

## REVIEW SERIES

## The pulmonary physician in critical care • Illustrative case 5: HIV associated pneumonia

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The case history is presented of a patient with HIV associated pneumonia who was successfully treated in the ICU. The mortality rate of HIV infected patients admitted to the ICU has improved since the introduction of prophylaxis for *Pneumocystis carinii* pneumonia and highly active antiretroviral therapy (HAART). The identification of objective outcome predictors will help clinicians to decide when to pursue aggressive treatment and when to withhold or withdraw it.

An estimated 36 million people worldwide are currently infected with HIV, about 1.46 million in North America and Western Europe and a further 25.3 million in sub-Saharan Africa.<sup>1</sup> An estimated 30 000 adults and children became infected with HIV in Western Europe during the year 2000. The continuing rate of infection, coupled with longer survival due to primary and secondary prophylaxis against opportunistic infection and highly active antiretroviral therapy (HAART), has resulted in the prevalence continuing to increase.<sup>1,2</sup>

Infection with HIV is associated with increased susceptibility to opportunistic infection with more than 100 viruses, bacteria, protozoa and fungi.<sup>3</sup> Primary and secondary prophylaxis against opportunistic infections and HAART has led to changes in the nature, incidence, and presentation of opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP), *Mycobacterium avium intracellulare* (MAI), and cytomegalovirus (CMV) retinitis.<sup>2,4</sup> New challenges are presented to physicians in medical high dependency units (HDUs) and intensive care units (ICUs). We report a patient who presented with HIV associated pneumonia and discuss the issues concerning admission to HDU/ICU of HIV infected individuals in the PCP prophylaxis and post-HAART era, drawing together current views of prognostic indicators and outcomes.

### CASE REPORT

A 39 year old white man presented with a 3 week history of increasing shortness of breath accompanied by a non-productive cough, fever, and 5 kg weight loss. A diagnosis of HIV infection with a low CD4 count of 30 cells/mm<sup>3</sup> had been made 6 months earlier. He was homosexual with no history of recreational intravenous drug use. He was not taking PCP prophylaxis or HAART but instead took homeopathic treatment. On physical examination oral candidiasis, oral herpes infection, axillary and inguinal lymphadenopathy

were identified. He had fever (38°C), tachypnoea, tachycardia, and oxygen saturation on air of 85%. There were no chest signs. A plain chest radiograph showed diffuse bilateral shadowing. Arterial blood gas measurements on air were as follows: Pao<sub>2</sub> 5.8 kPa, Pco<sub>2</sub> 3.54 kPa, O<sub>2</sub> saturation 82%. The erythrocyte sedimentation ratio was raised at 119 mm/h and the C reactive protein (CRP) level was raised at 144 mg/l. Liver and renal function tests were normal. The patient would not tolerate a diagnostic bronchoscopy.

A clinical diagnosis of PCP/community acquired pneumonia was made and he was started on high dose intravenous co-trimoxazole with adjunctive corticosteroid therapy, oral fluconazole, and intravenous cefuroxime/oral clarithromycin. Continuous positive airway pressure (CPAP) ventilation was started. Initially there was clinical improvement. In particular, the oxygen saturation improved to 93% on air and the CRP level fell to 7 mg/l. However, on day 9 he became unwell with fever (38°C), tachypnoea, and tachycardia. A chest radiograph showed increased diffuse bilateral change with a nodular appearance and patchy consolidation. Arterial blood gas measurements on air were as follows: Pao<sub>2</sub> 4.48 kPa, Pco<sub>2</sub> 4.39 kPa, O<sub>2</sub> saturation 71%. CRP had risen to 163 mg/l. He was treated for hospital acquired pneumonia with piperacillin/tazobactam and vancomycin in addition to the PCP treatment. Ganciclovir therapy was started. He was transferred to the ICU for increased respiratory support with bilevel positive airway pressure (BiPAP) ventilation via a nasal mask and subsequently improved clinically.

### DISCUSSION

#### Pneumonia and HIV

The case described was initially treated empirically for community acquired bacterial pneumonia and PCP. Table 1 outlines common HIV associated pulmonary infections. In the absence of confirmatory tests, a diagnosis of PCP was most likely based on the clinical presentation and chest radiographic appearance in this at risk patient. PCP is nowadays most commonly seen in newly diagnosed HIV infected patients with advanced disease or HIV infected individuals not taking PCP prophylaxis or HAART. In the case described the patient had recently been diagnosed with advanced disease (CD4 count 30 cells/mm<sup>3</sup>) and was not taking PCP prophylaxis or HAART. PCP typically presents when the CD4 count falls below 200 cells/mm<sup>3</sup> and is one of the most common opportunistic infections precipitating admission to the HDU and ICU for respiratory support.<sup>4,10-13</sup> The risk of a first episode of infection below a CD4 count of

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**Table 1** HIV associated pulmonary infections

Bacteria	Mycobacteria	Fungi	Parasites	Viruses
<i>Streptococcus pneumoniae</i> *	<i>M tuberculosis</i> **	<i>Pneumocystis carinii</i>	<i>Toxoplasma gondii</i> ,	Influenza
<i>Haemophilus influenzae</i> *	<i>M avium intracellulare</i>	<i>Cryptococcus neoformans</i> **	<i>Cryptosporidium</i> spp	Parainfluenza
<i>Staphylococcus aureus</i> *	<i>M kansasii</i>	<i>Candida albicans</i>	<i>Microsporidium</i> spp	Respiratory syncytial virus
<i>Klebsiella pneumoniae</i> *		<i>Aspergillus</i> spp	<i>Leishmania</i> spp	Rhinovirus
<i>Pseudomonas aeruginosa</i> *		<i>Penicillium marneffei</i>	<i>Strongyloides stercoralis</i>	Adenovirus
<i>Nocardia asteroides</i>		<i>Histoplasma capsulatum</i>		Cytomegalovirus
<i>Rochalimaea henselae</i>		<i>Coccidioides immitis</i>		Herpes simplex virus
		<i>Blastomyces dermatitidis</i>		Herpes varicella-zoster virus
Bacterial pneumonia occurs more frequently in HIV positive patients at all CD4 counts than HIV negative controls. The risk increases as the CD4 count falls below 200 cells/mm <sup>3</sup> and in intravenous drug users <sup>5</sup>	HIV positive individuals are at increased risk of infection with <i>M tuberculosis</i> , whatever the CD4 count, and should be offered an HIV test. <sup>7</sup> Extrapulmonary tuberculosis tends to occur at CD4 counts <150 cells/mm <sup>3</sup> . <i>M avium intracellulare</i> and <i>M kansasii</i> both occur late in the course of HIV infection when the CD4 count falls below 50–100 cells/mm <sup>3</sup>	Pulmonary infections with <i>Candida</i> and <i>Aspergillus</i> are relatively rare. Endemic mycoses caused by <i>Histoplasma capsulatum</i> , <i>Coccidioides immitis</i> and <i>Blastomyces dermatitidis</i> occur in patients who live in North America		Common respiratory viral infections occur comparably in HIV infected and non-infected people. CMV is frequently isolated in BAL, but its role in causing disease is not clear. The presence of CMV in BAL is associated with a worse prognosis in PCP <sup>9</sup>

\*The common causes of bacterial pneumonia are shown.<sup>5–6</sup> One third of the pneumonias are bacteraemic. Bacteraemia is more common in pneumococcal pneumonia. Pseudomonal pneumonia is associated with a lower CD4 count than with pneumococcal pneumonia.<sup>6</sup>

\*\*Multidrug-resistant (MDR) tuberculosis (resistant to isoniazid and rifampicin) is becoming an increasing problem among HIV positive individuals in North America. Antituberculous treatment requires careful monitoring for drug interactions and toxicity, especially if the patient is on HAART. Interactions such as those between the rifamycins and protease inhibitors or non-nucleoside reverse transcriptase inhibitors can lead to lower efficacy or increased toxicity of the anti-retroviral regimen.<sup>4</sup>

\*\*\*Cryptococcal infection presents either as a primary lung infection or as part of a disseminated infection with cryptococcaemia, pneumonia, meningitis, and cutaneous disease.<sup>8</sup>

200 cells/mm<sup>3</sup> (in patients not taking PCP prophylaxis or HAART) is estimated to be 18% at 12 months in asymptomatic individuals, rising to 44% in those with early symptomatic disease such as oral candidiasis as in the case described.<sup>14</sup> PCP prophylaxis with co-trimoxazole is recommended when the CD4 count falls to 200 cells/mm<sup>3</sup> or below. Patients with HIV infection on HAART with a CD4 count consistently improved to >200 cells/mm<sup>3</sup> have had PCP primary and secondary prophylaxis stopped without significant risk of subsequent PCP.<sup>15–20</sup>

Methods of diagnosis range from sputum induction to open lung biopsy. The diagnostic test of choice is fiberoptic bronchoscopy with lavage, providing the patient can tolerate the procedure. Transbronchial biopsy is useful but is occasionally complicated by haemorrhage and pneumothorax. Sputum induction with nebulised saline has a lower diagnostic sensitivity and should be carried out in a negative pressure facility. Patients unable to tolerate bronchoscopy should be treated empirically, based on clinical judgement and expert advice, as was the case here. The case discussed was treated with high dose co-trimoxazole and adjuvant high dose steroids, which is the most effective first line treatment for severe PCP. Table 2 describes first and second line treatment for PCP in mild to moderate and severe disease. Second line treatment should be used for patients intolerant of or who have not responded to co-trimoxazole. The optimal dose of steroid and preferred second line treatment has yet to be determined.

The deterioration on day 9 was probably secondary to hospital acquired pneumonia and the patient was started on appropriate antibiotic treatment for this. He was also started on intravenous gancyclovir. The role of CMV infection during PCP is controversial and difficult to evaluate. Studies carried out before the introduction of adjuvant corticosteroid treatment in severe PCP concluded that CMV co-infection did not influence the outcome of PCP.<sup>22–23</sup> A more recent study showed that culture of CMV in the lavage of patients receiving adjuvant corticosteroid treatment was, independently of CD4 count, associated with a 2.7-fold increased risk of death.<sup>9</sup> Based on these findings, it has been proposed that survival rates for patients with severe PCP might be improved with anti-CMV therapy. The use of corticosteroids has also been related to the subsequent develop-

ment of CMV retinitis and colitis in HIV infected patients.<sup>24</sup> Furthermore, in vitro studies have shown increased CMV replication in corticosteroid treated macrophages.<sup>25</sup> The mechanisms by which CMV shortens survival of patients on corticosteroid treatment are unknown. Further studies are needed to establish which patients receiving adjuvant corticosteroid therapy for severe PCP would benefit from treatment with foscarnet or gancyclovir.

#### ***Pneumocystis carinii* pneumonia (PCP) and respiratory support on HDU/ICU**

Survival after a diagnosis of PCP has improved in recent years. Among 4412 patients in the USA with 5222 episodes of PCP during follow up (1992–1998), 12 month survival increased from 40% in 1992–3 to 63% in 1996–8. Early death was associated with a history of PCP, age >45 years, and CD4 count <50 cells/mm<sup>3</sup>.<sup>26</sup> A recent study of 169 admissions of HIV positive individuals to the ICU found respiratory failure to be the most common reason for admission (38%).<sup>12</sup> PCP is the most common cause of respiratory failure leading to ICU admission in HIV infected individuals.<sup>4–10–13</sup>

Outcomes of mechanical ventilation for respiratory failure from PCP have changed since the start of the HIV epidemic.<sup>27</sup> Before 1985 a hospital mortality of about 80% was described in this group.<sup>28–30</sup> Table 3 shows a mortality rate for ventilated HIV positive patients with PCP from 1985 to 1997 of 50–79%. These changes are difficult to compare because of changing trends over the periods of studies, including the introduction of HAART and changes in the subgroup of patients with PCP progressing to mechanical ventilation on the ICU. Nevertheless, there appears to be an overall improvement in ICU survival. Furthermore, changes with respect to PCP prophylaxis and the use of adjunctive corticosteroids have yielded an overall improvement for HIV positive patients. PCP prophylaxis has resulted in fewer episodes of PCP, and the use of adjunctive corticosteroids has resulted in a smaller proportion of patients with PCP progressing to mechanical ventilation.<sup>35–39</sup>

A French study of 110 cases of PCP requiring intensive care between 1989 and 1994 showed a 3 month mortality rate of 34.6% and 1 year survival estimated at 47%. Most patients

**Table 2** Treatment of *Pneumocystis carinii* pneumonia (PCP)<sup>14 21</sup>

Drug**	Duration of treatment	Side effects	Comments
<i>First line treatment</i>			
*Co-trimoxazole 120 mg/kg daily in 2–4 divided doses po/iv (480mg co-trimoxazole consists of sulfamethoxazole 400 mg and trimethoprim 80 mg)	21 days	Nausea, vomiting, fever, rash (including Stevens-Johnson's syndrome, toxic epidermal necrolysis, photosensitivity), blood disorders (including neutropenia, thrombocytopenia, rarely agranulocytosis and purpura), rarely allergic reactions, diarrhoea, glossitis, stomatitis, anorexia, arthralgia, myalgia, liver damage, pancreatitis, antibiotic associated colitis, eosinophilia, aseptic meningitis, headache, depression, convulsions, ataxia, tinnitus, megaloblastic anaemia due to trimethoprim, crystaluria, renal disorders including interstitial nephritis	Intolerance common. Initial treatment with iv preparation. Comes in ampoule containing 480 mg; these should be diluted in at least 75 ml of 5% dextrose. Infuse over 60 minutes
Severe disease: *Adjuvant high dose steroids (e.g. prednisolone 40–80 mg daily po. Alternatively, hydrocortisone may be given iv)	5 days; reduce dose over 14–21 days		Indicated in severe disease. Optimal dose not determined. Consult HIV specialist for advice
<i>Second line treatment</i>			
Mild to moderate disease:			
*Trimethoprim 20 mg/kg/day po/iv in 2–3 divided doses and dapsone 100 mg po daily	21 days	Trimethoprim: gastro intestinal disturbance, pruritus, rash, depression of haematopoiesis; rarely erythema multiforme, toxic epidermal necrolysis; aseptic meningitis Dapsone: haemolysis, methaemoglobinaemia, neuropathy, allergic dermatitis, anorexia, nausea, vomiting, insomnia, psychosis, agranulocytosis; dapsone syndrome (rash with fever and eosinophilia) - stop immediately (may progress to exfoliative dermatitis, hepatitis, hypalbuminaemia, psychosis and death)	Avoid in G6PD deficiency
*Clindamycin 600 mg 6 hourly po/iv and primaquine 15 mg daily po	21 days	Clindamycin: diarrhoea, nausea and vomiting; jaundice, abnormal liver function tests; neutropenia, eosinophilia, agranulocytosis and thrombocytopenia; rash Primaquine: nausea and vomiting, abdominal pain; methaemoglobinaemia, haemolytic anaemia.	<i>Clostridium difficile</i> toxin associated diarrhoea is a complication of clindamycin therapy Primaquine: caution in G6PD deficiency
Atovaquone suspension 750 mg twice daily	21 days	Nausea, vomiting and diarrhoea; headache, insomnia; rash, fever; elevated liver enzymes and amylase; anaemia, neutropenia; hyponatraemia	Consider combination with iv pentamidine as resistance reported with monotherapy
Severe disease: *Pentamidine isethionate 4 mg/kg/day as a slow intravenous infusion	21 days	Severe reactions, sometimes fatal, due to hypotension, hypoglycaemia, pancreatitis and arrhythmias; also leucopenia, thrombocytopenia, acute renal failure, hypocalcaemia; also reported azotaemia, abnormal liver function tests, anaemia, hyperkalaemia, nausea and vomiting, dizziness, syncope, flushing, hyperglycaemia, rash, taste disturbance; Stevens-Johnson's syndrome reported; on inhalation, bronchoconstriction, cough, shortness of breath and wheeze; discomfort, pain, induration, abscess formation, and muscle necrosis at injection site.	Give over at least 1 hour with patient lying flat. Monitor blood pressure closely. Important side effects include severe hypotension and hypoglycaemia. Monitor BMstix during and after infusion for 12 hours. If changing from co-trimoxazole to pentamidine due to poor clinical response, continue co-trimoxazole for 3 days. If intolerant, give nebulised pentamidine 600 mg daily for first 3 days.
*Trimetrexate 45 mg/m <sup>2</sup> iv and folinic acid 80 mg/m <sup>2</sup>	21 days	Blood disorders (thrombocytopenia, granulocytopenia and anaemia); diarrhoea and vomiting, oral and gastrointestinal mucosal ulceration; fever; confusion, rarely seizures; disturbed liver function tests, plasma calcium, potassium and magnesium reported; rash, anaphylaxis and local irritation at the injection site.	Used as an alternative for patients intolerant of co-trimoxazole and pentamidine isethionate or who do not respond to these drugs. Trimetrexate is a potent dihydrofolate reductase inhibitor and must be give with calcium folinate. Administer calcium folinate during treatment and for 72 hours after last dose (to avoid potentially serious bone marrow suppression, oral and gastrointestinal ulceration, and renal and hepatic dysfunction); suspend myelosuppressive drugs (e.g. zidovudine)

po=by mouth; iv=intravenously.

\* Consult HIV specialist for advice.

\*\*Treatment of PCP infections should be undertaken where facilities for appropriate monitoring are available; consult a microbiologist/HIV specialist and the product literature before administering these drugs.

**Table 3** ICU admission, mechanical ventilation, and mortality in episodes of HIV related *Pneumocystis carinii* pneumonia (PCP) studied between 1985 and 1997

HIV related PCP episodes studied (n)	Country of study	Period of study	% of patients admitted to ICU	% of patients requiring mechanical ventilation	Mortality (%) of patients mechanically ventilated	Reference
348	USA	1985–89	6.3	5.7	60	31
2174	USA	1987–90	18	*	62–46**	32
110	France	1989–94	100***	31	79	33
257	USA	1990–95	8.2	4.7	50	31
1660	USA	1995–97	14	9	62	34

\*Data not available.

\*\*Episodes were stratified into patients receiving care in an ICU with (first figure) or without (second figure) a prior AIDS defining illness. Data relating to mechanical ventilation status not available for this study.

\*\*\*This study was limited to ICU admissions.

**Table 4** Prognostic markers significantly associated with mortality in ICU admissions of HIV positive patients with *Pneumocystis carinii* pneumonia (PCP) requiring mechanical ventilation

HIV related PCP episodes studied (n)	Period of study	Prognostic markers associated with ICU mortality*	Reference
110	1989–94	Respiratory status deterioration requiring delayed mechanical ventilation; mechanical ventilation for 5 days or more; nosocomial infection, pneumothorax	33
48*	1993–96	Low CD4 cell count within 2 weeks of admission**	40
176	1990–99	Low CD4 cell count; prior PCP prophylaxis, CMV in BAL fluid, age, initial anti-PCP therapy	9
155	1995–97	Prior PCP prophylaxis	34
21	1993–98	High APACHE II score >17, low serum albumin <25 g/l, ARDS, low CD4 cell count <150 cells/mm <sup>3</sup> , arterial pH <7.35	42

\*Rows cannot be directly compared since studies considered different sets of variables. In most of the studies shown here a low CD4 cell count is taken to mean <200 cells/mm<sup>3</sup>.

\*\*This study was limited to patients with CD4 count <200 cells/mm<sup>3</sup> and on ICU with mechanical ventilation. Mortality varied significantly depending on CD4 counts: >100 cells/mm<sup>3</sup>, 25%; 51–100 cells/mm<sup>3</sup>, 50%; 11–50 cells/mm<sup>3</sup>, 88%; 0–10 cells/mm<sup>3</sup>, 100%.

only required CPAP support. One third required mechanical ventilation and, of those, 79% died.<sup>33</sup> In another study in 1995–7 of 1660 patients with PCP only 9% required mechanical ventilation and the hospital mortality rate was 62%.<sup>34</sup> A study covering the period 1993–6 correlated CD4 lymphocyte count and mortality in AIDS patients requiring mechanical ventilation due to PCP. Mortality increased from 25% for patients with CD4 cell counts >100 cells/mm<sup>3</sup> to 100% in those with CD4 counts <10 cells/mm<sup>3</sup>.<sup>40</sup> A prospective study of 176 HIV positive patients with PCP identified PCP prophylaxis as predictive of progression to death, other factors being age, one or more episodes of PCP, treatment other than cotrimoxazole, and isolation of CMV from the BAL fluid.<sup>9</sup>

Attempts have been made to use staging systems to predict inpatient mortality from HIV associated PCP since the introduction of PCP prophylaxis and HAART. One such system generated from data relating to 1660 cases of PCP diagnosed between 1995 and 1997 identified an ordered five category staging system based on three predictors: wasting, alveolar-arterial oxygen gradient, and serum albumin level. The mortality rate increased with stage, ranging from 3.7% for stage 1 to 49.1% for stage 5.<sup>41</sup> The prognostic markers identified are summarised in table 4.

#### Impact of early HAART

Since 1996 HAART has had an enormous impact on the natural history of HIV infection. HAART usually involves triple therapy with two nucleoside reverse transcriptase inhibitors and either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. During the first 2 years of the widespread application of HAART there was a reduction in HIV related mortality, although this has since levelled out.<sup>1, 2, 43</sup> There are problems with adherence, pharmacology, and toxicity, but 50–90% of patients on HAART achieve sustained suppression of the virus and most patients show low persistent

viral replication. Unfortunately, the viral mutation rate is such that viral genomes with each possible nucleotide substitution can be generated daily in an infected host, making the speed with which drug resistant HIV mutants can arise extremely rapid.<sup>43</sup> This has led to predictions that about half of all patients may develop resistance to current treatments.<sup>43, 44</sup>

The success of HAART has led to a reappraisal of the role of prophylaxis for opportunistic infections such as PCP, CMV, and *M avium*. This is due to the decreased risk of opportunistic infections in the face of a reduced viral load and sustained or increased CD4 T cell levels, and because of problems of drug interactions between HAART and prophylactic therapies.<sup>4, 15–20, 45–48</sup> The Adult/Adolescent Spectrum of HIV Disease Cohort Study showed a decrease of 55% in opportunistic infections including PCP, CMV, and *M avium* between 1992 and 1997.<sup>49</sup> The EuroSIDA study (a prospective study involving about 7300 patients) looked at the risk of opportunistic infections or death for patients on HAART. Patients with CD4 counts that consistently rose from <200 cells/mm<sup>3</sup> to >200 cells/mm<sup>3</sup> on HAART were substantially protected against opportunistic infections compared with patients with CD4 counts persistently below 50 cells/mm<sup>3</sup> (3.7–8.1 v 72.9 episodes per patient year).<sup>50</sup> There is evidence to suggest that HAART is associated with improved early survival from PCP (odds ratio 0.2).<sup>26</sup> Patients with bacterial pneumonia or PCP were admitted to the ICU less frequently following the introduction of HAART in 1996.<sup>31</sup> The optimal timing for the introduction of HAART in patients with PCP is not known. Cases of severe acute respiratory failure have been described following the early introduction of HAART (1–16 days after the diagnosis of PCP) who recovered after HAART interruption or steroid reintroduction.<sup>51</sup> This phenomenon could be due to rapid recruitment of competent inflammatory cells responding to persistent *P carinii* cysts.



## CONCLUSION

Many studies have tried to identify prognostic markers for the survival of HIV infected patients admitted to the ICU, with relatively little consensus. The strongest single indicator seems to be the CD4 count. Identifying objective outcome predictors will help clinicians to decide when to pursue aggressive treatment and when to withhold or withdraw it. The mortality rate of HIV infected patients admitted to the ICU has improved and probably reflects improved outcome of HIV infection in general with the introduction of PCP prophylaxis, adjunctive corticosteroid use in the treatment of PCP, and HAART. For selected cases, ICU care of HIV infected individuals with respiratory failure secondary to pneumonia is associated with a positive outcome. HIV and intensive care physicians need to work in close collaboration to deliver optimal care.

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