Pneumocystis Pneumonia (PCP) - Full Clinical Guideline

REF: CG-RESP/2023/003

Guidance notes for the diagnosis and treatment of Pneumocystis jirovecii pneumonia in immunocompromised (non-HIV) patients

For further information consider contacting the on-call respiratory consultant, on-call microbiologist and for renal patients, ensure the renal consultant is aware (all available via switchboard)

Acknowledgements

This clinical guideline was a collaborative effort between Prith Venkatesan Nottingham, Tom Bewick, David Allotey, Craig Morris, Sue Shaw, Infection Control, Julia Lacey, Cathryn James, Lindsay Chesterton and the renal team.

WARNING

These notes are designed to be interpreted by senior clinicians. Investigations for opportunistic pneumonia are invasive, involve CT imaging and careful consideration. If in doubt, ask your consultant.

1. Background

Pneumocystis pneumonia (PCP) is caused by a fungus. Pneumocystis is species-specific, and in humans, the pathogen is termed Pneumocystis jirovecii. P. jirovecii infection is encountered worldwide and increasing evidence suggests that Pneumocystis has a human reservoir (lung) and is transmitted via the airborne route. The incidence of PCP is on the rise nationally in non-HIV patients. In those with impaired immunity, PCP may range from mild to severe with respiratory failure and death [1].

Detection of pneumocystis in individuals without symptoms or signs of pneumonia is defined as colonisation [2]. Other terms include “carriage” and “sub-clinical infection”. Approximately 80% children have antibodies by the age of 4 yrs and up to 20% healthy adults are colonised with PCP. Pneumocystis cannot yet be cultured in the laboratory. Methods of detecting Pneumocystis have also changed in favour of polymerase chain reaction (PCR). However, these results need to be interpreted with caution and in context with the history, examination and imaging because false-positive and false-negative results can both occur. The diagnosis of PCP can be challenging.

In general, the course and outcome of PCP pneumonia in HIV-negative patients is worse than in the HIV population [3]. Poor general and respiratory condition at the time of diagnosis are independent predictors of mortality [4].
With the rise of biologic agents, increasing numbers of patients are on immunosuppression and the evidence remains unclear about the risk factors for developing PCP pneumonia in this group. Glucocorticosteroid use and pre-existing respiratory disease are felt to be significant risk factors alongside biologic use [5]

2. Diagnosis and algorithm (see also appendix 1)

History and examination

A high index of suspicion will encourage early detection of PCP but it is important to be aware of the diagnostic challenges.

Usually, but not always, PCP presents in immunocompromised patients with an insidious onset over weeks or months, constitutional symptoms, a dry cough, fatigue,

dyspnoea and fever as a late sign. Classically, there are few chest signs. Desaturation with exercise is common in PCP. Patients can deteriorate rapidly despite treatment.

> NB- many renal immunocompromised patients present with viral symptoms of an upper respiratory tract infection, especially over the winter. If they present with laryngitis/pharyngitis, suspect alternative diagnoses other than PCP.

In a febrile, immunocompromised patient with respiratory symptoms, the suggested algorithm (appendix 1) for the diagnosis and detection of PCP and other causes of opportunistic pneumonia should be read in conjunction with the following notes:

Imaging

An initial CXR should be performed and a non-contrast spiral CT chest (with retro HR reconstructions) should be considered depending on the CXR findings within 24-48 hrs. For example, an alternative diagnosis may be evident i.e. lobar pneumonia, lung abscess or indeed malignancy. If the immunocompromised patient is febrile, with ground-glass (GG) shadowing on CT, consider opportunistic pneumonia, and early use of co-trimoxazole. Sufficient clinical information on the request card is vital to allow the radiologists to interpret the CT images appropriately. Early clinical discussion with a chest radiologist is recommended. The vast majority of the PCP cases had GG shadowing. Although this is a non-specific sign, the absence of GG shadowing should make you suspect an alternative diagnosis.

Bronchoscopy

A bronchoscopy should be discussed with the on-call respiratory consultant during working hours, and can be performed within 7 days of commencing treatment. The ensuing bronchial alveolar lavage (BAL) involves up to 250 mls warmed saline inserted into the lungs and aspirated. This is an excellent method of obtaining reliable material for P jiroveci polymerase chain reaction (PCR). Early bronchoscopy (before a patient deteriorates and may subsequently require assisted ventilation) will result in a safer procedure with a greater diagnostic yield, yet has its own risks. However, DO NOT WAIT for a positive BAL result before commencing anti-PCP therapy if the clinical suspicion is high.

Pneumocystis jiroveci detection

The gold standard for P jiroveci detection is direct visualisation of the organisms in bronchial washings. However, this test is not available in Derby (or Nottingham or Manchester). More recently PCR has become the accepted diagnostic test for P jiroveci, but there are pitfalls in arriving at a definitive diagnosis (see notes on colonisation).

The following specimens can be used for P jiroveci PCR detection (preferred specimens listed first):

- BAL PCR (the preferred sample)
- Sputum samples for PCR (ideally induced but not routinely available in Derby)
- Throat swabs for PCR
- Blood PCR (if positive this reflects severe disease, a negative blood PCR does not necessarily exclude the diagnosis of PCP)

P jiroveci PCR from any of these sources is not a perfect test, and does not always indicate the cause of the pneumonia. However, in a febrile immunocompromised patient with lung infiltrates it is extremely important to clinically decide upon the significance of positive P jiroveci PCR tests and act accordingly. The Manchester Public Health England (PHE) laboratory is currently providing cycle times (CT) from its quantitative P jiroveci PCR (personal communication). It is thought that CT <30 are indicative of 'true' disease, whereas a CT 38-45 may be more indicative of colonisation. However, this remains expert opinion rather than evidence-based medicine. Values of 31-37 require careful evaluation.

Several criteria are required for the diagnosis of PCP. This set of definitions is fairly typical, and is being used in Derby [6].

Definite PCP	Clinical signs of progressive pneumonia
	Ground glass opacities in chest CT
	Positive microbiological identification of P jiroveci
Probable PCP	Clinical signs of progressive pneumonia
	Ground glass opacities in chest CT
	Complete resolution of symptoms after full course anti-PCP treatment
	Absence of microbiological identification of P jiroveci
Possible PCP	Clinical signs of progressive pneumonia and:
	Either compatible radiological signs
	Or complete resolution of symptoms after anti-PCP treatment
	Absence of microbiological identification of P jiroveci
Other diagnosis	None of the above criteria

Other microbiological specimens

It is important to also consider other microbiological causes of pneumonia, and to investigate for bacterial, atypical bacterial, viral, opportunistic viral and other fungal cases of pneumonia. In addition, do not overlook TB, aspergillus, nocardia and actinomyces as potential culprits (usually cavitating lesions), see appendix 2.

Other available investigations

- Hypercalcaemia appears to be associated with PCP, perhaps as part of a prodrome, but anecdotally in the renal patient cohort, it is often present and appears to improve with treatment [7].

- Check for glucose-6-phosphate dehydrogenase deficiency (G6PD) at an early stage in case an alternative agent such as dapsone or primaquine is required.
- A baseline blood LDH and ß D glucan (the cyst wall of P. jirovecii and other fungi contains ß D glucan, the synthesis of which is inhibited by echinocandins (e.g. caspofungin)) should be considered. Although it has a sensitivity reportedly of 88-100% and specificity 96.4%, ß D glucan assays cannot distinguish between fungal species. False positives may occur in the setting of bacterial pneumonia or when ß-lactam antibiotics have been administered (particularly piperacillin-tazobactam) [8]. However, these tests may be useful in the monitoring of progress, rather than in the initial diagnostic phase.

Nursing requirements

All hospitalised patients with suspected or confirmed PCP should be nursed in isolated, single rooms with the doors and windows closed. Masks should be worn by staff if the patient is undergoing aerosol-generating procedures. Patients with suspected/proven PCP should wear masks when outside their room i.e. en route to CT/bronchoscopy etc. The airbourne route is probably important in the spread of PCP in a hospital environment. In previous outbreaks patients who have had no direct contact were found to have the same genotype of PCP [9].

3. Treatment options

CHECK FOR ALLERGIES

Co-trimoxazole (= sulphamethoxazole + trimethoprim)

This is the drug of choice. Commence 120mg/kg/day orally in 2-4 divided doses for 3 days then reduce to 90mg/kg/day. Start therapy once your ward-based (non-BAL) specimens have been obtained. Warn your patient of the potential side effects include nausea/vomiting/rash/marrow suppression/transaminase elevation and nephrotoxicity including hyperkalaemia. Treatment will ideally last for 14-21 days, (21 days at treatment dose is recommended) and secondary prophylactic dosing should commence thereafter. This is a toxic drug, reduce the dose at an early stage if concerned about side effects- seek advice.

The oral bioavailability of co-trimoxazole is excellent and intravenous co-trimoxazole and should be reserved for those who are nil by mouth or have absorption issues. Oral tablets are available in two strengths: 480mg and 960mg and doses should be rounded to the nearest whole tablet. A syrup preparation (480mg/5ml), suitable for nasogastric administration is also available. The oral doses are equivalent to the intravenous dose.

Co-trimoxazole needs adjusting for creatinine clearance (CrCl ml/min). BHIVA guidelines and the Renal Drug Database suggests the following:

CrCl (ml/min)	Total daily dose (in 2-4 divided doses)
≥30	120mg/kg/day for 3 days, then 90mg/kg/day
15-29, CAV/VVHD	120mg/kg/day for 3 days, then 60mg/kg/day
<15, HD, CAPD, HDF/High flux	60mg/kg/day

Additional antimicrobial therapy

It is important to consider other microbes that could also be causing pneumonia, especially whilst awaiting positive microbiological specimens. It is therefore suggested that the anti-microbial regime in febrile, immunocompromised renal patients with lung infiltrates (who may be deteriorating before positive microbiology has been identified)

could include (adjusted for renal function, consult pharmacy or the renal drug database):

Antibacterial therapy (ie. piperacillin/tazobactam)
Atypical bacterial cover (clarithromycin)
Other anti-fungal therapy (e.g. micafungin or caspofungin in renal patients, Ambisome in haematology patients)
If cytomegalovirus (CMV) is suspected, start oral valganciclovir or if concerns regarding absorption, intravenous ganciclovir.

Please be aware that co-trimoxazole and piperacillin-tazobactam have a similar spectrum of efficacy, although co-trimoxazole is not effective against *Pseudomonas*. Therefore, if co-trimoxazole is started, consider stopping piperacillin-tazobactam, unless there is a strong suspicion that *Pseudomonas* is contributing to the pneumonia.

Respiratory support

Early respiratory support is vital. Arterial blood gases should guide therapy, increasing oxygen requirements should be acted upon promptly, and continuous positive airways pressure (CPAP) and other ventilatory support may be required. Given the high risk of treatment failure and progression of NIV / CPAP to invasive mechanical ventilation, these interventions should be delivered on ITU only (not respiratory HDU). The improvement in outcome in HIV PCP is thought to reflect improved management of respiratory failure and ARDS rather than improvements in the management of PCP [10]. Pneumatoceles/pneumothoraces portend poorer survival. Fluid balance is also important, try to keep patients intravascularly euvolaemic wherever possible.

Steroids

In those with HIV, the early use of steroids in PCP is probably beneficial. In those without HIV, the evidence around steroid use remains unclear. Studies have not demonstrated any proven benefit of steroids [11,12]. One study by Lemiale et al retrospectively analysed 139 non-HIV cases of PCP and concluded that high dose steroids were associated with increased mortality via a mechanism independent from an increased risk of infection [13]. The German Haematology/Oncology 2014 guidelines do not recommend routine steroids and suggest consideration in individual cases [14]. A recent retrospective cohort study concluded that early vs late use of steroids in non-HIV PCP did not alter outcome [15].

We suggest that in renal transplant patients, steroids ARE required (because they are an important part of their immunosuppression).

If a steroid prescription pre-dated the onset of suspected or proven PCP, steroids should be continued and an increased dose is likely to be required.

In **renal transplant** patients with severe PCP, stop or at least reduce immunosuppression and start prednisolone 50mg od, with appropriate gastric/bone/candida/glycaemic cover. Further increases or reductions in steroids are at the renal consultant's discretion, but can be weaned according to clinical response from 7 days.

In non-HIV patients with suspected or proven PCP, steroids are NOT routinely required. However, they may be used if there is another indication for their use

4. Monitoring response to treatment

Drug levels

Co-trimoxazole components (sulphamethoxazole and trimethoprim) can be measured, although their interpretation and use in clinical settings is yet to be proven.

Similarly, aim for trimethoprim levels 5-7 microgrammes/ml pre dose and 10 microgrammes/mL post dose (as per table below). Levels of trimethoprim > 5 mcg/mL are needed to be efficacious (see appendix for details for specimen required). Paired (pre and post dose) levels are best. *Drug levels are useful for those patients requiring CVVHD etc*.

Drug level	**Pre-dose (mg/L)**	**Post-dose (taken 1 hour post if IV; 2 hours post if oral) (mg/L)**
Sulphamethoxazole	<100	120-150 but <200
Trimethoprim	5-7	5-10 but <20

Side effects with co-trimoxazole include hyponatraemia, vomiting, liver function test (LFT) derangement, anaemia, rash, acute kidney injury, hyperkalaemia, neutropenia and tremor. Therefore, in well patients, twice weekly monitoring (FBC, U+E's, LFT's) is required. In ill, hospitalised patients, daily FBC/U+E's and twice weekly LFT's etc. are suggested as a minimum.

If a rash occurs, co-trimoxazole should be stopped promptly (risk of Stevens-Johnsons syndrome).

If marrow suppression or LFT derangement occurs, suggested treatment changes are listed below. Do not delay the adjustments. Marrow suppression can have serious consequences.

Co-trimoxazole can also cause profound hypoglycaemia due to a sulfonylurea like effect and may require treatment with IV glucose or change of therapy.

Abnormality	Alteration in treatment
Neutrophils 0.5-0.7 $x10^9$/l Platelets 50-70 $x10^9$/l	Reduce to 90mg/kg/day; could add folinic acid 15 mg od
Neutrophils <0.5 $x10^9$/l Platelets <50 $x10^9$/l	Stop septrin, change therapy Could consider G-CSF 300 mcg stat
Liver enzymes >x5 normal	Stop septrin, change therapy

NB - marrow suppression in the context of chemotherapy is to be expected. If in doubt, consult Haematology consultants for advice.

5. Other treatment options

Although co-trimoxazole is first-line treatment, if treatment changes are required, the following alternatives are available, in descending order of preference.

Clindamycin + Primaquine

Ideally, ensure G6PD levels are normal before prescribing. If levels are unavailable e.g. over the weekend AND co-trimoxazole is not suitable (i.e. allergy etc) AND there is an urgent clinical need for PCP treatment, then there is a need to balance the potential risk of toxicity with any of the drugs in this section including pentamidine.

We recommend that clindamycin and primaquine can be used even if the G6PD levels are unknown in the short-term. It is extremely important to send the sample before starting treatment. The guideline writers suggest that this risk is less likely to be significant than the risks from using agents such as pentamidine.

Clindamycin (600 mg qds iv or oral) can be given with Primaquine 30 mg od orally or NG for 21 days.

Primaquine (and therefore this regimen) should be avoided in patients with G6PD deficiency as it may cause methaemaglobinaemia and haemolytic anaemia. Clindamycin may cause antibiotic associated diarrhoea. Severe side-effects will necessitate a change of therapy.

FBC, U&E's and LFT's should be monitored at least twice weekly.

Dapsone + Trimethoprim

DAPSONE- YOU MUST CHECK G6PD levels are normal first; suitable for mild/moderate disease only. However, care is need if previous sensitivity to co-trimoxazole because there is a small risk of cross-sensitivity with dapsone.

IF ALLERGIC TO CO-TRIMOXAZOLE DUE NOT USE TRIMETHOPRIM
Haemolysis may still occur even with normal G6PD levels- monitor carefully

Dapsone is given at a dose of 100mg / day orally for 21 days with

Trimethoprim 20 mg / kg / day oral 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 G6PD deficient. 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, hyperkalaemia and depressed haematopoiesis related to folate deficiency. Dosage adjustment is required in renal impairment as per the above table for co-trimoxazole.

FBC, U&E's and LFT's should be monitored at least twice weekly.

Pentamidine

An unpleasant drug, avoid if at all possible. Use only in an HDU/ITU setting.

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. Therefore patients should be lying down in bed and blood pressure 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. Blood glucose should be checked daily and bed side blood glucose monitored. At least twice weekly there should be checks on FBC, U&Es, LFTs, Ca and Mg. When indicated amylase and ECGs should be checked.

For further information consider contacting the on-call respiratory consultant, on-call microbiologist and for renal patients, ensure the renal consultant is aware (all available via switchboard)

There is no facility to give nebulised pentamidine in our Trust.

Because of renal effects, concomitant drugs with the potential for nephrotoxicity should be avoided. Significant side-effects necessitate a change of therapy.

Atovaquone

Atovaquone is given as 750 mg bd orally (liquid suspension) for 21 days.

Generally used only in mild/moderate PCP and its use in this clinical setting is unlicensed. Oral absorption is better with meals.

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

Atovaquone has been found to be useful in the treatment and prophylaxis for renal transplant patients and is well tolerated.

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Chest. 2018 Sep;154(3):636-644

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Other sources of useful information:

https://thorax.bmj.com/content/59/9/731

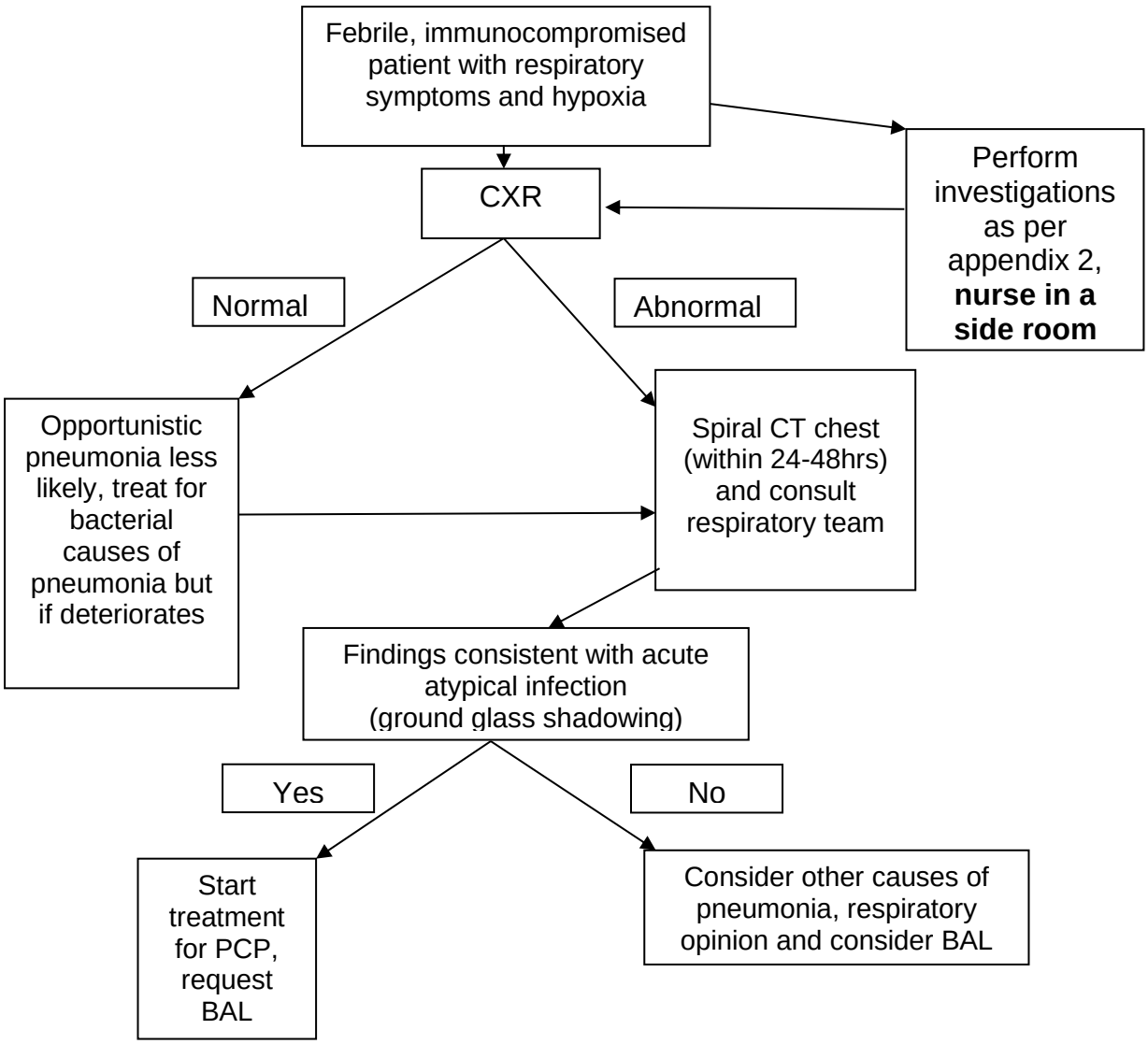
British Transplant Society/Renal association guidelines
https://bts.org.uk/guidelines-standards/

The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis—Executive summary
Rheumatology, Volume 58, Issue 2, 1 February 2019, Pages 220–226
https://academic.oup.com/rheumatology/article/58/2/220/5076445#

BHIVA guidelines 2011
British HIV Association and British Infection Association Guidelines for the Treatment of Opportunistic Infection in HIV-seropositive individuals
https://www.bhiva.org/OI-guidelines

For further information consider contacting the on-call respiratory consultant, on-call microbiologist and for renal patients, ensure the renal consultant is aware (all available via switchboard)

Appendix 1: Diagnostic pathway for febrile immunocompromised patients with suspected pneumonia



WARNING
This pathway should only be used in conjunction with the guidance notes under the supervision of a senior clinician.
It is intended for guidance only.

For further information consider contacting the on-call respiratory consultant, on-call microbiologist and for renal patients, ensure the renal consultant is aware (all available via switchboard)

Appendix 2

Investigations in febrile immunocompromised patients with suspected pneumonia

Tests to request	Specimen	Container	Laboratory	ICM/hand-written form
Bacterial				
Sputum culture	Sputum	Plain, silver top	Derby	Electronic ICM request
Blood cultures	Blood	Blood cult bottles	Derby	Electronic ICM request
Atypical				
Pneumococcal	Urine	Plain, MSU bottle	Derby	Electronic ICM request
Legionella antigen	Urine	Plain, MSU bottle	Derby	Electronic ICM request
Mycoplasma	Blood	Red top	Derby	Electronic ICM request
Viral				
Respiratory viruses PCR virology	Throat swab	Red top viral swab bottle	Derby	Electronic ICM request
Opportunistic viral				
CMV PCR viral load	Blood/micro	Purple, EDTA	Cambridge	Electronic ICM request
EBV PCR	Blood/micro	Purple, EDTA	Cambridge	Electronic ICM request
Fungal				
PCP (PJP)	Sputum PCR	Plain, silver top	Manchester PHE	Electronic ICM request
	Blood PCR	Purple, EDTA	Manchester PHE	Electronic ICM request
	BAL for PCR		Manchester PHE	Electronic ICM request
	Throat swab PCR	Red, viral swab bottle	Manchester PHE	Electronic ICM request
Aspergillus	Aspergillus galactomanan	Red blood bottle		Electronic ICM request
TB	Sputum x3/BAL	Plain, silver top		Electronic ICM request
Nocardia	BAL			
Actinomyces	BAL			
Other				
Sulphamethoxazole and trimethoprim	Blood/micro	Red top	Bristol	Hand-written micro form
LDH	Blood/biochem	Gold top	Derby	Electronic ICM request
ß D glucan	Blood/micro	Red top	Wythenshawe	Electronic ICM request
CD 4	Blood/haem	**Purple EDTA**	Derby	Electronic ICM request
G6PD deficiency	Blood/Biochem	Purple	Derby	Electronic ICM request

(BAL= bronchoalveloar lavage)

G6PD= Glucose 6 phosphate dehydrogenase deficiency

For further information consider contacting the on-call respiratory consultant, on-call microbiologist and for renal patients, ensure the renal consultant is aware (all available via switchboard)

Appendix 3

Pathogens causative for lung infiltrates: likely and unlikely

Clinical assessment of microbiological findings in febrile neutropenic patients with lung infiltrates (German Haem/Onc guidelines 2014)

The following findings **indicate** pathogens causative for lung infiltrates:

- *Pneumocystis jirovecii*, Gram-negative aerobic pathogens, pneumococci, *Nocardia*,
- *Mycobacterium tuberculosis* or *Aspergillus* spp. or Mucorales obtainedfrom bronchoalveolar lavage or sputum samples;
- CMV detection
- Isolation of pneumococci, alpha-hemolytic streptococci, *Bacillus cereus* or Gram-negative aerobic pathogens from blood culture
- Any detection of pathogens with invasive growth in biopsy material
- Positive *Legionella pneumophila* serogroup 1 antigen in urine
- Positive *Aspergillus* galactomannan in blood (threshold 0.5) or BAL samples (cut-off of ≥ 1.0 might be more appropriate)
- Positive quantitative *P.jirovecii* PCR with >1450 copies/ml
- Conversely, negative beta-D-glucan in blood samples makes p*neumocystis* pneumonia highly unlikely

The following findings **do not** represent pathogens causative for lung infiltrates:

- Isolation of enterococci from blood culture, swabs, sputum or BAL
- Coagulase-negative staphylococci or *Corynebacterium* spp. obtained from any sample
- Isolation of *Candida* spp. from swabs, saliva, sputum or tracheal aspirates
- Findings from surveillance cultures, faeces and urine cultures

Potentially relevant findings include:

- common respiratory viruses, isolation of *Staphylococcus aureus*, *Legionella* spp. or atypical mycobacteria in respiratory secretions
- *Pneumocystis*-PCR (without confirmation by other methods) from BAL

Documentation Controls

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