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PULMONARY INFILTRATES IN THE IMMUNOCOMPROMISED: DIAGNOSIS AND MANAGEMENT

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Introductory articles

Pulmonary infiltrates in non-HIV immunocompromised patients: a diagnostic approach using non-invasive and bronchoscopic procedures

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*Background: The development of pulmonary infiltrates is a frequent life threatening complication in immunocompromised patients, requiring early diagnosis and specific treatment. In the present study non-invasive and bronchoscopic diagnostic techniques were applied in patients with different non-HIV immunocompromised conditions to determine the aetiology of the pulmonary infiltrates and to evaluate the impact of these methods on therapeutic decisions and outcome in this population. Methods: The non-invasive diagnostic methods included serological tests, blood antigen detection, and blood, nasopharyngeal wash (NPW), sputum and tracheobronchial aspirate (TBAS) cultures. Bronchoscopic techniques included fibrobronchial aspirate (FBAS), protected specimen brush (PSB), and bronchoalveolar lavage (BAL). Two hundred consecutive episodes of pulmonary infiltrates were prospectively evaluated during a 30 month period in 52 solid organ transplant recipients, 53 haematopoietic stem cell transplant (HSCT) recipients, 68 patients with haematological malignancies, and 27 patients requiring chronic treatment with corticosteroids and/or immunosuppressive drugs. Results: An aetiological diagnosis was obtained in 162 (81%) of the 200 patients. The aetiology of the pulmonary infiltrates was infectious in 125 (77%) and non-infectious in 37 (23%); 38 (19%) remained undiagnosed. The main infectious aetiologies were bacterial (48/125, 24%), fungal (33/125, 17%), and viral (20/125, 10%), and the most frequent pathogens were Aspergillus fumigatus (n=29), Staphylococcus aureus (n=17), and Pseudomonas aeruginosa (n=12). Among the non-infectious aetiologies, pulmonary oedema (16/37, 43%) and diffuse alveolar haemorrhage (10/37, 27%) were the most common causes. Non-invasive techniques led to the diagnosis of pulmonary infiltrates in 41% of the cases in which they were used; specifically, the diagnostic yield of blood cultures was 30/191 (16%); sputum cultures 27/88 (31%); NPW 9/50 (18%); and TBAS 35/55 (65%). Bronchoscopic techniques led to the diagnosis of pulmonary infiltrates in 59% of the cases in which they were used: FBAS 16/28 (57%), BAL 68/135 (51%), and PSB 30/125 (24%). The results obtained with the different techniques led to a change in antibiotic treatment in 93 cases (46%). Although changes in treatment did not have an impact on the overall mortality, patients with pulmonary infiltrates of an infectious aetiology in whom the change was made during the first 7 days had a better outcome (29% mortality) than those in whom treatment was changed later (71% mortality; p=0.001). Conclusions: Non-invasive and bronchoscopic procedures are useful techniques for the diagnosis of pulmonary infiltrates in immunocompromised patients. Bronchial aspirates (FBAS and TBAS) and BAL have the highest diagnostic yield and impact on therapeutic decisions. (**Thorax** 2001;56:379–87)*

Role of bronchoalveolar lavage in immunocompromised patients with pneumonia treated with a broad spectrum antibiotic and antifungal regimen

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Background: In a retrospective study the value of bronchoalveolar lavage (BAL) in the diagnosis of pneumonia was investigated in 95 immunocompromised patients suffering from haematological disorders and receiving a regimen of broad spectrum antibiotics and antifungal agents (BSAR). Methods: With the exception of four afebrile patients, all had fever, raised C reactive protein (CRP) levels, and new infiltrates visible on chest radiography. All patients underwent BAL to identify the organism causing the pneumonia

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*and surveillance cultures were performed regularly for pathogens at different sites. Following classification of the isolates, patients with positive cultures were subdivided into two groups, pathogenic or contaminated. We investigated whether relevant pathogens were cultured only from the BAL fluid and whether they were susceptible to BSAR. Results: Although 77 of the 95 patients were thrombocytopenic, bleeding during BAL occurred in only 15% of all patients. Ten days after the procedure the fever improved in 88% of patients, radiographic findings improved in 71%, and CRP levels improved in 75% of patients; 22% of patients died within 28 days. Pathologically relevant isolates were found in 65% of all patients. Respiratory pathogens were detected only in the BAL fluid of 29 of the 95 patients (35% Gram positive species, 40% Gram negative species, 11% Mycobacterium, 11% fungi, and 3% cytomegalovirus). In 16 of these 29 patients (55%) the pathogens cultured only from the BAL fluid were resistant to treatment. Pathogens detected only in the BAL fluid were not susceptible to a standard broad spectrum antibiotic and antifungal regimen including teicoplanin, ceftriaxon, tobramycin, and amphotericin B in 12 of the 29 patients (41%). Conclusions: Our data suggest that 12 patients were treated with broad spectrum antimicrobial agents which were not directed at the appropriate organism on in vitro sensitivity tests without BAL. BAL is a relatively safe procedure in the diagnosis of pneumonia, supplying important information in immunocompromised patients as well as in immunocompromised patients receiving BSAR. (**Thorax** 2001;56:115–20)*

Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure

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*Background: Avoiding intubation is a major goal in the management of respiratory failure, particularly in immunosuppressed patients. Nevertheless, there are only limited data on the efficacy of non-invasive ventilation in these high risk patients. Methods: We conducted a prospective, randomized trial of intermittent non-invasive ventilation, as compared with standard treatment with supplemental oxygen and no ventilatory support, in 52 immunosuppressed patients with pulmonary infiltrates, fever, and an early stage of hypoxemic acute respiratory failure. Periods of non-invasive ventilation delivered through a face mask were alternated every 3 hours with periods of spontaneous breathing with supplemental oxygen. The ventilation periods lasted at least 45 minutes. Decisions to intubate were made according to standard predetermined criteria. Results: The baseline characteristics of the two groups were similar; each group of 26 patients included 15 patients with hematologic cancer and neutropenia. Fewer patients in the non-invasive ventilation group than in the standard treatment group required endotracheal intubation (12 v 20, p=0.03), had serious complications (13 v 21, p=0.02), died in the intensive care unit (10 v 18, p=0.03), or died in the hospital (13 v 21, p=0.02). Conclusions: In selected immunosuppressed patients with pneumonitis and acute respiratory failure, early initiation of non-invasive ventilation is associated with significant reductions in the rates of endotracheal intubation and serious complications and an improved likelihood of survival to hospital discharge. (**N Engl J Med** 2001;344:481–7)*

The development of pulmonary infiltrates in immunocompromised patients is life threatening and when combined with acute respiratory failure has a poor prognosis, especially when intubation and mechanical ventilation are required.[1 2] Managing such patients is a clinical challenge both in terms of making a diagnosis and providing effective supportive care. Early intervention is essential as it predicts better outcome.[2]

DIAGNOSTIC STRATEGIES

Patients often present with non-specific radiological signs and the clinical course can be variable. Deterioration may be acute or chronic and classical features of sepsis are frequently absent. While the most important cause of acute respiratory failure in the immunocompromised patient is infection, there are other non-infectious conditions which need to be considered. These may be drug related, disease specific (such as graft versus host disease, malignancy and acute rejection), a result of sepsis induced adult respiratory distress syndrome (ARDS), or as a consequence of non-specific conditions such as bronchiolitis obliterans organising pneumonia (BOOP).[2 3]

While the generic term "immunosuppressed patient" is often used, the word can be misleading as it includes a diverse group of conditions with very different complications and outcomes. When assessing patients with pulmonary complications, several factors need to be considered. Firstly, the aetiology and prevalence of lung infiltrates will be related to the disease process which

has caused immunocompromise and/or to the dose, type, and duration of immunosuppressant used.[4] Secondly, the spectrum of opportunistic pathogens will be altered by the use of prophylactic regimens—for example, *Pneumocystis carinii* (PCP).[4 5] Finally, the possibility that there is more than one aetiological agent should always be considered.[6]

The spectrum of infectious agents is predominantly affected by whether the primary abnormality is of humoral or of cell mediated immunity. In neutropenic patients, early empirical broad spectrum antibiotics are often given first line with the addition of antifungal therapy where appropriate.[3 7] This policy has been shown to reduce infection related morbidity and mortality as long as the regimen is targeted against the most frequent pathogens.[7] These include Gram positive cocci, Gram negative bacilli, and invasive aspergillosis.[3 7 8] Prognosis is particularly poor in patients who develop invasive pulmonary mycosis with survival rates being as low as 10% in those who undergo bone marrow transplantation.[3] Without appropriate treatment, bacterial infection will often lead to a rapid clinical deterioration and the development of septic shock and ARDS.

In contrast, blind antibiotic therapy is not usually given to the non-neutropenic immunocompromised patient. Although bacterial infections are common in this group, there is a predisposition to a wider spectrum of opportunistic organisms including bacteria, viruses, protozoa, and fungi such as legionella, cytomegalovirus (CMV), and PCP.[7 9] Delay in the diagnosis and treatment of CMV pneumonitis is associated with a high mortality rate, especially in bone marrow transplant recipients.[10] In other conditions such as myeloma and chronic lymphocytic pneumonia, humoral immunity will be impaired. This results in a particular susceptibility to bacterial infection by encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.[7]

Conventional radiology

In the non-HIV immunosuppressed patient, conventional radiology is often non-specific and unhelpful in characterising the aetiology of pulmonary infiltrates but can be useful in detecting new changes and monitoring response to treatment.[11 12] Against this background, Logan *et al* conducted a retrospective study to look at the diagnostic accuracy of chest radiographs in a diverse group of immunocompromised patients.[12] In the non-HIV group a correct first choice diagnosis was made in only 34% of cases. The authors conclude that, in non-AIDS patients, a confident diagnosis can seldom be made and pathological confirmation should be sought, although the extent and distribution of parenchymal abnormalities can provide some clues to the disease process. For example, in *P carinii* pneumonia there is frequently sparing of at least one lung zone, in ARDS all zones tend to be affected, and in drug induced lung disease sparing of the upper zones often occurs.

Computed tomographic (CT) scanning

In contrast, computed tomographic (CT) scanning is much more sensitive and can be a useful tool for the early detection of pulmonary infection, localisation of disease before bronchoscopic or surgical procedures, and provides a relevant differential diagnosis.[3 11 13 14] More invasive procedures such as CT guided percutaneous needle aspiration and biopsy can also be used for both histological and microbial sampling.[13]

Transbronchial aspiration and bronchoscopy

A diagnosis can be obtained in most patients who present with pulmonary infiltrates by a combination of non-invasive and bronchoscopic techniques. In a recent prospective study, Rano *et al* reported their findings on the usefulness of such procedures in determining the aetiology of pulmonary infiltrates in a large diverse population of 200 non-AIDS immunocompromised patients.[2] Using this approach they identified the aetiology in 81% of cases (162/200), 77% of which were due to infection and 23% to other causes such as pulmonary oedema and diffuse alveolar haemorrhage. Among the non-infectious causes serological tests, blood cultures, antigen detection, nasopharyngeal wash, sputum and tracheobronchial aspirates (TBA) led to the diagnosis in 40% of cases. Bronchoalveolar lavage (BAL) provided the highest diagnostic yield being positive in 51% of cases (68/135) where it was used and identifying a diagnosis in 69% of patients (56/81) with an infectious aetiology. Eleven transbronchial biopsy (TBB) specimens were obtained and resulted in a specific diagnosis in 55% of cases, two being BOOP, two lymphoma, and two bacterial pneumonia. An earlier study by Cazzadori and colleagues supports the superiority of TBB as a diagnostic tool in the non-HIV immunocompromised patient, especially in cases relating to malignancy, tuberculosis, and fungal disease.[3 8] However, this procedure does carry potential complications such as pneumothorax and bleeding which can be fatal in patients with acute respiratory failure. Direct comparison of the sensitivity and specificity of the various bronchoscopic techniques could not be made in the study by Rano *et al* as the procedures were not carried out consecutively in all cases.

Hohenadel *et al*[15] have recently investigated the role of BAL in 95 immunocompromised patients suffering from haematological disorders with pneumonia. Pathogenic isolates were identified in 65% of all cases and BAL provided the only definitive diagnosis in 29 cases (31%). Of these 29, 16 organisms proved to be resistant to ongoing treatment. More worryingly, Rano and colleagues concluded in their study that treatment had little overall impact on patient mortality[2] although, if changes were made during the first 7 days of presentation, this was reduced to 29% compared with 71% of those in whom treatment was changed later.

Bronchoscopy needs to be considered early in non-HIV immunocompromised patients unresponsive to treatment. The procedure is low risk and can be safely carried out in most patients including those with hypoxia, and it can even be performed during continuous positive airway pressure (CPAP)[16] and non-invasive ventilation (NIV),[17] although this should be on an ICU in case of deterioration. While BAL is particularly useful in cases of infection, it has an important role to play in the identification of non-infectious disorders such as pulmonary haemorrhage, eosinophilic pneumonia, hypersensitivity pneumonitis, and malignant disease. In ventilated patients less invasive procedures such as tracheobronchial aspiration should be considered in those too unstable to undergo bronchoscopic procedures.[2 18] In cases where the diagnosis still remains unclear, open lung or video assisted thoracoscopic surgery (VATS) biopsy specimens may be required.

Non-invasive ventilation

Despite treatment, some patients will deteriorate and develop acute respiratory failure. Deciding whether it is appropriate to institute intubation and mechanical ventilation can be difficult as it results in such a high mortality. More recent emphasis has been placed on the potential of NIV as a means of avoiding the complications of intubation. This is in part a result of the successful use of NIV in the treatment of acute on chronic ventilatory failure due to chronic obstructive pulmonary disease (COPD) where the particular benefit

from starting NIV early, before ventilatory support would usually be considered necessary, was recently confirmed in the largest study to date.[19]

NIV has been used in patients with hypoxaemic respiratory failure resulting from a number of different conditions[20–22] and, again, the picture emerges that most is to be gained when it is instituted early. Antonelli *et al*[20] compared intubation and conventional mechanical ventilation with NIV in patients with acute hypoxic respiratory failure of different aetiologies. Post hoc subgroup analysis of patients with simplified acute physiological scores (SAPS) of <16 and those of ⩾16 showed that patients in the latter group had similar outcomes irrespective of the type of ventilation. However, NIV was superior to conventional mechanical ventilation in patients with SAPS <16. One problem of studies of this type is that the outcome from intensive care is critically dependent upon the aetiology of the respiratory failure; small studies of patients with heterogeneous causes of respiratory failure lack sufficient power to determine confidently the effectiveness of the intervention. The same group[22] evaluated the use of NIV in patients undergoing solid organ transplantation, although respiratory failure was due to a number of different causes. They found a sustained improvement in the Pao_2/Fio_2 ratio in more patients (60% *v* 25%, p=0.03) and a reduction in the intubation rate (20% *v* 70%, p=0.002), rate of fatal complications (20% *v* 50%, p=0.05), length of stay in the ICU by survivors (5.5 *v* 9 days, p=0.03), and ICU mortality (20% *v* 50%, p=0.05) in the NIV group. However, there was no difference in hospital mortality.

Against this background and given the effectiveness of NIV in reducing the need for intubation in hypoxaemic respiratory failure, Hilbert *et al*[23] conducted a prospective randomised controlled trial of NIV compared with standard treatment with supplemental oxygen and no ventilatory support in 52 immunosuppressed patients with pulmonary infiltrates and fever. Each group of 26 patients included 15 patients with haematological malignancy and neutropenia. Patients were recruited at an early stage of hypoxaemic respiratory failure. NIV (for at least 45 minutes) was alternated every 3 hours with periods of spontaneous breathing with supplemental oxygen. The level of pressure support was titrated against the expired tidal volume and respiratory rate (mean (SD) 15 (2) cm H_2O) and the level of positive end expiratory pressure (PEEP) to achieve an Fio_2 of less than 65% (6 (1) cm H_2O). During the first 24 hours patients achieved 9 (3) hours NIV and 7 (3) hours NIV in the second 24 hour period. The mean duration of ventilation was 4 (2) days. Fewer patients in the NIV group required endotracheal intubation (12 *v* 20, p=0.03), had serious complications (13 *v* 21, p=0.02), died in the ICU (10 *v* 18, p=0.03), or died in hospital (13 *v* 21, p=0.02). The time to intubation in those who required it in the control and NIV groups was 51 (23) hours and 63 (18) hours, respectively. The need for intubation was determined by a priori criteria; the most common reason was a failure of oxygenation (5 *v* 9), followed by an increase in $Paco_2$ and the development of acidosis (2 *v* 4), with encephalopathy, haemodynamic instability, and failure to control secretions making up the remainder. The reason why relatively short periods of assisted ventilation should have been effective is interesting and open to speculation. Possible reasons include redistribution of extravascular fluid, alveolar recruitment and re-expansion of atelectatic lung, as well as the beneficial effects of pressure support on work of breathing, helping to maintain an adequate tidal volume, and possibly allowing respiratory muscle recovery during periods of muscle unloading when on NIV.

CPAP has similar physiological effects, is easier and cheaper to deliver, and has been used in a number of studies.[24 25] An improvement in gas exchange is a consistent finding and, in an uncontrolled trial, Hilbert *et al*[26] found that CPAP alone eliminated the need for intubation in 25% of 64 patients with neutropenia. However, in the only prospective randomised trial published to date comparing CPAP with standard treatment, there was no improvement in outcome (intubation rate and survival) although CPAP did result in a more rapid physiological improvement.[27] More adverse events occurred with CPAP treatment (18 *v* 6; p=0.01). A number of patients in the CPAP group had respiratory arrests, suggesting that non-invasive CPAP delayed intubation. Current data therefore favour NIV as the non-invasive mode of ventilatory support of choice.

A reduction in complications, particularly infections, with NIV is a consistent feature.[20 28–31] In intubated patients there is a 1% risk per day of developing nosocomial pneumonia.[32] This complication of invasive ventilation is associated with a longer ICU stay, increased costs, and a worse outcome.[33] The reduction in nosocomial infections is probably the most important advantage of avoiding endotracheal intubation with NIV. This benefit has also been seen in the "real" world outside the setting of a clinical trial.[34] In a 3 week survey of 42 French ICUs the incidence of both nosocomial pneumonia (10% *v* 19%, p=0.03) and mortality (22% *v* 41%, p<0.001) was lower in patients treated with NIV than in those who underwent endotracheal intubation. In the study of Hilbert *et al*[23] pneumonia and sinusitis occurred only in patients who required intubation and ventilator associated pneumonia was associated with a 100% mortality. The non-invasive studies suggest that it is not the ventilator that is the problem but, more likely, the endotracheal tube, and the condition should perhaps more correctly be termed "tube associated pneumonia".

The findings of Hilbert *et al*[23] are in keeping with those of other studies in suggesting that early NIV can prevent intubation and is best introduced early. The criteria on which patients were recruited to their study are a useful starting point (respiratory distress with a respiratory rate of >30 breaths/min and a Pao_2/Fio_2 ratio of <200), and NIV should now be strongly considered in such patients provided there are no contraindications. There have been no comparative trials of CPAP and NIV but, on the evidence available, NIV is the preferred mode of non-invasive support. The finding of an increased number of cardiorespiratory arrests in the study by Delclaux *et al*[27] is a cautionary reminder that some patients will continue to deteriorate to the point at which invasive ventilation becomes mandatory and that, if intubation is delayed too long, the risk of death may be increased. However, the outcome in the patients who were intubated (none precipitated by cardiorespiratory arrest) was universally poor with none surviving to hospital discharge, and the question remains whether invasive ventilation is an exercise in futility, at least in those with haematological malignancy.[1]

Conclusions

In immunocompromised patients with pulmonary infiltrates on a chest radiograph early diagnostic intervention with bronchoscopic BAL and, in selected cases, high resolution CT scanning is warranted. The early institution of NIV should be considered in all immunocompromised patients with dyspnoea, respiratory rate >30 breaths/min, and a $Pao_2/$

Learning points

- The aetiology of the immunocompromise is important in determining possible causes of pulmonary infiltrates
- Early diagnosis is advantageous; bronchoscopic BAL and high resolution CT scanning in selected patients gives the best balance between safety and diagnostic accuracy
- Early lung biopsy samples should be taken if there is deterioration, particularly if no diagnosis has been made using less invasive techniques
- The possibility of more than one aetiological agent should be considered
- Early NIV is advantageous
- If NIV fails invasive ventilation may be futile, particularly in patients with haematological malignancy

Fio_2 ratio of <200. The prognosis if NIV fails is poor, and the question of whether escalation to invasive ventilation is appropriate should be very carefully considered on an individual basis.

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