Pneumocystis jirovecii pneumonia diagnosis in the HAART and PCR era

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Introduction:

In the HAART era, *Pneumocystis jirovecii* Pneumonia (PJP) continues to be a leading opportunistic infection, second only to oesophageal candidiasis (3.9/1000 patient years in a longitudinal study of 8070 HIV-infected patients)¹. BHIVA Guidelines for the treatment of opportunistic infections² recommend PJP diagnosis by histochemical or immunohistochemical staining of induced sputum, followed if necessary, by Broncho-alveolar lavage (BAL) (Table 1). PJ Polymerase Chain Reaction (PCR) is increasingly available to support the diagnosis of PJP (Table 1). Upper respiratory tract samples are safer and simpler to obtain. A ‘low level’ PCR result may represent PJ colonisation or a poor-quality specimen. Upper airway samples such as throat swabs (T/S) are more likely to yield a negative or low level positive.

	Study design	Population	Sample & investigation	Findings
Cruciani, 2002 ³	Meta-analysis of diagnostic procedures (7 studies)	HIV-infected patients n=322 total	Cytochemical or immunohistochemical staining of Induced sputum (compared with ‘gold standard’ BAL staining)	<ul style="list-style-type: none">Immunohistochemical stain of IS sensitivity 0.67 (0.58-0.7, 95% Confidence interval) , specificity 0.97 (0.88-0.99)Cytochemical stain of IS sensitivity 0.43 (0.33-0.46), specificity 0.96 (0.86-0.99)
Lu, 2011 ⁴	Meta-analysis of prospective cohort studies (10 studies)	AIDS	PCR of BAL, induced sputum, and oral swabs PCR technique not detailed	<ul style="list-style-type: none">Pooled diagnostic sensitivity 0.99 (0.98-1.0)Pooled diagnostic specificity 0.91 (0.86-0.95) (heterogeneity between studies)
Fauchier, 2016 ⁵	Single centre prospective study of BAL specimens	All HIV-infected n=30 PJP n=14 no PJP (BAL investigation for another reason)	BAL, real-time qPCR	<ul style="list-style-type: none">Ct value>30 effectively exclude PJP (sensitivity 0.8; specificity 0.79)Ct value<27 confirmed PJP (sensitivity 0.73, specificity 0.8)

Table 1: Selected previous studies of PJP diagnosis in HIV-infected patients

Ct: cycle threshold; IS: Induced sputum; qPCR: quantitative PCR

Method:

Retrospective review of all HIV-infected adults with respiratory tract PCR-confirmed PJP and pneumonia over an 18 month period (April 2015 – September 2016). Demographics, clinical features, management, clinical outcome and laboratory parameters were recorded.

Figure 1a: site of respiratory samples; 1b: real-time PCR amplification plot. The greater the starting copy number of PJ nucleic acid target, the sooner the significant increase in fluorescence is observed (and the lower the Ct value)

Results:

A third (4/12) of PJP patients had negative PJP PCR test before the diagnosis was confirmed (Table 2). The mean Ct value for throat swabs was 34.04. The mean Ct value for sputum was 32.05.

Of patients admitted to hospital with a diagnosis of community acquired pneumonia, the median time to PJP diagnosis was 4 days (range 0 – 10). Eight out of ten patients diagnosed with PJP and HIV during the same episode had a previous HIV indicator disease.

Age at HIV diagnosis gender, behavioural risk	Category	CD4+ count at PJP diagnosis, PJP severity	PJP test 1 (Ct value, site)	PJP test 2 (Ct value, site)	Clinical outcome
39, M IDU	Known HIV On ART for 4 weeks, not on PJP prophylaxis	200, mild	37.0, TS	n/a	Survived
38, M MSM	Defaulted from care, not on ART	10, severe	Neg., TS	32.5, TS	ICU care, survived
	Missed opportunity to diagnose HIV				
53, M MSM	Unexplained diarrhoea and weight loss	70, severe	30.0, SPU	26.2, SPU	ICU care, deceased
43, F heterosexual	Unexplained lymphadenopathy and weight loss	50, severe	26.4, SPU	Neg., TS	Readmitted with hypoxia, survived
32, F heterosexual	Campylobacter gastroenteritis	50, severe	36.4, TS	25.3, SPU	ICU care, survived
56, M unknown	-	30, severe	Neg., TS	31.5, SPU	ICU care, deceased
39, M heterosexual	Unexplained weight loss	20, mild	Neg., TS	25.0, SPU	Survived
62, M MSM	Unexplained weight loss	20, mild	26.0, BAL	n/a	Survived
55, M MSM	Bacterial pneumonia	20, mild	33.0, SPU	n/a	Survived
52, M heterosexual	-	10, severe	30.3, SPU	34.9, SPU	ICU care, survived
57, M MSM	Unexplained weight loss	10, severe	39.0, SPU	n/a	ICU care, survived
52, M heterosexual	Chronic diarrhoea, bacterial pneumonia	0, severe	Neg., SPU	28.0, SPU	ICU care, hypoxia requiring long-term home-O ₂

Table 2: Patients with PJP (in order of immunosuppression)

Note- BAL: broncho-alveolar lavage; F: female; M: male; ICU: intensive care unit; IDU: intravenous drug user; MSM: men who have sex with men; n/a: not available; Neg.: PCR not detected; SPU: sputum, TS: throat swab PJP severity (‘mild’: mild-moderate, or ‘severe’: moderate-severe, by BHIVA criteria)

Seven patients required ICU care, of whom two died. All patients commenced treatment with Co-trimoxazole (and Prednisolone, if clinically indicated by severity score). One third (4/12) switched to second-line antimicrobial treatment due to Co-trimoxazole intolerance. All patients received treatment in keeping with BHIVA opportunistic infection guidelines².

Discussion:

One third of patients had a negative test on initial upper respiratory tract (URT) screening. Therefore, patients with a negative URT PCR and clinical suspicion of PJP should receive empiric treatment and where appropriate proceed to BAL, as per national guidance. PJP PCR is a useful investigation. PCR will detect more cases than traditional tests (direct organism visualisation). This leads to earlier PJP treatment and earlier screening for HIV. While there is a trend towards lower Ct value results in sputum when compared to throat swabs, any positive PJP result should trigger the offer of a HIV test. Prospective research is needed to determine URT PJ test performance in HIV-infected patients with, and without, PJP.

This small case series included eight patients where there was a missed opportunity to diagnose HIV. Earlier HIV diagnosis would have probably prevented the development of PJP. Due to high rates of morbidity, adverse drug reactions, and mortality, patients with opportunistic infections should be looked after in specialist units.