

A persistent challenge: the diagnosis of respiratory disease in the non-AIDS immunocompromised host

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The diagnostic and therapeutic approach to respiratory disease in the immunocompromised host remains a challenge for several reasons: (1) the current increase in both the number of immunocompromised hosts and their length of survival; (2) the high frequency of lung disease in these patients,^{1–3} and (3) the severity of these lung diseases.^{3–5} A good example is given in a recent review by Paterson *et al* of the epidemiology of invasive aspergillosis in transplant recipients.⁵ The incidence of this opportunistic infection, which mainly affects the lung, varies from 1% in kidney recipients to 9% in lung recipients (with 2% in liver recipients and 7% in bone marrow recipients). In this population it has a mortality rate of 55–92% and accounts for 10–15% of deaths of all transplant recipients.

What new data are available on the diagnostic and therapeutic approach?

IS THERE AN EVOLUTION IN THE TYPE AND SEVERITY OF THE UNDERLYING IMMUNODEFICIENCIES?

The data from the literature clearly show the continuous changes both in the indications for immunosuppressive treatment and in the nature and dosages of the immunosuppressive drugs used. For example, steroids are increasingly used in patients with chronic lung disease such as lung cancer, chronic obstructive lung disease, idiopathic pulmonary fibrosis, or sarcoidosis⁶; the use of combined treatment for solid tumours—for example, chemotherapy and thoracic radiotherapy for lung cancer⁷ or intensive chemotherapy combined with total body irradiation, transplantation of autologous bone marrow, and 13-cis-retinoic acid for neuroblastoma⁸; and the performance of solid organ transplantations for lung, liver, cardiac or kidney complications following bone marrow transplantation or the performance of bone marrow transplantation for aplastic anaemia or haematological malignancies following solid organ transplantation.⁹

ARE THERE NEW CAUSES OR NEW CLINICAL FEATURES IN OLD CAUSES OF RESPIRATORY DISORDERS?

There are numerous reports in the literature of new drug induced pneumonitis^{10 11} or new pneumonia in the immunocompromised host. Fatal acute respiratory failure following the

sequential administration of dacarbazine and fotemustine,¹² adult respiratory distress syndrome (ARDS) resulting from treatment with gemcitabine,¹³ and diffuse alveolar haemorrhage with underlying pulmonary capillaritis due to the use of all-trans retinoic acid¹⁴ are three striking examples of new drug induced pneumonitis. Respiratory syncytial virus pneumonia in adult patients with leukaemia,¹⁵ pneumonia due to *Mycobacterium xenopi*, *Mycobacterium fortuitum* or *Mycobacterium chelonae* in children with leukaemia,¹⁶ and *Scedosporium apiospermum* pneumonia in children with chronic granulomatous disease¹⁷ are several examples of new pneumonia or of pneumonia reported in new populations of immunocompromised hosts.

Even if most new clinical features in the immunocompromised host—for example, cytomegalovirus induced alveolar haemorrhage¹⁸ and atypical presentation of tuberculosis¹⁹—have mainly been reported in patients with AIDS, they have also been observed in non-AIDS immunocompromised subjects. For example, the development of a migratory organising pneumonitis has been reported following unilateral radiation therapy for breast carcinoma which clearly differs from radiation pneumonitis.²⁰

DOES THE CLINICIAN HAVE NEW DIAGNOSTIC PROCEDURES AND NEW LABORATORY TESTS AT HIS/HER DISPOSAL?

In the 1980s the diagnostic and therapeutic approach was limited to empirical treatment or open lung biopsy.²¹ Today the clinician has at his/her disposal a number of diagnostic procedures including: (1) non-invasive procedures such as computed tomographic (CT) scanning, radionuclide scanning, pulmonary function tests, expectorated or induced sputum, and therapeutic testing with antibiotics in cases of probable bacterial pneumonia; (2) collection of extrapulmonary specimens such as blood or urine samples or nasopharyngeal washings or swabs; (3) performance of fiberoptic bronchoscopy with protected bronchial brushing (PBB) and bronchoalveolar lavage (BAL); and (4) more invasive procedures such as transbronchial biopsy (TBB), percutaneous needle aspiration or biopsy, open lung biopsy (OLB), and videothorascopic biopsy.

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Similarly, the microbiologist may still use classical techniques such as direct examination, tinctorial stains, immunofluorescence stains, serological examination or routine cultures, but he also has at his disposal new techniques such as antigen detection (for example, for *Aspergillus* spp, *Cryptococcus neoformans*, or *Histoplasma capsulatum* in serum or BAL fluid and for *Legionella pneumophila* serotype 1 in urine²²⁻²⁵); new antibody detection (for example, antipneumolysin detection for pneumococcal pneumonia); special methods of culture (for example, BACTEC radiometric culture for mycobacteria); and procedures using nucleic acid detection such as polymerase chain reaction (PCR).²⁶⁻²⁸ Indeed, recent studies have used PCR to detect *Pneumocystis carinii* in BAL fluid, sputum, blood and saliva,^{29, 30} *Toxoplasma gondii* in BAL fluid and cerebrospinal fluid (CSF),³¹ cytomegalovirus in BAL fluid, CSF and blood,^{32, 33} *Mycobacterium tuberculosis* in BAL fluid, sputum and blood,³⁴ *Aspergillus* spp in BAL fluid,³⁵ and *Chlamydia pneumoniae* in BAL fluid in the immunocompromised host.³⁶

CONSEQUENCE OF THIS EVOLUTION: THE NEED TO RETURN TO CLINICAL ANALYSIS

The practical consequence of this great diversity of new available diagnostic and laboratory procedures is a need for the clinician to return to a strict analysis of the clinical and radiological data in each case. Indeed, not all these new procedures can be used for each immunocompromised host. In each case the clinician must formulate one or more pertinent hypotheses and determine the best type of specimen to submit and the tests that must be done. As a guideline, Schelhamer *et al* have listed the preferred specimens for direct detection or culture according to the diagnostic hypotheses, and the types of laboratory tests that can be done according to these hypotheses.²⁸

What current changes are there in the diagnostic and therapeutic approach in neutropenic patients?

RANGE OF POSSIBLE CAUSES

Classically, the majority of respiratory disorders in neutropenic patients are caused by bacterial or fungal infections with either pneumonia or ARDS due to sepsis.³⁷ However, in the last 20 years some series have shown that pulmonary oedema, specific localisation of the underlying disease such as blastic infiltration or leucostasis,^{38, 39} opportunistic pneumonia resulting from previous immunoglobulin or T cell defect, alveolar proteinosis resulting from macrophage defects (particularly in cases of myeloid disorder⁴⁰), and alveolar haemorrhage^{41, 42} may also be involved. Finally, lung injury due to drugs such as liposomal amphotericin B,⁴³ cytosine arabinoside,⁴⁴ or all-trans retinoic acid¹⁴ has also been reported.

CLASSICAL APPROACH

Infection remains the main target for the diagnostic and therapeutic approach. Indeed, in neutropenic patients infection rapidly leads to septic shock, ARDS, and death in the absence

of antibiotic treatment. The guidelines therefore recommend that empirical treatment with antibiotics should be started immediately in cases of fever, with or without respiratory symptoms, regardless of the result of chest radiography.⁴⁵⁻⁴⁷ Reliable diagnostic procedures such as transtracheal aspiration, PBB, or BAL may be performed but this should never delay the administration of antibiotics.

In theory, clinical and epidemiological data may help the clinician to select the antibiotics but, in practice, because of the absence of neutrophils, clinical and radiological data are frequently absent or not specific⁴⁸ and the choice of antibiotic relies on the epidemiological data. We have previously reported that 55 of 73 cases (75%) of microbiologically documented pneumonia in neutropenic patients with haematological malignancy were caused by Gram-negative bacilli (n = 22), *Staphylococcus* or *Streptococcus* species (n = 11), or fungi (mainly *Aspergillus* spp (n = 22)) compared with only 11 of 46 cases (24%) in patients treated with haematological malignancy but without neutropenia.⁴⁹ This major difference, also shown by others using reliable diagnostic procedures,⁵⁰⁻⁵² clearly justifies the separation of immunocompromised hosts into those with and those without neutropenia.

In neutropenic patients the first line antibiotics must be active against both Gram negative bacilli and Gram positive cocci.⁴⁵ In cases with an unfavourable course, empirical modifications must take into account *Staphylococcus* spp, nosocomial agents, and also *Aspergillus* spp after seven days of neutropenia, particularly in cases of nodules, with or without cavitations.^{53, 54} However, this exclusively empirical approach may be unsuccessful in some cases and attempts are underway to evaluate the usefulness of three additional diagnostic and therapeutic procedures in such circumstances—namely, CT scans, BAL, and surgery.

INDICATIONS FOR THORACIC CT SCAN

In a recent study by Heussel *et al* a CT scan performed in neutropenic patients with unexplained fever and a normal chest radiograph identified pneumonia in 60% of cases five days before radiological abnormalities were apparent.⁵⁵ In two other studies^{23, 56} the CT scan suggested the diagnosis of invasive aspergillosis by the presence of opacities with a “peripheral halo” at an early stage or an “air crescent formation” at a late stage. Moreover, the CT scan determined precisely the location of the lesions and helped to evaluate the risk of haemoptysis.²³ Thus, CT scanning may be of value in some neutropenic patients, but its usefulness remains to be proved and its indications precisely defined.

INDICATIONS FOR BRONCHOALVEOLAR LAVAGE

In neutropenic patients previous studies have clearly shown the low diagnostic value of sputum examination for a microbiological diagnosis of pneumonia^{48, 51} with the exception of the high positive predictive value of *Aspergillus* in the diagnosis of invasive aspergillosis.^{23, 57}

Recently, Cordonnier *et al* performed BAL in 60 neutropenic patients with an unfavourable course in spite of empirical antibiotics. Surprisingly, no complications occurred. A diagnosis was obtained in 36% of cases by direct examination and in 57% of cases using a combination of methods. The established diagnoses were bacterial pneumonia, aspergillosis, pneumocystosis, cytomegalovirus pneumonia, alveolar haemorrhage, and alveolar proteinosis. Treatment was modified in 46% of cases. However, it should be noted that false negative results were observed in 16% of cases, mainly due to aspergillosis.⁵² Other authors have also used BAL in neutropenic patients without major complications.^{23 53 58 59}

At present, BAL is considered to be of use for the diagnosis of: (1) patients with extensive pneumonia despite recommended empirical therapy, even after addition of vancomycin and amphotericin B, (2) patients with non-resolving pneumonia, even after recovery of neutrophils, and (3) patients with an additional immune defect other than neutropenia and/or with unusual clinical data. For example, we have previously shown that opportunistic pneumonias other than aspergillosis are rarely observed in patients with neutropenia following first induction chemotherapy given for haematological malignancy but, in contrast, they are relatively frequent in patients with neutropenia resulting from consolidation chemotherapy, especially when given for lymphocytic malignancy.⁶⁰

INDICATIONS FOR SURGERY

Lung resection may be performed in patients with clinical, radiological, and biological data highly suggestive of invasive aspergillosis. The results of two recent series^{23 61} suggest that wedge resection or lobectomy may be useful in two situations: (1) a lesion close to a pulmonary vessel with a high risk of massive haemoptysis (in such cases surgery would be indicated even during the neutropenic stage) and (2) a unique residual lesion in a patient for whom another course of chemotherapy would be needed with a high risk of relapse (in such cases surgery would be indicated after recovery of neutrophils).

What current changes are there in the diagnostic and therapeutic approach in the immunocompromised host without neutropenia?

RANGE OF POSSIBLE CAUSES

As with respiratory diseases in neutropenic patients, the range of possible causes in those without neutropenia is very broad but four are mainly encountered: pneumonia, specific localisation of the underlying disease, drug or radiation induced pneumonitis, and pulmonary oedema. In a series of 347 cases of identified respiratory disorders observed in immunocompromised hosts without neutropenia admitted to a respiratory intensive care unit, we found that infection remained the major cause and that non-infectious diseases were also frequently observed, their incidence varying with the underlying immunodeficiency.⁶²

Specific localisation of the underlying disease (23% of cases) was frequently reported in patients treated for collagen vascular disease, haematological malignancy, or solid tumour; treatment induced pneumonitis (13% of cases) mainly occurred in patients treated for haematological malignancy or solid tumour; and pulmonary embolism or oedema (8% of cases) were also found in several groups of patients. Similarly, the field of pathogens responsible for pneumonia was wide and varied according to the underlying immunodeficiency. In our series usual bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Legionella pneumophila* occurred frequently in all the groups of immunocompromised hosts. In contrast, opportunistic agents, which frequently cause respiratory diseases in patients with haematological malignancy or in transplant recipients, were seldom involved in patients with solid tumour.⁴⁹ A low frequency of opportunistic pneumonia⁶³ and a high frequency of pulmonary embolism⁶⁴ in patients treated for solid tumours have also been reported by others. Finally, new drug induced lung diseases continue to emerge—for example, subacute or acute respiratory failure due to the use of nilutamide, recombinant interleukin 2, or lymphokine activated killer cells.¹⁰

CLASSICAL APPROACH

Unlike respiratory diseases in neutropenic patients, there is a considerable range of causes for which the first line or alternative treatments differ. Moreover, in most of these patients receiving immunosuppressive drugs the attitude towards their usual treatment differs according to the cause. An increase may be indicated for specific pulmonary localisation of their underlying disease; a decrease may be indicated for severe infection; a change may be indicated for drug induced pneumonitis; and, finally, adjuvant steroids may be indicated for specific inflammatory pneumonitis such as organising pneumonitis. Consequently, in contrast to the approach in neutropenic patients, an early diagnosis and selective treatment are more appropriate than empirical regimens with the double risk of lack of success and toxicity.

Usually the practical approach consists of four steps: collection of epidemiological, clinical and radiological data, confrontation of these data with those defining schematic reference situations, formulation of diagnostic hypotheses, and selective choice of investigations with the aim of “one diagnosis-one treatment”.^{65 66} In our group, five reference situations have been defined from the retrospective analysis of three parameters collected prospectively: the rate of progression of lung disease, the presence of fever, and the radiographic pattern.⁶²

The first reference situation is defined by a slow progression of the disease, the absence of fever (or mild fever), and diffuse opacities. Pulmonary oedema, pulmonary localisation of the underlying disease, or toxic treatment induced pneumonitis are usually the cause, even if non-specific pneumonitis may also be responsible, particularly in bone marrow transplant

recipients. Non-invasive investigations of choice are echocardiography and CT scanning. Fruitful invasive investigations include bronchoscopy with BAL and, if necessary, lung biopsy.

The second situation, defined by a rapid progression of the condition, fever, and diffuse opacities, usually indicates an opportunistic pneumonia but, in a few cases, a hypersensitivity drug induced pneumonitis (for example, to methotrexate) or a localisation of the underlying disease—for example, in cases of vasculitis or collagen vascular disease—may be the cause. In the absence of new extrapulmonary symptoms, *Pneumocystis carinii* must be considered and induced sputum may be the first line diagnostic procedure. In contrast, the presence of new extrapulmonary symptoms or signs suggests an association or another opportunistic infection such as cytomegalovirus, cryptococcosis, toxoplasmosis, or tuberculosis. Emergency bronchoscopy with BAL should be performed.

In the third situation the clinical feature is that of bacterial pneumonia or sepsis with ARDS. The pathogens responsible are usually *Streptococcus pneumoniae* or *Haemophilus influenzae* and, to a lesser degree, *Legionella* spp. Blood cultures and PBB performed in severe cases enable identification of the pathogen. Emergency treatment including β -lactamin is needed.

The fourth situation with rapid to moderate progression of the condition, fever, nodules or round infiltrates evolving towards dissemination and/or cavitation is highly suggestive of fungal pneumonia. However, legionellosis, tuberculosis and even pulmonary infarction or specific localisation of vasculitis may also result in similar manifestations. A CT scan is useful to characterise and localise the nodules. Bronchoscopy remains the first line diagnostic procedure but percutaneous aspiration or biopsy may be required in cases of peripheral nodules.⁶⁷

The last situation is certainly the most complex. The clinician is confronted with focal pulmonary infiltrates which do not respond to antibiotics. Opportunistic agents such as *Mycobacteria* spp, *Nocardia* spp, or *Rhodococcus equi*, organising pneumonia or tumour may be the cause. In such situations, when no clear diagnosis results from an endoscopic examination with PBB and BAL, a lung biopsy may be required.

LIMITS OF CLASSICAL APPROACH

Although attempts to define reference situations are of practical interest, there are several limits to this approach: (1) any pathogen may produce a variety of radiological features; (2) tuberculosis may be the cause of any clinical and radiological situation; (3) different causes may be associated in any immunocompromised host. Similarly, if fiberoptic bronchoscopy with PBB and BAL remains the cornerstone for a definitive diagnosis of lung infection, there are persistent limits to this diagnostic procedure. Indeed, BAL contributes only indirectly to the diagnosis of treatment induced pneumonitis and does not contribute

to the diagnosis of most pulmonary localisations of the underlying disease. Moreover, the BAL results may mislead the clinician. *Candida* spp,⁶⁸ siderophages,⁴² or cytomegalovirus in AIDS patients⁶⁹ may all be found, even if they are not responsible for the respiratory disease. On the other hand, the BAL results may be negative in cases of aspergillosis, tuberculosis, nocardiosis, or tumour.

Because of the limits of a diagnostic approach based only on clinical analysis and bronchoscopic examination with BAL, attempts are being made to evaluate the usefulness of additional procedures.

WHAT MIGHT BE THE USE OF NEW LABORATORY TESTS ON BAL PRODUCTS?

A first option might be a broader use of new laboratory tests on BAL products. However, the clinical usefulness of most of these tests remains to be shown. Some of them, such as *Cryptococcus* antigen detection or *Toxoplasma gondii* PCR, have a high positive predictive value for the diagnosis of pneumonia but the lung infections concerned are infrequent in non-AIDS immunocompromised subjects.^{24 31} The diagnostic value of other tests is limited to well defined populations—for example, cytomegalovirus PCR for the early diagnosis of cytomegalovirus pneumonia in bone marrow transplant recipients^{32 33} or *Aspergillus* antigen or PCR for the early diagnosis of aspergillosis in neutropenic patients.^{23 35} Finally, the clinical usefulness of most of these new tests depends on the specimen, the technique, and the population studied.²⁶⁻²⁸ For example, *Pneumocystis carinii* PCR might avoid the need for a bronchoscopic examination with BAL when positive on saliva, induced sputum, or blood^{29 30} and might help the clinician to choose the most appropriate treatment when showing resistance associated mutations in patients previously receiving prophylactic treatment,^{70 71} but is of poor diagnostic value when performed on BAL fluid.^{26 28} Similarly, *Mycobacterium tuberculosis* PCR may rapidly identify an acid-fast bacilli found by direct examination or after BACTEC culture,^{26 28} and detect resistance mutations^{72 73} and consequently may help the clinician to choose the most appropriate treatment but is of debatable diagnostic value when performed on BAL fluid,^{26 28} partly because of the poor reliability of results in international collaborative quality studies.⁷⁴ At the present time the indications for most of these new laboratory tests have not been well defined because their sensitivity, specificity, positive and negative values, and cost have not been evaluated in the different populations of immunocompromised hosts.

The other option is a more appropriate use of thoracic CT scanning and lung biopsy specimens.

INDICATIONS FOR CT SCAN

Recent studies have shown that chest radiography alone is of limited diagnostic accuracy for the diagnosis of acute lung disease in the immunocompromised host.⁷⁵ The diagnostic accuracy may be improved by combining it

with clinical data. It may also be improved by performing a CT scan.⁷⁶ Indeed, CT scanning may detect abnormalities not shown on the chest radiograph or when findings are questionable. Moreover, in patients with chest radiographic abnormalities, all comparative studies have shown that CT scanning is superior in demonstrating the morphological characteristics (for example, the presence of pulmonary cavitation) and the distribution of these abnormalities.

Nowadays, except for cases with a typical clinicoradiological presentation such as bacterial pneumonia or pneumocystosis, the indications for CT scanning in the non-AIDS immunocompromised patient are numerous,⁷⁷ and it is particularly useful in three circumstances: (1) in patients with respiratory symptoms or unexplained fever and a normal chest radiograph; (2) in those with puzzling radiographic findings, initially or during the course of the condition; and (3) in patients in whom a lung biopsy is undertaken, as guidance for the optimal type and site of the biopsy.

FURTHER INDICATIONS FOR LUNG BIOPSY

A lung biopsy may be considered as the second diagnostic procedure in cases where a bronchoscopic examination with BAL has not helped with the diagnosis. In patients with peripheral pulmonary nodules the usefulness of CT guided percutaneous investigations or videothoroscopic biopsy has been clearly shown,⁶⁷ and the current discussion mainly concerns transbronchial biopsy (TBB) and open lung biopsy (OLB) specimens. In non-AIDS immunocompromised patients Cazzadori *et al* showed the superiority of TBB specimens over BAL for the diagnosis of respiratory disease (sensitivities of 55% and 20%, respectively, in patients with haematological malignancy and 57% and 27%, respectively, in renal transplant recipients). The superiority of TBB specimens was especially clear in cases of tuberculosis, fungal pneumonia, and pulmonary localisation of haematological malignancies.⁷⁸ In the same way, we have shown in a prospective study in HIV infected patients that, after a negative first line procedure including BAL, a second BAL performed at the site of the greatest abnormality and combined with TBB allowed a definitive diagnosis in 90% of cases with nodules or focal infiltrates.⁷⁹ Moreover, in patients with haematological malignancies Toledo-Pereyra *et al* have shown the superiority of OLB specimens over TBB specimens for the diagnosis of respiratory disease, especially when pulmonary localisation of the haematological malignancy or organising pneumonia were the cause.⁸⁰ More recently, in a retrospective study in a similar population, Wong *et al* showed that OLB specimens enabled a diagnosis of pulmonary localisation of the haematological malignancy to be made in 18% of cases, of pneumonia (mainly aspergillosis or tuberculosis) in 21% of cases, and of specific inflammatory pneumonitis with a favourable course under steroids in 25% of cases.⁸¹ In our series the use of TBB specimens resulted in a change of treatment in 93% of cases and 83%

of patients were alive at six months. Similarly, Wong *et al* reported that the use of OLB specimens resulted in a change of treatment in 45% of cases and 88% of patients with a specific diagnosis were alive at three months.⁸¹ Clearly, these results confirm the continued usefulness of lung biopsy specimens in well defined cases.

At the present time lung biopsy might be included in the following diagnostic strategy: (1) bronchoscopy with BAL is indicated as the first line procedure in all cases except where there is a suspicion of embolism, oedema, or usual bacterial pneumonia; (2) in the absence of a diagnosis, lung biopsy is indicated as the second line procedure, the choice between a second bronchoscopy with BAL and TBB, a percutaneous biopsy, or a videothoracoscopy biopsy depending on the size of the abnormalities; (3) if such a lung biopsy does not help the diagnosis, OLB should be considered. However, in cases of probable drug induced pneumonitis, organising pneumonia, or lung fibrosis, the dilemma between treatment with empirical steroids and OLB remains.

Conclusion

A clinical approach combined with fibreoptic bronchoscopy remains the cornerstone for the diagnosis of respiratory disease in non-AIDS immunocompromised patients. Clinicians must be careful of the changes in epidemiological and clinical data resulting from the use of new immunosuppressive regimens and/or of prophylaxis in non-AIDS immunocompromised subjects. New diagnostic tests are becoming available. However, microbiologists must develop tests in their own institutions that are appropriate to their immunocompromised population, and clinicians must evaluate the clinical relevance of each positive result for each individual patient.

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