Management of the pulmonary complications of haematological malignancy

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Summary

The high frequency of pulmonary complications of haematological malignancy and the increasing number of patients treated for these disorders make it important that the respiratory physician has a structured diagnostic approach according to: 1 the immune deficiency due to the malignancy and/or the treatment administered; 2 the factors that can modify the risk of infection (anti-infection prophylaxis and/or pre-emptive treatment); 3 co-morbidities; 4 extra-pulmonary manifestations.

Two main situations can be identified: The patient is aplasic: Initially the pneumonias are predominantly of bacterial origin but may be fungal if the neutropenia is prolonged. The respiratory physician is faced with two problems: 1 the diagnosis of pneumonia; this may be helped by CT scanning; 2 The choice of antibiotics; this will depend on previous investigations. The patient is not aplasic: The lung disease may have many causes, mainly infectious but also drug related, tumoral, haemorrhagic or embolic. The main problem is the correct choice of investigations to establish an aetiological diagnosis.

The collection of data according to a pre-established protocol based on simple factors (study of the notes and clinical examination) is one of the key elements for improving the prognosis of these patients whose management should be multidisciplinary following a pre-defined plan.

Key-words: Bronchoscopy • Alveolar lavage • Infectious pulmonary disease • invasive aspergillosis • Immunosuppression.
Background

Pulmonary disease is frequent and serious in patients with haematological malignancies. Their management requires: 1°) standardized analysis of pulmonary and immunohaematological manifestations to adapt investigations and treatments to individual patients; 2°) prior organization of cooperation between specialists in respiratory medicine, haematology, radiology, microbiology and intensive care medicine. This organization is vital for the patient as a delay in diagnosis worsens the prognosis.

The respiratory physician must perform two functions simultaneously:

- **diagnosis:**
  - to identify the possible causal pathogens because pulmonary disease in patients with haematological disorders is mainly infectious,
  - to search for non-infectious causes which can be multiple, inter-associated, and also associated with an infection;
- **prognosis:** taking into account the severity of the pulmonary disease itself, possible comorbid conditions, and also the haematological malignancy.

Diagnostic approach

The major element in deciding on the diagnosis is thorough examination of the patient’s file, and above all organized following a precise plan.

**Analysis of immune deficiency attributable to the haematological disorder and/or to treatments**

By analogy with the classification of primary immune deficiencies, three broad immunohaematological categories can be identified (table I) [1]:

<table>
<thead>
<tr>
<th>Neutropenia</th>
<th>Cytotoxic agents +++</th>
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<tbody>
<tr>
<td></td>
<td>Bacteria: Gram +; Gram-positive cocci, Gram-negative bacilli</td>
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<tr>
<td></td>
<td>Fungi: aspergillus, candida</td>
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<table>
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<tr>
<th>Humoral deficiency</th>
<th>Chronic lymphocytic leukemia Multiple myeloma Waldenström macroglobulinaemia</th>
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<tr>
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<td>Encapsulated bacteria: S. pneumoniae H. influenzae</td>
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<tr>
<th>Monocytopenia</th>
<th>Hairy cell leukaemia</th>
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<td></td>
<td>Mycobacteria Legionella, aspergillus</td>
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<tr>
<th>Cell-modulated deficiency</th>
<th>Hodgkin disease Fludarabine, 2-CdA, Campath-1H Prolonged corticosteroid therapy HTLV-I leukaemia</th>
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<tbody>
<tr>
<td></td>
<td>Mycosis: P. jirovicii, aspergillus Intracellular bacteria: mycobacteria, nocardia Virus: CMV, HSV</td>
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**Enterococcus.** Fungal infections occur when neutropenia is prolonged, mainly after 5 to 7 days. Because the neutropenia induced is short in duration, these fungal infections (aspergillosis, candidiasis, mucormycosis) rarely complicate chemotherapy for non-Hodgkin lymphoma, chronic lymphocytic leukaemia and multiple myeloma, in the absence of prolonged corticosteroid therapy. They are however a major complication observed in bone marrow failure after induction therapy for acute lymphocytic and myeloid leukaemia and in haematopoietic stem cell transplantation (HSCT).

**Humoral immune deficiency**

Chronic lymphocytic leukaemia, multiple myeloma, and Waldenström macroglobulinaemia are often accompanied by hypogammaglobulinaemia and impaired antibody response exposing the patient to infections with encapsulated bacteria (Streptococcus pneumoniae, Haemophilus influenzae) which sometimes reveal the haematological disorder.

Patients who have undergone splenectomy, whether surgical or functional after radiotherapy, present infections caused by the same encapsulated bacteria which are particularly severe because of their frequency and type of bacteraemia.
Cell modulated deficiency

This is mainly secondary to immunosuppressive treatments, particularly prolonged corticosteroid therapy. This is more difficult to assess with laboratory tests than neutropenia and humoral immune deficiency. The quantification of T-lymphocyte subpopulations in peripheral blood is not as clearly correlated with a risk of infection as during HIV infection. Purine analogue therapy (Fludarabine, 2-CdA) causes a particularly deep and long reduction in cell count which can exceed a year.

A precise summary of chemotherapy dosages and administration dates is thus indispensable.

In the particular context of allogeneic haematopoietic stem cell transplantation

Several elements should be specifically sought [2, 3]:
- the exact date of transplantation;
- whether the donor was HLA-identical or not;
- type of transplant: currently mainly peripheral blood; bone marrow and umbilical cord blood are also used which result in bone marrow failure and a longer T-lymphocyte regeneration phase, and encourage opportunistic infections in the first year as the T-lymphocytes are predominantly naive and have a diminished capacity for Th1 type cytokine production;
- ex-vivo manipulation of the transplant (T-cell depletion): performed when HLA identity is not complete to reduce the risk of graft versus host disease (GVH), which causes frequent severe post-transplant immune deficiency;
- conditioning regimen: with standard bone marrow suppression (administration of whole-body irradiation is to be sought) or without bone marrow suppression, which is increasingly used in elderly patients; this is associated with less pulmonary toxicity;
- the presence of signs of acute graft versus host reaction (GVH), or chronic (after the 100th post-transplant day).

Predictive analysis of the pathogens responsible for infections varies with the date of onset of pulmonary disease after the transplant:
- initial phase: neutropenia is often deep and predictably longer with HSCT from bone marrow than from peripheral blood. When the conditioning regimen uses bone marrow suppression, in addition to the immune deficiency due to neutropenia, there is a more extensive deficiency involving B-cell lymphopenia and deficiencies in T-lymphocytes and NK cells;
- second phase: T-lymphocyte deficiency associated with GVH for which the preventive immunosuppressant treatments (cyclosporin, methotrexate, corticosteroids) increase both the humoral and cell modulated immune deficiencies. The main causal pathogens are cytomegalovirus and aspergillus;
- third phase: later, usually after the 100th day. Immunosuppression at this stage mainly depends on the chronic GVH associated with its treatment: corticosteroids, cyclosporin, mycophenolate mofetil, and monoclonal antibodies.

However, this time-related classification is more technical than strictly operational.

Investigation of factors which can modify probabilistic analysis of causal pathogens

Environmental factors

Previous hospitalization: development of pulmonary disease then indicates hospital-acquired pneumonia.

Renovation or building work in the hospital, and absence of respiratory tract protection in a laminar airflow isolation room before allogeneic HSCT, which increase the risk of aspergillosis [4].

Stay in a tropical region with a risk of strongyloidiasis after corticosteroid therapy, and possible exotic fungal infections (histoplasmosis) [5].

Physical factors

Mucositis [6]; catheter insertion (increases the risk of Gram-positive cocci infections, particularly S. aureus) [7]; diarrhea (risk of Enterobacter infection with translocation through gastrointestinal tract walls damaged by chemotherapy); bronchial obstruction causing pulmonary atelectasis.

Prophylaxis against infection

Intravenous immunoglobulin reduces the frequency of infections with encapsulated bacteria in patients presenting hypogammaglobulinaemia in the context of chronic lymphocytic leukaemia, multiple myeloma, or after allogeneic HSCT [8-10].

Pneumococcal vaccination and antibiotic prophylaxis in splenectomized patients reduces the frequency of severe infections with encapsulated bacteria [11].

Trimethoprim-sulfamethoxazole, prescribed in the absence of digestive tract disorders, makes the diagnosis of Pneumocystis carinii pneumonia highly unlikely in febrile interstitial lung disease [12]. The probability of pulmonary toxoplasmosis is also very low.

Administration of fluconazole, which seems to increase the risk of infection with Candida strains showing reduced sensitivity to azole antifungal agents [13].

Ganciclovir, used pre-emptively depending on cytomegalovirus antigenaemia and blood PCR, reduces the frequency of cytomegalovirus pneumonia in HSCT recipients [14].

Valaciclovir, for which the effect on the frequency of herpes simplex virus pulmonary disease is poorly understood [15].
Investigation of comorbid conditions induced by the disease and/or the treatments

- Thrombocytopenia: chemotherapy-induced or part of the haematological disorder, can cause alveolar haemorrhage.
- Renal failure: secondary to multiple myeloma, chemotherapy (cisplatin), contributed to by dehydration, injections of iodine contrast medium, and antibiotic therapy (aminosides).
- Heart failure: secondary to infusion of large volumes, cardiopathy after administration of anthracyclines (assess the total dose administered), or mediastinal radiotherapy. Verification required of the patient’s weight curve, diuresis curve, and the volumes of infusion administered before the pulmonary disease.
- Lower limb deep vein thrombosis: contributed to by compression of the venous trunks by a tumour mass, and the use of thalidomide in patients with multiple myeloma [16].

Analysis of respiratory signs

- Possible pulmonary disease must be considered in a febrile patient in the absence of respiratory signs, or in the presence of mild clinical signs (cough, shortness of breath on exertion). Two clinical parameters must be systematically measured: respiratory rate and arterial oxygen saturation.

The pulmonary signs and symptoms do not generally indicate the cause of the pulmonary disease. However, invasive pulmonary aspergillosis should be suspected in the presence of infarction-like signs and symptoms (pleural pain, haemoptysis) if the immunohaematological context exposes the patient to this risk.

Signs of pleural involvement are not specific in patients with haematological disorders but should be sought systematically.

- speed of onset of signs and symptoms: this parameter can provide an indication of the type of causal pathogen though there is no precise information formally associating onset times with pathogens. Pulmonary disease is usually classified as:
  - rapid progression, in 2 to 3 days: indicating probable bacterial (S. pneumoniae, S. aureus, Gram-negative bacilli) or fungal infection, mainly invasive pulmonary aspergillosis in bone marrow failure patients; community-acquired respiratory virus infections (respiratory syncytial virus, adenovirus, parainfluenza virus and influenza virus A and B). As in immunocompetent patients, these viral infections are frequently accompanied by signs of upper airway involvement;
  - subacute progression, in 4 to 10 days: indicating possible aspergillosis, pneumocystosis, cytomegalovirus pneumonia, legionellosis;
  - more gradual progression, over 10 days: mycobacterial infection (tubercular or non-tubercular), nocardiosis.

Extra-respiratory signs

These can sometimes be of major significance in establishing the diagnosis; they should be sought systematically with a thorough physical examination:

- visual disorders: these require fundoscopy which can reveal cytomegalovirus retinitis, and candida endophthalmitis;
- skin examination: biopsies should be taken from all suspicious skin lesions for histology and microbiology studies;
- diarrhoea: stool cultures and parasite examinations should be performed;
- joints: in search of arthritis;
- neurological disorders: in particular of the higher functions in search of meningitis and/or meningo-encephalitis.

At this stage, the respiratory physician must summarize and organize the various systematically recorded data for future management of the diagnostic (imaging studies, microbiology), and treatment processes. Concerning the prognosis, collaboration with the haematologist is indispensable in assessing the prognosis for the haematological malignancy. All blood diseases can be classified in risk groups, the details of which cannot be provided in this article. Certain contexts can be identified in haematological disorders for which resuscitation measures would not be implemented; however decisions can only be made in collaboration with the haematology team to ensure the absence of other haematology treatments not yet used, in particular autologous or allogeneic transplant, as these are performed in increasingly elderly patients thanks to conditioning regimens without bone marrow suppression [17].

- There are three different immune deficiency patterns: neutropenia, humoral deficiency and cell modulated deficiency.
- The depth and duration of neutropenia are to be taken into account.
- In neutropenia, infections are initially bacterial, then fungal.
- Hypogammaglobulinaemia exposes patients to the risk of infections with encapsulated bacteria.
- Cell modulated deficiency is mainly due to immunosuppressant treatments.
- Several factors can modify the probabilistic analysis of causal pathogens: environmental, physical (mucositis, catheterization, diarrhoea, bronchial obstruction), prophylaxis against infection.
- Comorbid conditions induced by the disease and/or treatments are thrombocytopenia, renal failure, heart failure, and lower limb deep vein thrombosis.
- Two simple clinical parameters should always be assessed: respiratory rate and arterial oxygen saturation.
- The speed of onset of signs and symptoms can provide an indication of the causal pathogen.
- All extra-respiratory signs (visual, cutaneous, diarrhoea, articular, neurological) should be sought out.
**Management strategy**

Patients with neutropenia can be distinguished from non-immunosuppressed patients using the following principles [18]. Briefly:

– patients with neutropenia practically always present pulmonary diseases infectious in origin: bacterial, then fungal depending on the duration of neutropenia. The principal objective of the respiratory physician will be to start treatment of the infection as quickly as possible;
– in non-immunosuppressed patients: the main issue is aetiologic; infectious pulmonary diseases remain frequent but many non-infectious causes are possible, individually, inter-associated, or associated with an infection. The objective of the respiratory physician will be to establish the cause in order to start appropriate treatment.

**Pulmonary disease in patients with bone marrow failure**

Clinical semiology in respiratory disorders can be deceptive: the more subtle the symptoms, the deeper the neutropenia. Pneumonia presents the most often as isolated fever (temperature over 38.3°C or over 38°C on two occasions an hour apart); expectoration and crepitus are often absent [19].

The chest radiograph is often normal at first and can rapidly worsen later. A normal chest radiograph does not rule out pulmonary disease in a patient with bone marrow failure.

The main issue is the appropriateness of a CT scan. A CT scan has many advantages: 1°) it provides a higher frequency of diagnosis than chest radiography in pulmonary disease; 2°) it can show features suggesting a cause, in particular aspergillosis: a peripheral halo of haemorrhage surrounding a necrotic zone, an early sign in 90% of cases of invasive pulmonary aspergillosis but less frequent (44%) when aspergillosis presents later after allogeneic HSCT, then secondarily an aspergilloma creating an air-crescent sign; 3°) endobronchial samples can be taken with the patient under non-invasive ventilation (beta-lactam antibiotics) [26, 27]. Performance of a CT scan poses the problem of antibiotic therapy unless the patient presents clinical signs suggesting an infection cutaneous in origin (mainly around catheters) or is in shock [28].

An antifungal agent is added from the 5th day if there is no improvement, and sometimes as early as the 3rd day depending on the severity of the patient’s condition. An antifungal agent is also added if new pulmonary opacities appear when the patient is already treated with antibiotics and remains febrile. A thoracic CT scan is also useful in this situation for analysis of the radiological appearance, and also guidance when taking endobronchial samples. Bronchoscopy with alveolar lavage can be performed, even in a patient presenting thrombocytopenia. However, a telescopic brush is not generally used because of the risk of haemorrhage. In the case of severe respiratory failure, endobronchial samples can be taken with the patient under non-invasive ventilation [29]. Bronchoscopy should also be performed when the patient presents complex immune deficiency associating bone marrow failure with humoral or cell modulated deficiency secondary to previously administered treatments. As much information as possible must be obtained from the samples obtained in this situation using, apart from the usual...
alveolar lavage analysis techniques (cell count and differential) and the usual stains to detect infectious agents, immunofluorescence to detect *Pneumocystis jirovecii*, Indian ink staining to detect *Cryptococcus*, PCR for herpes virus, antigen detection assays and PCR for the usual respiratory tract viruses (*adenovirus*, *respiratory syncytial virus*, and *influenza virus A and B*).

At the same time as managing diagnosis and treatment of the pulmonary disease, the respiratory physician must correct the cytopenia: red cell transfusions when haemoglobin is below 8 g, or 9 g when there is associated severe thrombocytopenia with a risk of red cell loss by lysis in a patient with coronary disease; platelet transfusion is systematic when the patient has a platelet count below 20,000/mm³ [30]. Patients who have undergone allogeneic HSCT should be administered irradiated blood products to avoid inducing post-transfusion graft versus host reaction.

- The pulmonary diseases presented by patients with neutropenia are practically always infectious.
- A CT scan is very useful when the chest radiograph is normal despite a suspicious clinical picture or in aspergillosis.
- Blood and catheter cultures are systematic, as well as ELisa detection of aspergillus galactomannan antigen when there is a risk of invasive pulmonary aspergillosis.
- First line treatment is probabilistic antibiotic therapy with the addition of antifungal agents if there is no improvement after 3-5 days.
- Bronchoscopy with bronchoalveolar lavage is performed, even if the patient presents thrombocytopenia.
- Cytopenia must be corrected at the same time.

**Patient not presenting bone marrow failure**

The causes of pulmonary disease in patients with haematological disorders without bone marrow failure are varied. Infection remains the most frequent cause but isolated non-infectious disorders can be involved, inter-associated, and also associated with infectious pulmonary disease [31]. This diversity in aetiology makes their diagnosis essential. Diagnosis will thus be the primary objective of the respiratory physician.

A thoracic CT scan is practically always performed, as well as bronchoscopy with endobronchial samples for microbiology (protected distal samples, telescopic brush), and above all bronchoalveolar lavage with processing of samples according to the possible diagnoses, and the patient’s immunohaematological and pulmonary status.

Bronchoscopy with bronchoalveolar lavage and samples for microbiology only provides a diagnosis for half of the pulmonary diseases occurring in patients who do not present bone marrow failure and have undergone allogeneic HSCT, but it does result in more frequent modifications in treatment for nearly three quarters of these patients [32]. Deciding on the indication for surgical lung biopsy is difficult. Information from the literature is not really applicable to individual patients given the diversity of published cases. Several parameters require analysis: diagnostic yield, effect on treatment, and improvement in prognosis. The risks involved in this procedure, in particular for a patient with acute respiratory failure, should be taken into account [33]. The decision process must be multidisciplinary involving haematologists, anaesthesiologists and surgeons.

The search for all non-infectious aetiologies must be systematic, even when a cause has been identified, because of possible associations.

**Fluid overload**

Suggested by radiographic features with bilateral pleural effusion and Kerley lines. Contributed to by renal and/or heart failure, it is corroborated by analysis of infusion volumes, and patient weight and diuresis. This can be verified with the administration of furosemide.

**Toxic pneumonitis**

Drug and/or radiation therapy induced.

Diagnosis is difficult because the signs and symptoms mimic those of infectious pulmonary disease: rapid progression, febrile patient, great variations in radiographic features. There are no specific tests for the diagnosis of drug-induced pulmonary disease. Diagnosis is based on elimination of other causes of pulmonary disease, in particular infectious, and knowledge of administration of agents that induce pulmonary toxicity. Many of the cytostatic agents known for several decades can be involved: cyclophosphamide, melphalan, bleomycin, methotrexate [34]. Concerning methotrexate, it should be noted that alveolar lymphocyte populations vary greatly depending on the day bronchoalveolar lavage is performed. Alveolar T-lymphocyte phenotyping is not useful for diagnosis [35]. Non-infectious pulmonary disease is regularly reported with the more recent cytostatic agents: fludarabine causes diffuse interstitial pulmonary disease in approximately 9% of patients treated, which can occur at the first cycle and sometimes as late as the 7th, and the most often responds to corticosteroid therapy [36]; gemcitabine causes acute pulmonary disease which is often severe, mainly when administered in association with bleomycin [37]; rare cases of alveolar and interstitial pulmonary disease have been reported with imatinib mesylate between the 3rd and 9th months of treatment which regressed on stoppage [38]; exceptional cases of acute alveolar and interstitial pulmonary disease occurring two weeks after administration of rituximab have been reported which regressed under corticosteroid treatment [39]; a specific search should be made for administration of G-CSF which can increase bleomycin-
induced acute pulmonary toxicity [40]; all-trans-retinoic acid, when administered in acute promyelocytic leukaemia, is complicated in approximately 25% of cases by oedema with pleuropericarditis similar to capillary leakage syndrome, responding the most often to corticosteroid therapy, and unusual as it is sometimes associated with manifestations similar to Sweet syndrome [41].

Acute radiation pneumonitis is easy to diagnose when it occurs in the irradiated zone, but diagnosis can sometimes be more difficult when it occurs outside the irradiated zone. It is accompanied by alveolar lymphocytosis, with the histological features of bronchiolitis obliterans organizing pneumonia. Radiation pneumonitis usually responds to corticosteroid therapy [42, 43].

Tumor localizations

These concern all blood diseases; acute myeloid leukaemia sometimes presents pulmonary tumor infiltrate in patients with only mild blastosis. In patients with lymphoid leukaemia bronchoscopy can sometimes visualize endobronchial localizations [44]. In patients with suspected pulmonary localization of non-Hodgkin lymphoma, PCR clonality analysis of alveolar B-lymphocytes in bronchoalveolar lavage must be systematic; this examination has a specificity of 97% and a negative predictive value of 95%, and can thus avoid a surgical lung biopsy when lymphoma in another organ is proven histologically [45].

Alveolar haemorrhage

Can occur in the absence of thrombocytopenia in autologous or allogeneic HSCT recipients, with onset on average around the 13th day after transplantation. The semiology is often deceptive with the clinical picture of febrile alveolar disease, rapidly progressive without haemoptysis. Its frequency is very variable. Diagnosis is obtained with alveolar lavage which is not always macroscopically haemorrhagic but Perls’ stain reveals haemosiderin-laden macrophages [46].

Alveolar proteinosis

Mainly a complication of myeloid leukaemia. It must be sought systematically in the bronchoalveolar lavage fluid with PAS staining which reveals amorphous alveolar material not found with alcin blue staining. The diagnosis can be suggested by a mosaic pattern on the CT scan. Alveolar proteinosis can be associated with an infection (mycobacteria, nocardia).

Pulmonary embolism

Its frequency is increased when the blood disease is progressive, and with certain treatments such as thalidomide for multiple myeloma [16].

Transfusion-related complications

The clinical presentation is respiratory distress with alveolar and interstitial pulmonary disease (TRALI = transfusion-related-acute-lung-injury) due to the presence of donor anti-HLA or anti-polymorphonuclear neutrophil antibodies reacting with recipient polymorphonuclear neutrophils. The diagnosis is suggested by the chronology with onset a few hours after transfusion [47].

- The pulmonary diseases presented by non-neutropenic patients are due to infection, and many other causes.
- A CT scan and bronchoalveolar lavage are practically systematic.
- A surgical lung biopsy is sometimes required.
- Non-infectious causes should always be sought: fluid overload, toxic pneumonitis, tumor infiltrate, alveolar haemorrhage, alveolar proteinosis, pulmonary embolism, transfusion-related complications.

Conclusions

In conclusion, the elements required for appropriate management of pulmonary disease occurring in patients with haematological disorders are straightforward, but must be recorded methodically following a pre-established plan to ensure no information is omitted. A precise clinical investigation carried out in collaboration with the haematologist, obtaining a thoracic CT scan without delay, and efficient management of samples, are required for continuous improvement in prognosis for these patients, together with progress in medical treatments (particularly antifungal agents) and ventilation techniques, which will be discussed further in other articles [48, 49].

Acknowledgements

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LEARNING POINTS

- The diagnostic workup includes analysis of immune deficiency, investigation of factors contributing to a particular type of infection, investigation of comorbid conditions, respiratory and extra-respiratory assessments.
- A distinction is made between patients with and without bone marrow failure.
- In the case of bone marrow failure, management concentrates on the pulmonary disease and the cytopenia.
• In the absence of bone marrow failure, a workup for infection is performed and non-infectious causes are also sought (fluid overload, toxic pneumonitis, tumors, alveolar hemorrhage or proteinosis, pulmonary embolism, transfusion-related complications).

References


