94.8% (95CI 90.8-97.1) and specificity 86.3% (95CI 81.7-89.9) with a positive likelihood ratio of 6.9 and negative likelihood ratio of 0.06. Levels of ≥ 80 picograms/ml of BDG in blood is regarded as positive. BDG may also be assayed on bronchial washings.

**D. MANAGEMENT** (Evidence grade - 1b)

1. **Treatment**
   Treatment can commence before bronchoscopy as samples can remain positive for several days. The treatment choice depends on whether the PCP is severe, moderate or mild. Despite treatment, mortality rates of 10-15% have been reported. Rates are higher for those on Intensive Care Units. Response to treatment takes time and failure to respond clinically cannot be decided until the end of the first week of treatment. Adverse reactions are described with all choices and usually occur during the second week. Depending on the treatment choice, up to one half of patients have to change treatment because of adverse reactions.

2. **Adjunctive steroids (Grade 1b)**
   **HIV patients**
   When treatment starts to kill the organism there is an increased inflammatory response in the lung and a fall in oxygen saturation. Use of adjunctive steroids is associated with reduced mortality in those patients with an initial pO₂ <9.3. For maximal benefit the steroids should be commenced at the same time as the PCP treatment and not later than 72 hours.

   **Prednisolone** 40 mg bd for the first 5 days (or equivalent dose of an IV steroid)
   40 mg in the morning for the next 5 days
   20 mg in the morning for the next 5 days and then
   Taper to zero by day 21 and stop simultaneously with or before acute anti-PCP treatment

   **Non-HIV patients**
   Whilst the use of steroids in HIV patients with PCP is standard, its benefit in other groups is controversial. International Renal guidelines vary in their recommendations. Lemiale et al (2013) found that steroids increased mortality in 139 HIV negative patients with PCP. This likely reflects underlying variation in immunocompromise, risks of other opportunistic infections and the need for immunosuppression for underlying disease. In Renal patients there may be a need to withdraw some immunosuppression, whilst retaining the flexibility of ongoing steroid dosage. In general steroid doses are actually increased in renal transplant patients. However in Haematology steroids need to be discussed with Consultants as there are added risks of CMV infection or haematological disease relapse.
**Choice of anti-PCP treatment**

If a patient has been on PCP prophylaxis, but despite this develops PCP, the choice of treatment should be different to the prophylactic agent if thought to have been compliant. Otherwise the choices are as below.

<table>
<thead>
<tr>
<th>First line</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>- All degrees of severity</td>
<td>co-trimoxazole (Grade 1b)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second line&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Severe</td>
<td>In descending order of preference</td>
</tr>
<tr>
<td></td>
<td>- clindamycin + primaquine</td>
</tr>
<tr>
<td></td>
<td>- iv pentamidine</td>
</tr>
<tr>
<td>- Moderate / Mild</td>
<td>In descending order of preference</td>
</tr>
<tr>
<td></td>
<td>- clindamycin + primaquine</td>
</tr>
<tr>
<td></td>
<td>- dapsone + trimethoprim</td>
</tr>
<tr>
<td>- Mild</td>
<td>In descending order of preference</td>
</tr>
<tr>
<td></td>
<td>- dapsone + trimethoprim</td>
</tr>
<tr>
<td></td>
<td>- atovaquone</td>
</tr>
</tbody>
</table>

**Co-trimoxazole** (First line)

Co-trimoxazole is given at 30 mg / kg four times a day for 14 – 21 days. After three days the dose may be reduced to 30 mg / kg three times a day as this may be equi-effective and have a lower incidence of side-effects.

For ill patients who require hospitalisation and are hypoxic co-trimoxazole should be given intravenously. Once there is clinical improvement treatment can be switched to the same dose orally.

Intravenous doses should be rounded to the nearest millilitre (available as 96 mg/ml) e.g. for a 70 kg patient with normal renal function: 70 x 30 = 2100mg, rounded to the nearest 96 mg = 2112 mg (22 ml) four times a day. Oral doses should be rounded to the nearest half tablet (240 mg).

The dose should be adjusted in renal impairment and this can be discussed with pharmacy. Please calculate the creatinine clearance from the Antibiotic Website, rather than use the eGFR.

<table>
<thead>
<tr>
<th>Creatinine clearance ml/min</th>
<th>Co-trimoxazole dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-50</td>
<td>Normal dose</td>
</tr>
<tr>
<td>15-30</td>
<td>Normal dose for 3 days then 30 mg/kg every 12 hours</td>
</tr>
<tr>
<td>&lt;15</td>
<td>30 mg/kg every 12 hours</td>
</tr>
</tbody>
</table>

P.Venkatesan/ 1.2.17

Review by January 2020
Side effects include hyponatraemia (94%), nausea and vomiting (50%), disturbance of LFTs (44%), anaemia (40%), rash (33%), rise in creatinine (33%), neutropaenia (15%) and tremor. Nausea and vomiting may settle with standard anti-emetics, require dose reduction to 30 mg/kg tds or reversion back to iv dosing if on oral drugs. Severe tremor may respond to propanolol 40 mg bd or tds or require dose reduction to 30 mg/kg tds. Mild rashes near the end of treatment may be controlled by the use of steroids and chlorphenamine. Severe rashes including Stevens-Johnson Syndrome necessitate a change of therapy. When allergic reactions occur desensitisation is sometimes performed (see below for desensitising regimes).

Because of these side-effects FBC, U&Es and LFTs should be monitored at least twice weekly during treatment. With abnormal blood results the following changes are required:

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Alteration in treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils &lt; 0.7</td>
<td>Stop co-trimoxazole and change therapy</td>
</tr>
<tr>
<td>Platelets &lt;50</td>
<td>Stop co-trimoxazole and change therapy</td>
</tr>
<tr>
<td>Neutrophils 0.5 - 0.7</td>
<td>Reduce to 30 mg / kg tds</td>
</tr>
<tr>
<td>Platelets 50-70</td>
<td>could add calcium folinate 15 mg od</td>
</tr>
<tr>
<td>Liver enzymes &gt; x5 normal</td>
<td>Stop co-trimoxazole and change therapy</td>
</tr>
</tbody>
</table>

**Clindamycin + Primaquine**
Clindamycin is given at 600 mg qds iv or oral for 21 days with Primaquine 15 mg od orally for 21 days

Primaquine (and therefore this regimen) should be avoided in patients with G6PDH deficiency as it may cause methaemaglobinaemia and haemolytic anaemia. G6PDH is part of baseline screening of HIV patients. Clindamycin may cause antibiotic associated diarrhoea. Severe side-effects will necessitate a change of therapy.

FBC, U&Es and LFTs should be monitored at least twice weekly.

**Pentamidine**
Pentamidine is given iv at 3mg/kg/day as a single dose for 14-21 days.
(the dose of 3mg/kg/day is regarded as equi-effective with a dose of 4 mg/kg/day).

Intravenous infusion is associated with hypotension. Baseline blood pressure should be established and patients should receive the drug lying down in bed. Blood pressure should be monitored every 15 minutes during the 1 hour infusion. If there is a drop in blood pressure the infusion can be slowed to 2 hours.
Other side-effects include disturbance of LFTs (63%), rise in creatinine (60%), pancreatitis, rise or fall in glucose (57%), hyponatraemia (56%), other electrolyte disturbance, anaemia (33%), neutropaenia (32%), cardiac dysrhythmias and others.

On treatment blood glucose should be checked daily and bedside blood glucose monitored. At least twice weekly there should be checks on FBC, U&Es, LFTs, Calcium and Magnesium. When indicated amylase and ECGs should be checked.

Because of renal effects concomitant drugs with renal toxicity should be avoided. Significant side-effects necessitate a change of therapy.

**Dapsone + Trimethoprim**
Dapsone is given at a dose of 100mg OD orally for 21 days with Trimethoprim 20 mg / kg / day oral / iv in 3-4 divided doses for 21 days.

Dapsone and trimethoprim increase each other’s serum levels. Side effects associated with dapsone include gastrointestinal upset, hepatitis, peripheral neuropathy, rash and Stevens Johnson Syndrome. Cross allergy with other sulphonamides does not necessarily occur. Mild rashes may settle with anti-histamines and topical steroids but more severe rashes necessitate a change of treatment.

Haemolysis and methaemoglobinaemia are also possible, especially if G6PDH deficient. Therefore G6PDH levels should first be checked. Significant methaemoglobinaemia necessitates a change in treatment. Anaemia without haemolysis may improve with a reduction in dosage of dapsone from 100 mg to 75 mg per day.

Trimethoprim is associated with gastrointestinal upset, rashes and depressed haematopoiesis related to folate deficiency. Dosage adjustment is required in renal impairment as per the above table for co-trimoxazole.

FBC, U&Es and LFTs should be monitored at least twice weekly.

**Atovaquone**
Atovaquone is given as 750 mg bd orally for 21 days.

Oral absorption is better after meals and with suspension.

Side-effects are less common than other PCP treatments and include vomiting, diarrhoea, constipation, dizziness, fever, rash, pruritis, liver dysfunction, neutropaenia and anaemia.

**2. Monitoring**
In addition to bloods being checked regularly, with slight variations between treatment regimens as above, there should be regular monitoring of
- oxygen saturation
- pulse
- blood pressure and
temperature

A deterioration in the condition of the patient may be due to
- a pneumothorax
- an additional concomitant infection
- progression of PCP despite therapy
- treatment toxicity

3. Ventilation
As PCP is a treatable infection, ventilation is a consideration in all patients and
discussions need to take place with critical care staff on a case by case basis. Newly
diagnosed HIV patients with modern treatment for HIV they may have a reasonable
subsequent life span. However despite maximal treatment and intervention the
acute mortality rate for ventilated HIV patients with PCP can still be up to 60%.

4. Secondary prophylaxis
Having completed a treatment course, patients should be put on secondary
prophylaxis until sufficient immune reconstitution. For HIV patients this is when two
consecutive CD4 counts are >200 three months apart. Some evidence suggests that
prophylaxis may be discontinued with CD4 counts >100 provided that the HIV viral
load is persistently undetectable. Patients who do not take any secondary
prophylaxis have a 40% risk of recurrence of PCP in the next 18 months. In Renal
Medicine prophylaxis is given lifelong, unless the patient loses their transplant or
comes off immunosuppression

In descending order of preference options for secondary prophylaxis are

1. Co-trimoxazole
   The best evidence for efficacy is for a dose of 960 mg od every day, but this is
   associated with more side-effects than a dose of 480 mg od every day. In HIV
   patients daily dosing is now preferred over 960 mg od thrice weekly. In both HIV
   and Renal Medicine a dose of 480 mg od is used. In Haematology the standard
   practice is to use 960 mg bd on Mondays and Thursdays. Patients who develop
   an allergic reaction may be desensitised (see below). Prophylactic co-trimoxazole
   may increase creatinine levels in renal patients.

2. Dapsone
   Dapsone has been used at a dose of 100 mg daily or 100 mg thrice weekly. The
   former dose is of comparable efficacy with co-trimoxazole.

   Dapsone levels can be reduced with concomitant didanosine or rifampicin,
   resulting in prophylactic failure.

   Dapsone has also been used in combination with pyrimethamine 25 mg in a
   thrice weekly regimen.
3. **Atovaquone**
   Atovaquone 750 mg bd.

4. **Aerosolised pentamidine via a Respirgard II nebuliser**
   Pentamidine 300 mg is nebulised monthly. This should be given in a negative pressure side-room / treatment room. Product literature instructs staff in the room to wear goggles, mask and gloves. Pharmacy reconstitute the nebulised solution. Contact your ward pharmacist if required.

**Co-trimoxazole desensitisation**
Desensitisation involves administering an incremental dose of drug from a very small concentration to a normal dose. After a grade 3 reaction desensitisation should be deferred for 2 weeks. After a grade 4 reaction desensitisation should not be attempted. Desensitisation may be undertaken rapidly over the course of several hours or on consecutive days as an inpatient. For rapid desensitisation resuscitation facilities should be available and there should be venous access. A rapid regime was originally devised by Gluckstein and experience published in 1995, with dosing as shown in the table below.\(^8\)

<table>
<thead>
<tr>
<th>Gluckstein co-trimoxazole RAPID desensitisation regime</th>
<th>Dose of Co-trimoxazole (suspension 96mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hour</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.024 mg (0.00025ml)</td>
</tr>
<tr>
<td>1</td>
<td>0.24 mg (0.0025ml)</td>
</tr>
<tr>
<td>2</td>
<td>2.4 mg (0.025ml)</td>
</tr>
<tr>
<td>3</td>
<td>24 mg (0.25ml)</td>
</tr>
<tr>
<td>4</td>
<td>240 mg (half a 480mg tablet)</td>
</tr>
<tr>
<td>5</td>
<td>960 mg (2 x 480mg tablets)</td>
</tr>
</tbody>
</table>

Following successful desensitisation the patient should be placed on the required dose daily. For more gradual outpatient desensitisation the following regime may be used.\(^9\)

<table>
<thead>
<tr>
<th>Outpatient co-trimoxazole GRADUAL desensitisation regime</th>
<th>Dose of Co-trimoxazole (suspension 96mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.4 mg (0.025ml)</td>
</tr>
<tr>
<td>2</td>
<td>4.8 mg (0.05ml)</td>
</tr>
<tr>
<td>3</td>
<td>9.6 mg (0.1ml)</td>
</tr>
<tr>
<td>4</td>
<td>19.8 mg (0.2ml)</td>
</tr>
<tr>
<td>5</td>
<td>28.8 mg (0.3ml)</td>
</tr>
<tr>
<td>6</td>
<td>60 mg (0.625ml)</td>
</tr>
<tr>
<td>7</td>
<td>120 mg (1.25ml)</td>
</tr>
<tr>
<td>8</td>
<td>240 mg (half a 480mg tablet)</td>
</tr>
<tr>
<td>9</td>
<td>480 mg (1 x 480mg tablet)</td>
</tr>
<tr>
<td>10</td>
<td>480 mg (1 x 480mg tablet)</td>
</tr>
<tr>
<td>11</td>
<td>960 mg (2 x 480mg tablets)</td>
</tr>
</tbody>
</table>
E. **NURSING ISSUES**

1. Samples to be collected will include sputum for M,C&S, AFB
2. Observations include
   - Standard temperature, pulse, BP
   - Oxygen saturation
   - Respiratory rate
   - Early Warning Score
3. The patient should be weighed as doses may be calculated on the basis of weight

F. **REFERENCES**


Also

Further recent references on [www.medadvocates.org](http://www.medadvocates.org)
