25. HIV and Pulmonary Diseases

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The spectrum of lung diseases in HIV-infected patients encompasses complications typical for HIV such as tuberculosis, bacterial pneumonia, lymphomas and HIV-associated pulmonary hypertension, but also includes typical everyday pulmonary problems like acute bronchitis, asthma, COPD and bronchial carcinomas (Table 1). Classical diseases such as PCP have become rarer as a result of HAART and chemoprophylaxis, so that other complications are on the increase (Grubb 2006). None other than acute bronchitis is the most common cause of pulmonary problems in HIV patients (Wallace 1997). However, particularly in patients with advanced immune deficiency, it is vital to take all differential diagnoses into consideration. Anamnestic and clinical appearance are often essential clues when it comes to telling the difference between the banal and the dangerous.

<table>
<thead>
<tr>
<th>Infections</th>
<th>Neoplasia</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>Pneumocystis jiroveci</td>
<td>Kaposi sarcoma</td>
<td>Lymphocytic interstitial pneumonia</td>
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<tr>
<td>Bacterial pneumonia</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Non-specific interstitial pneumonia</td>
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<tr>
<td>S. pneumoniae</td>
<td>Hodgkin’s lymphoma</td>
<td>Pulmonary hypertension</td>
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<td>S. aureus</td>
<td>Bronchial carcinoma</td>
<td>COPD</td>
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<td>H. influenzae</td>
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<td>Bronchial hyperreactivity</td>
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<td>B. catarrhalis</td>
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<td>P. aeruginosa</td>
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<td>Rhodococcus equi</td>
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<td>Nocardia asteroides</td>
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<tr>
<td>Mycobacteria</td>
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<tr>
<td>M. tuberculosis</td>
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<tr>
<td>Atypical mycobacteria</td>
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<tr>
<td>Other</td>
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<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Aspergillus spp.</td>
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<td>Cryptococcus neoform.</td>
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<td>Histoplasma capsulatum</td>
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<tr>
<td>Toxoplasma gondii</td>
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</tbody>
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This chapter presents an outline of differential diagnoses in patients with respiratory complaints. PCP, mycobacterioses and pulmonary hypertension are covered in detail in chapters elsewhere.
Anamnesis

What are the previous illnesses of the patient?
Someone who has suffered from a PCP once is at a higher risk of having another one. A patient with hyperlipidaemia and carotid stenosis might have coronary heart disease.

What medication does the patient take?
Taking cotrimoxazol regularly makes a PCP unlikely, and the risk of bacterial pneumonia may also be reduced (Beck 2001). In the case of PCP prophylaxis with Pentamidine inhalation, however, atypical, often apically pronounced manifestations of a PCP are to be expected.

Has the patient recently started HAART?
Particularly HAART can induce pulmonary problems:
During a newly begun course of treatment with abacavir, asthma could also be due to hypersensitivity. Dyspnea (13 %), cough (27 %) and pharyngitis (13 %) are common symptoms (Keiser 2003). Some patients even develop pulmonary infiltrates.
T-20 seems to increase the risk of bacterial pneumonia, at least among smokers.
Dyspnea and tachypnea are also seen in lactic acidosis secondary to nuke therapy.
In addition, pulmonary symptoms after institution of HAART might result from the Immune Reconstitution and Inflammatory Syndrome (IRIS). The list of etiologies includes a number of infective and non-infective causes (Grubb 2006). Low CD4+ T-cell count and high viral load are risk factors. In a retrospective analysis, IRIS was seen in 30 % of patients with TB, atypical mycobacteriosis and cryptococcosis (Shelburn 2005).

Does the patient smoke?
Although smoking is more harmful to HIV-positive than to HIV-negative persons, it is still more common among HIV-positives (Royce 1990). All HIV-associated and HIV-independent pulmonary diseases are more common in smokers than in non-smokers. This starts with bacterial pneumonia and PCP, but also applies to asthma, COPD and pulmonary carcinomas (Hirschtick 1996). Smoking promotes the formation of a local immune deficit in the pulmonary compartment: it reduces the number of alveolar CD4+ cells and the production of important pro-inflammatory cytokines such as IL-1 and TNF-α (Wewers 1998). Furthermore, smoking suppresses the phagocytosis capacity of alveolar macrophages. This effect is more pronounced in HIV patients than in HIV-negative patients. HIV infection itself, however, does not seem to have any direct influence on the capability for bacterial killing (Elssner 2004).
Motivating the patient to restrict nicotine intake is thus an important medical task, particularly in HIV consultation. Strategies which promise success and are supported by the evidence of studies include participation in motivational groups, nicotine substitutes and taking Buproprion, whereby interactions, particularly with Ritonavir, should be taken into consideration.
Where does the patient come from?

Another important question is that of the travelling history and/or the origin of the patient. There are places where disease such as histoplasmosis and coccidiomycosis occur endemically. Histoplasmosis, for example, is more widespread in certain parts of the USA and in Puerto Rico than PCP, while it is rare in Europe. Tuberculosis plays a greater role among immigrants.

How did the patient become infected with HIV?

Intravenous drug users suffer more often from bacterial pneumonia or tuberculosis (Hirschtick 1995). Pulmonary Kaposi’s sarcomas are almost exclusively found in MSM (men who have sex with men).

What are the symptoms?

Occasionally, some valuable information can be gained above the more uniform symptoms such as coughing and shortness of breath, which might be useful for differentiation between PCP and bacterial pneumonia. Thus, for example, it is typical for the onset of bacterial pneumonia to be more acute. Patients usually go to the doctor after only 3-5 days of discomfort, whereas patients with PCP suffer from symptoms for an average of 28 days (Kovasc 1984). PCP patients typically have dyspnea and a non-productive cough. A large quantity of discoloured sputum is more likely to indicate a bacterial cause or a combination of infections.

What does the chest X-ray look like?

Table 2: Chest X-ray findings and differential diagnosis

<table>
<thead>
<tr>
<th>Chest X-ray</th>
<th>Typical differential diagnosis</th>
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</thead>
<tbody>
<tr>
<td>Without pathological findings</td>
<td>PCP, asthma, KS of the trachea</td>
</tr>
<tr>
<td>Focal infiltrates</td>
<td>Bacterial pneumonia, mycobacteriosis, lymphoma, fungi</td>
</tr>
<tr>
<td>Multifocal infiltrates</td>
<td>Bacterial pneumonia, mycobacteriosis, PCP, KS</td>
</tr>
<tr>
<td>Diffuse infiltrates</td>
<td>PCP (centrally pronounced), CMV, KS, LIP, cardiac insufficiency, fungi</td>
</tr>
<tr>
<td>Miliary image</td>
<td>Mycobacteriosis, fungi</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>PCP</td>
</tr>
<tr>
<td>Cavernous lesions</td>
<td>Mycobacteriosis (CD4 &gt;200), bacterial abcess (Staph., Pseudomonas)</td>
</tr>
<tr>
<td>Cystic lesions</td>
<td>PCP, fungi</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Bacterial pneumonia, mycobacteriosis, KS, lymphoma, cardiac insufficiency</td>
</tr>
<tr>
<td>Bihilar lymphadenopathy</td>
<td>Mycobacteriosis, KS, sarcoidosis</td>
</tr>
</tbody>
</table>

The most important question: What is the immune status?

The number of CD4+ T-cells provides an excellent indication of the individual risk of a patient to suffer from specific opportunistic infections. More important than the nadir is the current CD4+ T-cell count. In patients with more than 200/µl, infection with typical opportunistic HIV-associated diseases is very unlikely. Here, as with HIV-negative patients, one generally tends to expect more „normal“ problems like acute bronchitis and bacterial pneumonia. However, tuberculosis should always be considered. Although the risk of becoming infected with tuberculosis grows along
with increasing immunodeficiency, more than half of all tuberculosis infections in
HIV patients occur at a CD4+ T-cell count of above 200/µl (Lange 2004, Wood
2000).

At less than 200 CD4+ T-cells/µl, PCP and, more rarely, pneumonia/pneumonitis
with cryptococci, occurs. At this stage too, however, bacterial pneumonia is the
most common pulmonary disease overall.

Below 100 CD4+ T-cells/µl, there is an increase in the number of pulmonary Ka-
posi sarcomas and toxoplasma gondii infections. At a cell count of under 50/µl,
infections with endemic fungi (histoplasma capsulatum, Coccioidioides immitis),
non-endemic fungi (Aspergillus, Candida species), atypical mycobacteria and dif-
ferent viruses (mostly CMV) occur. Especially in patients with advanced immuno-
deficiency, it must be remembered that pulmonary illness may only represent an
organ manifestation of a systemic infection. Rapid, invasive diagnostic procedure is
thus advisable in such patients.

**Pulmonary complications**

**Bacterial pneumonia**

Bacterial pneumonia occurs more often in HIV-positive than in HIV-negative pa-
tients, and, like PCP, leaves scars in the lung. This often results in a restriction of
pulmonary function which goes on for years (Alison 2000). Although bacterial
pneumonia occurs in the early stages of HIV infection, the risk grows along with
increasing immunosuppression. A case of bacterial pneumonia significantly wors-
ens the long-term prognosis of the patient (Osmond 1999). Thus, contracting bacte-
rial pneumonia more than once a year is regarded as AIDS defining. The introd-
uction of HAART went hand in hand with a significant reduction in the occurrence of
bacterial pneumonia (Jeffrey 2000).

Clinically and prognostically speaking, there is no great difference between bacte-
rial pneumonia in HIV-infected patients and pneumonia in an immunocompetent
host. However, the HIV-patient more often presents with less symptoms and a
normal leucocyte count (Feldman 1999). Etiologically, pneumococci and haemo-
philus infections are most common. In comparison with immunocompetent pa-
tients, infections with Staphylococcus aureus, Branhamella catarrhalis, and in the
later stages (< 100 CD4+ T-cells/µl) Pseudomonas spp. occur more often. In the
case of slow-growing, cavitating infiltrates, there is also the possibility of rare
pathogens such as Rhodococcus equi and nocardiosis. Polymicrobial infections and
co-infections with Pneumocystis jiroveci are common (10-30 %), which makes
clinical assessment difficult (Miller 1994).

What is also important for the risk stratification of the patient, in addition to the
usual criteria (pO2, extent of infiltrate, effusion, circulatory condition, extrapulmo-
nary involvement and confusion of the patient) is the CD4+ T-cell count. The
mortality of patients with < 100 cells/µl is increased more than sixfold. Therefore it
probably makes sense when dealing with patients with a pronounced immune de-
fect not to rely on the risk scores validated for immunocompetent patients and to
admit apparently less severely ill patients to the hospital for treatment (Cordero
2000).
Should there be no suspicion of mycobacteriosis, a calculated antibacterial treatment of patients with a CD4+ T-cell count of > 200/µl with medication effective against *S. pneumoniae*, *H. influenzae* und *S. aureus* is indicated. However, there are no controlled studies available to support this. In accordance with recommended therapies for community acquired pneumonia with co-morbidity, the prescription of a Group 2 Cephalosporin such as Cefuroxim or group 3a such as Cefotaxim/Ceftriaxon, or an aminopenicillin with betalactamase inhibitor (Ampicillin/Sulbactam or Amoxicillin/clavulanic acid, e.g. Augmentan™ 875/125 mg, twice daily) can be recommended. In the case of regionally increased incidence of legionella infection, combination with a macrolide is advisable (e.g. Klacid™ 500 mg twice daily). Once positive culture results have been obtained, the patient should receive further specific treatment. With advanced immunodeficiency (CD4+ T-cells < 200/µl), primary consideration should be given to bronchoscopic diagnostics, due to the broader spectrum of pathogens (Dalhoff 2002). In patients with a high risk of pseudomonas infection (low CD4 count, nosocomial infection, sepsis) initial therapy should include antibiotics active against pseudomonas.

Pneumococcus vaccination is recommended. At a CD4+ T-cell count lower than 200/µl, however, there is no proof of vaccination benefit. Due to the frequency of secondary bacterial infections, an annual influenza vaccination is also advisable.

**Which diagnostic strategy makes sense with pulmonary infiltrates?**

The intensity of the diagnostic workup in a patient with pulmonary infiltrates is based on the HIV stage and the expected spectrum of pathogens. With a CD4+ T-cell count of > 200/µl, non-invasive basic diagnostics and a calculated antibiotic therapy are justified. This basic diagnostic investigation includes taking two blood cultures and a microscopic and cultural sputum examination. The bacteremia rate seems to be higher than in immunocompetent patients (Miller 1994). The main value of sputum culture is the demarcation of mycobacterial and aspergillus infec-

In individual cases the possibility of antigen detection in the urine should be considered (e.g. pneumococcus, legionella, cryptococcus, histoplasma). The determination of the cryptococcus antigen in serum has a high predictive value for the detection of invasive cryptoccocosis (Saag 2000). A chest CT is sometimes helpful in the diagnostic workup (high-resolution CT, HR-CT). A PCP, for example, might be depicted in an HR-CT, but might be missed in a conventional chest X-ray.

In advanced stages (< 200 CD4+ T-cells/µl), bronchoscopic investigation is primarily recommended (Dalhoff 2002). The diagnostic success rate of a bronchoscopy in HIV-infected patients with pulmonary infiltrates is 55-70 % and rises to 89-90 % when all techniques including the transbronchial biopsy are combined (Cad-ranel 1995). The sensitivity of a bronchoalveolar lavage (BAL) amounts to 60-70 % in bacterial pneumonia (patients without previous antibiotic treatment), and 85-100 % in PCP (Baughman 1994). Due to the high sensitivity of the BAL, transbronchial biopsy with possible complications is only recommended in the diagnosis of PCP if there is a negative initial diagnostic workup and in patients taking chemoprophy- laxis (Dalhoff 2002). If invasive pulmonary aspergillosis or CMV is considered, a transbronchial biopsy should be the preferred method in order to differentiate be-
tween colonisation and tissue invasion. Surgical open biopsies and CT-controlled trans-thoracic pulmonary biopsies are rarely necessary.

**Asthma bronchiale**

One would think that an immunosuppressing disease like HIV infection would at least protect patients from manifestations of exaggerated immune reaction such as allergies and asthma. However, the opposite is the case: in a study from Canada concerning HIV-infected men, more than 50% had suffered an episode of wheezing within the previous 12 months, and nearly half of those showed evidence of bronchial hyperreactivity. These findings were particularly distinct among smokers (Poirier 2001). As the disease progresses, it probably comes to an imbalance between too few „good“ TH1 cells producing interferon and Interleukin 2, and too many „allergy-mediating“ TH2 cells with an increased total IgE. In cases of unclear coughing, dyspnoea or recurrent bronchitis, the possibility of bronchial hyperreactivity, asthma or emphysema should be kept in mind.

**Emphysema**

Smokers with HIV infection develop pulmonary emphysema more often than non-infected smokers. It is possible that a pathogenetic synergy arises from smoking and the pulmonary infiltration with cytotoxic T-cells due to HIV infection (Diaz 2000). Smoking crack increases the risk of pulmonary emphysema even more. Here, it seems that superficial epithelial and mucosal structures are destroyed (Fliegil 1997). Furthermore, cocaine can lead to unusual manifestations with pneumothorax or alveolar infiltrates.

**Lymphoid interstitial pneumonia (LIP):**

LIP is a form of pneumonia which takes a chronic or subacute course and is extremely rare in adults. Radiologically, its reticulonodular pattern makes it similar to PCP. This illness occurs paraneoplastic, rarely, idiopathic and as in HIV and EBV disease parainfectious. In contrast to PCP, patients with LIP usually have a CD4+ T-cell count of > 200/µl and normal LDH values. A CD8-dominated lymphocytic alveolitis with no pathogen detection is characteristic. Definite diagnosis often calls for an open pulmonary biopsy. LIP is considered sensitive to steroids. The role played by HAART is unclear, especially as LIP has occasionally been observed in the context of immune reconstitution during HAART.

**Bronchial carcinoma**

HIV patients are at considerably higher risk of bronchial carcinoma. A retrospective analysis covering 8,400 patients from the years 1986-2001 showed an eightfold increased incidence of bronchial carcinoma in the period after 1996 than that for the normal smoking population. Interestingly, the majority of bronchial carcinomas are, histologically, adenocarcinomas, which results in discussion of whether HIV infection itself leads to a genetic instability (Bower 2003). Patients with bronchial carcinomas and HIV are younger, the disease is often more advanced at presentation and takes a more aggressive course than in HIV-negative patients (White 1996, Karp 1993). Whether to treat with chemotherapy, and what kind, has to be decided for
each case individually. A small cohort study has shown that HIV-infected patients with advanced bronchial carcinoma have a similarly bad prognosis to that of HIV negative patients, regardless of immune status during HAART and chemotherapy (Powles 2003).

**Less common opportunistic infections**

The detection of CMV in BAL repeatedly gives rise to discussion regarding clinical relevance. Seroprevalence is high (90%), and colonisation of the respiratory tract is common. CMV pneumonia is the primary reason for 3.5% of pulmonary infiltrates in AIDS patients. The significance of the pathogen in the later stages may well be underestimated, since histological examination of autopsy material showed pulmonary CMV infections in up to 17% (Afessa 1998, Waxman 1997). Regarding invasive pulmonary aspergillosis, which only occurs in the late stages and usually in conjunction with additional risk factors such as neutropenia or steroid therapy (Mylonakis 1998), please refer to the OI-Chapter.

**References**