Detection of non-infectious conditions mimicking pneumonia in the intensive care setting: usefulness of bronchoalveolar fluid cytology


Departments of *Medical Microbiology, †Intensive Care Unit and ‡Pulmonology, University Hospital Maastricht and §Department of Pathology, Onze Lieve Vrouwen Gasthuis, Amsterdam, The Netherlands

The present study investigated the usefulness of bronchoalveolar (BAL) fluid cytology in the identification of non-infectious pulmonary conditions in patients hospitalized in the intensive care unit (ICU) and suspected of pneumonia. A total of 182 BAL fluid samples obtained during a 27-month period from 130 ICU patients with suspected pneumonia were quantitatively cultured and investigated for opportunistic pathogens. Cytocentrifuged preparations stained with the May-Grünwald Giemsa and Perls's methods were reviewed. A non-infectious aetiology was considered when cultures yielded micro-organisms in quantities < 10^3 colony-forming units (CFU) per ml, in the absence of any other pathogen and in conjunction with one or more of the following cytological findings: >20% haemosiderin macrophages, > 10% lymphocytes, the presence of activated lymphocytes, plasma cells, > 5% eosinophils, a preponderance of foamy macrophages, reactive type II pneumocytes or malignant cells. Patients' clinical records were reviewed to identify a clinical diagnosis for these episodes.

In thirty-five (19.2%) BAL fluid samples from 26 patients, the cytological findings pointed to a non-infectious origin. An alternative diagnosis was ascertained in 20 of 26 patients. Diagnoses included: drug-induced pneumonitis (n = 7), aspiration of gastric contents (n = 2), pulmonary emboli (n = 3), adult respiratory distress syndrome (n = 4), lung contusion (n = 1), cardiogenic pulmonary oedema (n = 1), and carcinomatous lymphangitis (n = 2). The BAL fluid cytological findings were readily discernable and proved to be useful in the diagnostic work-up of samples obtained from ICU patients with suspected pneumonia.

Introduction

Pneumonia is common in patients in intensive care units (ICUs), especially in mechanically ventilated patients. Establishing the diagnosis of pneumonia in these patients is notoriously difficult as clinical and radiological parameters offer a high sensitivity at the cost of an unacceptably low specificity (1). Adding the results of quantitative cultures of bronchoalveolar lavage (BAL) fluid increases the diagnostic specificity (2) but preliminary and definitive culture results take 24 h and up to 72 h, respectively.

Apart from infectious pneumonia, a number of non-infectious pulmonary conditions may explain the clinical symptoms of the ICU patient with suspected pneumonia. Such conditions include pulmonary haemorrhage, malignancy, drug-induced toxicity, the adult respiratory distress syndrome (ARDS) and cardiogenic pulmonary oedema. It is important to distinguish these conditions from pneumonia as the management and prognosis of these entities is quite different (3,4). Distinctive findings in BAL fluid cytology, such as lymphocytosis, the presence of activated lymphocytes, plasma cells and eosinophils or the preponderance of foamy macrophages point to drug-induced pulmonary disease (5,6), and the presence of reactive type II pneumocytes has been described in association with ARDS (7). BAL fluid cytological findings in ARDS are characterized by a marked predominance of neutrophils in the early phase and a recruitment of macrophages, lymphocytes and eosinophils in the late phase (8). A number of >20% haemosiderin macrophages has been demonstrated to be indicative for alveolar haemorrhage (9). Until now, however, the usefulness of BAL fluid cytology in the diagnosis of these non-infectious pulmonary conditions in ICU patients has received little attention in the
in daily practice, the use of BAL fluid cytology is limited to the enumeration of infected cells and to the identification of squamous epithelial cells which are indicative of oropharyngeal contamination (10,11).

In our hospital, bronchoscopy with BAL is routinely used in the diagnosis of pneumonia in the ICU setting (2). Recently, we introduced a standardized protocol for the cytocentrifugation process and included the differential cell count as part of the routine microbiological work-up of BAL fluid specimens. As we collected a series of consecutive BAL fluid samples performed in ICU patients with suspected pneumonia, we decided to evaluate the usefulness of BAL fluid cytology in the prediction of non-infectious pulmonary conditions. We therefore retrospectively looked for the diagnosis in those BAL fluid samples that showed cytological findings consistent with a non-infectious condition.

Materials and Methods

STUDY POPULATION

Over a 27-month period (January 1996 to April 1998), BAL fluid samples from ICU patients in the University Hospital Maastricht were obtained. All patients were suspected of having pneumonia as defined by clinical and radiological criteria (2).

SAMPLING TECHNIQUE

A fiber-optic bronchoscope (Pentax FB-15H/FB-15X, Pentad Medicals, Tokyo, Japan) was introduced through a special adaptor (Swivel Connector, Gibeck Respiration, Upplands Väsby, Sweden) and 'wedged' into the affected segmental or subsegmental bronchus. The fluid was instilled into the subsegment through the biopsy channel of the bronchoscope in four aliquots of 50 ml sterile saline (0.9% NaCl, room temperature) and immediately aspirated and recovered. The BAL fluid samples were transported to the laboratory within 15 min of collection and analysed within 1 h of arrival in the laboratory.

PROCESSING OF BAL FLUID SPECIMENS

The volume of the recovered BAL fluid was recorded. The first fraction, representing the bronchial fraction, was separated for mycobacterial culture and the remaining fractions were pooled for further analysis. The total cell count was performed in a Fuchs-Rosenthal haemocytometer chamber. BAL fluid samples were quantitatively cultured for bacteria and yeasts by means of a calibrated loop technique (12). They were also cultured for filamentous fungi and mycobacteria and, if clinically indicated, for viruses and Legionella spp. In addition, stains for detection of Pneumocystis carinii and Legionella pneumophila (immunofluorescent monoclonal antibody stainings), filamentous fungi (Methenamine-silver stain) and acid-fast bacteria (auramine-rhodamine stain) were performed on cytocentrifuged preparations. When a community-acquired pneumonia was suspected, serology for detection of viral pathogens was done and polymerase chain reactions for detection of Chlamydia pneumoniae and Mycoplasma pneumoniae were performed.

Cytocentrifugation was done with the Cytospin 3 apparatus (Shandon Scientific Ltd, Astmoor, U.K.) as previously described (13). Differential cell counts were made on May-Grünewald Giemsas (MGG) stained preparations, by the first or second author examining 500 nucleated cells. Both macrophages and neutrophils were screened for the presence of intracellular organisms and the number of infected cells was expressed as a percentage of the 500-cell aliquot counted. The preparations were sealed (Xylene substitute mountant, Shandon) and stored at room temperature. When basophilic granules were seen in macrophages or polymorphonuclear cells, Perls' stain for haemosiderin visualization was performed (14).

REJECTION CRITERIA

BAL fluid samples were excluded if the retrieved volume was less than 20 ml, if the cytocentrifuged preparations showed excessive amounts of red blood cells, intercellular debris or damaged nucleated cells, or if the differential cell count yielded 1% squamous epithelial cells or ≥5% ciliated cells.

DEFINITION

BAL fluid samples were categorized into four groups based on the following diagnostic criteria.

Group I, pneumonia microbiologically confirmed: this group consisted of samples for which quantitative cultures yielded micro-organisms in quantities ≥10⁶ colony forming units per millilitre (cfu ml⁻¹), or for which an obligatory respiratory pathogen such as P. carinii was demonstrated.

Group II, pneumonia not conclusive: BAL fluid samples were categorized as "not conclusive" when they had borderline quantitative culture results, i.e. counts ≥10³ and <10⁴ cfu ml⁻¹.

Group III, pneumonia excluded, no cytological abnormalities: infectious pneumonia was considered as microbiologically excluded at a culture threshold of <10³ cfu ml⁻¹ and <2% infected cells, and with no obligatory respiratory pathogen demonstrated. On cytological examination of the BAL fluid, none of the findings cited for Group IV was observed.

Group IV pneumonia excluded, non-infectious aetiology: BAL fluid samples were considered as 'non-infectious etiology' when pneumonia was microbiologically excluded (criteria as for Group III) in the absence of previous (within 72 h) antimicrobial therapy and when one or more of the following cytological findings were observed: the presence of malignant cells, a count of >10% lymphocytes, a count of >5% eosinophils, the presence of activated lymphocytes...
or plasma cells and the preponderance of foamy macrophages. Moreover, a number of >20% haemosiderin laden macrophages was considered as diagnostic for alveolar haemorrhage (9).

**REVIEW OF CLINICAL RECORDS**

The patients' clinical records were reviewed for clinical, radiological and laboratory evidence to identify diagnoses of non-infectious aetiology.

**Results**

During the study period, 1721 patients were admitted to the ICU and 228 bronchoscopies with BAL were performed (Fig. 1). Forty-six BAL fluid samples were excluded from analysis, resulting in 182 BAL fluid samples obtained from 130 patients.

Seventy-seven BAL fluid samples were considered as microbiologically proved pneumonia and allocated to Group I. *L. pneumophila* was identified as the pathogen in one BAL fluid sample, *P. carinii* in four BAL fluid samples (three patients) and a viral pneumonia was detected in three BAL fluid samples obtained in two patients (RSV and para-influenza virus, respectively). At a threshold of $10^4$ cfu ml$^{-1}$, infectious pneumonia was further confirmed in 69 BAL fluid samples. Group II (pneumonia not conclusive) consisted of 23 BAL fluid samples and 47 BAL fluid samples were included in Group III (pneumonia microbiologically excluded, no cytological abnormalities).

Based on the exclusion of a microbiological pathogen and on the presence of one or more of the cytological findings, 35 BAL fluid samples were assigned to Group IV ("non-infectious etiology"). These 35 BAL fluid samples accounted for 19.2% of the 182 included BAL fluid samples and were obtained from 26 (20%) of 130 patients (nine patients underwent repeat bronchoscopy with BAL).

Table 1 lists the non-infectious conditions identified by review of the clinical records in the 26 patients and the differential cell counts together with the cytological findings in the corresponding BAL fluid samples.

The patients' mean age was $62.8 \pm 14.2$ years, and the male to female ratio 1:36:1. Half (13) of the patients were admitted from the community, one patient was admitted from a nursing home and 12 were transferred from another hospital ward.

Bronchoscopy was performed after $11.2 \pm 13.9$ days of ICU admission (range 1–57 days), with seven BAL fluid samples obtained on the day of the patient's admission to the ICU. Twenty-six of 35 BAL fluid samples were obtained from ventilated patients; in 21 samples the patient was ventilated for more than 72 h prior to suspicion of pneumonia. For two BAL fluid samples, no data on ventilation were retrieved upon chart review.

Three patients demonstrated amiodarone-induced pneumonitis, which was confirmed histologically in one case. Nortriptyline pulmonary toxicity was observed after an accidental overdose in a psychiatric patient. Carbamazepine-induced pneumonitis occurred due to self-poisoning. Methotrexate-induced pneumonitis occurred in a patient treated because of rheumatoid arthritis. Mefloquine-induced pneumonitis was seen in a patient with hemizygote glucose-6-phosphate-dehydrogenase deficiency. Aspiration of gastric contents was documented in a patient during surgical treatment for achalasia and in another patient who aspirated enteral feeding during a prolonged ICU

![Flow chart of BAL fluid selection and definitions. Numbers exceed the total number of patients included as several patients underwent repeat bronchoscopy with BAL. **Bacteria <10^3/ml^-1 and <2% cells containing intracellular organisms.](image-url)
TABLE 1. Patients with microbiologically excluded pneumonia and with cytological evidence of a non-infectious pulmonary condition. The clinical diagnoses, the day of ICU stay at which bronchoscopy with BAL was performed, the BAL fluid differential cell counts and striking cytological findings are listed.

<table>
<thead>
<tr>
<th>No.</th>
<th>Patient Gender, age (years)</th>
<th>Clinical diagnosis</th>
<th>Day</th>
<th>TCC*</th>
<th>Pmn</th>
<th>Lym</th>
<th>Am</th>
<th>Eos</th>
<th>Mc</th>
<th>P</th>
<th>BAL fluid cytological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F, 74</td>
<td>Amiodarone pulmonary toxicity</td>
<td>2</td>
<td>213</td>
<td>9·6</td>
<td>18·0</td>
<td>69·7</td>
<td>0·2</td>
<td>2·5</td>
<td>0·0</td>
<td>Activated lymphocytes, foamy macrophages</td>
</tr>
<tr>
<td>2</td>
<td>M, 77</td>
<td>Amiodarone pulmonary toxicity</td>
<td>16</td>
<td>157</td>
<td>10·6</td>
<td>14·0</td>
<td>75·0</td>
<td>0·0</td>
<td>0·4</td>
<td>0·0</td>
<td>Activated lymphocytes, foamy macrophages</td>
</tr>
<tr>
<td>3</td>
<td>M, 74</td>
<td>Amiodarone pulmonary toxicity</td>
<td>11</td>
<td>159</td>
<td>74·7</td>
<td>7·9</td>
<td>16·2</td>
<td>0·8</td>
<td>0·4</td>
<td>0·0</td>
<td>Foamy macrophages</td>
</tr>
<tr>
<td>4</td>
<td>M, 70</td>
<td>Nortryptiline-intoxication</td>
<td>57</td>
<td>76</td>
<td>30·2</td>
<td>38·0</td>
<td>15·8</td>
<td>10·4</td>
<td>5·4</td>
<td>0·2</td>
<td>Activated lymphocytes, plasma cells, elevated eosinophil count</td>
</tr>
<tr>
<td>5</td>
<td>F, 35</td>
<td>Overdose with carbamazepine</td>
<td>2</td>
<td>159</td>
<td>89·4</td>
<td>4·6</td>
<td>6·0</td>
<td>0·0</td>
<td>0·0</td>
<td>0·0</td>
<td>Activated lymphocytes, foamy macrophages, reactive type II pneumocytes</td>
</tr>
<tr>
<td>6</td>
<td>F, 70</td>
<td>Methotrexate-induced toxicity</td>
<td>3</td>
<td>80</td>
<td>9·2</td>
<td>67·6</td>
<td>21·2</td>
<td>1·8</td>
<td>0·0</td>
<td>0·2</td>
<td>Marked lymphocytosis, plasma cells</td>
</tr>
<tr>
<td>7</td>
<td>M, 64</td>
<td>Mefloquine-induced pulmonary toxicity</td>
<td>6</td>
<td>103</td>
<td>0·2</td>
<td>75·2</td>
<td>22·6</td>
<td>0·0</td>
<td>1·0</td>
<td>1·0</td>
<td>Marked lymphocytosis, plasma cells</td>
</tr>
<tr>
<td>8</td>
<td>M, 53</td>
<td>Aspiration of gastric contents</td>
<td>5</td>
<td>400</td>
<td>77·6</td>
<td>5·4</td>
<td>15·2</td>
<td>1·8</td>
<td>0·0</td>
<td>0·0</td>
<td>Activated lymphocytes, foamy macrophages</td>
</tr>
<tr>
<td>9</td>
<td>M, 65</td>
<td>Aspiration of gastric contents</td>
<td>21</td>
<td>215</td>
<td>25·4</td>
<td>38·0</td>
<td>35·0</td>
<td>1·0</td>
<td>0·6</td>
<td>0·0</td>
<td>Activated lymphocytes, foamy macrophages</td>
</tr>
<tr>
<td>10</td>
<td>M, 72</td>
<td>Pulmonary embolisms</td>
<td>1</td>
<td>207</td>
<td>73·8</td>
<td>10·4</td>
<td>14·6</td>
<td>1·0</td>
<td>0·2</td>
<td>0·0</td>
<td>Reactive type II pneumocytes</td>
</tr>
<tr>
<td>11</td>
<td>M, 66</td>
<td>Pulmonary embolisms</td>
<td>1</td>
<td>124</td>
<td>18·9</td>
<td>49·2</td>
<td>30·5</td>
<td>0·6</td>
<td>0·8</td>
<td>0·0</td>
<td>Activated lymphocytes</td>
</tr>
<tr>
<td>12</td>
<td>F, 73</td>
<td>Pulmonary embolisms</td>
<td>3</td>
<td>254</td>
<td>73·4</td>
<td>9·8</td>
<td>16·8</td>
<td>0·0</td>
<td>0·0</td>
<td>0·0</td>
<td>Foamy macrophages, alveolar macrophages with large and distinct vacuoles</td>
</tr>
<tr>
<td>13</td>
<td>F, 52</td>
<td>ARDS</td>
<td>1</td>
<td>110</td>
<td>44·0</td>
<td>17·7</td>
<td>30·9</td>
<td>5·8</td>
<td>1·2</td>
<td>0·4</td>
<td>Activated lymphocytes, plasma cells, reactive type II pneumocytes</td>
</tr>
<tr>
<td>14</td>
<td>F, 66</td>
<td>ARDS</td>
<td>10</td>
<td>403</td>
<td>68·4</td>
<td>8·8</td>
<td>22·2</td>
<td>0·0</td>
<td>0·0</td>
<td>0·0</td>
<td>Activated lymphocytes</td>
</tr>
<tr>
<td>15</td>
<td>F, 67</td>
<td>ARDS</td>
<td>17</td>
<td>130</td>
<td>58·0</td>
<td>19·4</td>
<td>21·6</td>
<td>1·0</td>
<td>0·0</td>
<td>0·0</td>
<td>Activated lymphocytes, presence of foamy macrophages</td>
</tr>
<tr>
<td>16</td>
<td>M, 47</td>
<td>ARDS</td>
<td>32</td>
<td>658</td>
<td>8·8</td>
<td>58·8</td>
<td>29·8</td>
<td>0·0</td>
<td>0·2</td>
<td>2·4</td>
<td>Activated lymphocytes, plasma cells, presence of foamy macrophages</td>
</tr>
<tr>
<td>17</td>
<td>M, 34</td>
<td>Lung contusion</td>
<td>43</td>
<td>224</td>
<td>58·4</td>
<td>18·8</td>
<td>22·8</td>
<td>0·0</td>
<td>0·0</td>
<td>0·0</td>
<td>Activated lymphocytes, presence of foamy macrophages</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45</td>
<td>421</td>
<td>51·0</td>
<td>8·0</td>
<td>40·4</td>
<td>0·6</td>
<td>0·0</td>
<td>0·0</td>
<td>Activated lymphocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>460</td>
<td>84·9</td>
<td>8·7</td>
<td>2·0</td>
<td>4·4</td>
<td>0·0</td>
<td>0·0</td>
<td>Activated lymphocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>320</td>
<td>13·4</td>
<td>28·6</td>
<td>58·0</td>
<td>0·0</td>
<td>0·0</td>
<td>0·0</td>
<td>Elevated lymphocyte count</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>210</td>
<td>48·2</td>
<td>5·2</td>
<td>45·6</td>
<td>0·8</td>
<td>0·2</td>
<td>0·0</td>
<td>Activated lymphocytes, foamy macrophages, 20% haemosiderin macrophages</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>------------------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>--------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>F, 77</td>
<td>Pulmonary oedema with alveolar haemorrhage</td>
<td>5</td>
<td>184</td>
<td>1-4</td>
<td>3-5</td>
<td>94-9</td>
<td>0-2</td>
<td>0-0</td>
<td>0-0 Alveolar macrophages with haemosiderin granules, 60% haemosiderin macrophages</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>M, 78</td>
<td>Carcinomatous lymphangitis</td>
<td>9</td>
<td>1280</td>
<td>93-6</td>
<td>2-2</td>
<td>4-2</td>
<td>0-0</td>
<td>0-0</td>
<td>0-0 Malignant cells</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>M, 65</td>
<td>Carcinomatous lymphangitis</td>
<td>6</td>
<td>300</td>
<td>11-8</td>
<td>21-2</td>
<td>65-6</td>
<td>0-0</td>
<td>1-4</td>
<td>0-0 Malignant cells</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>F, 64</td>
<td>No diagnosis ascertained</td>
<td>4</td>
<td>432</td>
<td>2-2</td>
<td>2-0</td>
<td>95-4</td>
<td>0-4</td>
<td>0-0</td>
<td>0-0 Abundance of foamy macrophages</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>F, 49</td>
<td>No diagnosis ascertained</td>
<td>1</td>
<td>237</td>
<td>52-0</td>
<td>16-8</td>
<td>31-2</td>
<td>0-0</td>
<td>0-0</td>
<td>0-0 Abundance of foamy macrophages</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>F, 27</td>
<td>No diagnosis ascertained</td>
<td>6</td>
<td>346</td>
<td>27-7</td>
<td>15-7</td>
<td>53-2</td>
<td>3-2</td>
<td>0-2</td>
<td>0-0 Lymphocytosis, abundance of foamy macrophages</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>M, 72</td>
<td>No diagnosis ascertained</td>
<td>19</td>
<td>84</td>
<td>26-2</td>
<td>35-6</td>
<td>34-0</td>
<td>4-2</td>
<td>0-0</td>
<td>0-0 Abundance of foamy macrophages</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>M, 65</td>
<td>No diagnosis ascertained</td>
<td>25</td>
<td>90</td>
<td>31-2</td>
<td>31-6</td>
<td>35-4</td>
<td>1-8</td>
<td>0-0</td>
<td>0-0 Lymphocytosis, activated lymphocytes</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>M, 76</td>
<td>No diagnosis ascertained</td>
<td>3</td>
<td>73</td>
<td>9-0</td>
<td>16-0</td>
<td>73-8</td>
<td>0-6</td>
<td>0-6</td>
<td>0-0 Activated lymphocytes, foamy macrophages with distinct vacuoles</td>
<td></td>
</tr>
</tbody>
</table>

* TCC = total cell count, values expressed in $10^3$ ml$^{-1}$.
† Counts performed on 500 nucleated cells. Pmn = polymorphonuclear neutrophils, Lym = lymphocytes, Am = alveolar macrophages, Eos = eosinophils, Mc = mast cells, P = plasma cells.
stay. Pulmonary emboli were found at autopsy in two patients and a third patient developed multiple pulmonary emboli after surgical revision of a hip prosthesis. Based on respiratory parameters and a clinical picture, the diagnosis of ARDS was assessed in four patients; in one of them the diagnosis was confirmed on histological examination at post-mortem. Numerous iron-laden macrophages were seen in one patient with lung contusion and in another patient with severe cardiogenic pulmonary oedema. Malignant cells originating from a disseminated lung adenocarcinoma were seen in two patients; in one of them, the BAL fluid cytology findings provided the first suspicion of malignancy.

Overall, in seven patients the aetiological diagnosis was established by histology obtained by biopsy or autopsy and in 13 patients the diagnosis was supported by clinical, radiological and laboratory findings. In the six remaining patients, data regarding the clinical status were not conclusive.

Discussion

Based upon the absence of a microbiological pathogen and upon cytological evidence present in MGG-stained cytocentrifuged preparations, in this study we classified 35/182 (19.2%) BAL fluid samples as of non-infectious origin. These BAL fluid samples were obtained in 26 ICU patients with suspected pneumonia. Retrospectively, we identified a diagnosis explaining the non-infectious condition in 20 of the 26 patients.

We realize that one of the major limitations of this study was its retrospective design. This design did not allow tracing of all cases of non-infectious lung conditions. As the use of antimicrobial agents prior to bronchoscopy was not systematically documented, reliable exploration of Group II (pneumonia not conclusive, BAL fluid with borderline quantitative culture results) and Group III (pneumonia excluded, no cytological abnormalities) was not possible. Neither were we able to identify a diagnosis in all non-infectious BAL fluid samples. In particular, difficulties were encountered in the retrospective diagnosis of ARDS and drug-induced pneumonitis. In the case of a suspected drug-induced pneumonitis, a definite role for a particular drug cannot be proven in the absence of rechallenge. In the present series, rechallenge supported the diagnosis of carbamazepine-induced toxicity as the patient was re-admitted with a second auto-intoxication. The role of meloquine was confirmed by restarting of the drug prior to the drug being suspected. Both cases have been described elsewhere in detail (15,16). Among others, amiodarone, methotrexate and anti-depressants are known to be capable of causing drug-induced pneumonitis (17-19). In the cases presently described, these drugs were considered as causative because withdrawal of the drug resulted in clinical and radiological improvement.

Reviewing a large number of studies, Timsit et al. concluded that about two-thirds of the episodes of suspected pneumonia in ventilated patients do not meet quantitative culture criteria but are related to other conditions. The authors however admitted that no data definitely supported their conclusion, as many of these episodes were believed to be false-negative pneumonias in which bacterial growth was suppressed by the administration of antimicrobial agents prior to bronchoscopy (20). In view of their supposition, it is striking that few studies list an alternative diagnosis for those episodes with no microbiological evidence of pneumonia (3,4,21,22). The reported incidences of non-infectious conditions in these studies were higher than in the present study, but non-infectious BAL fluid samples were defined at a culture threshold of $<10^4$ CFU ml$^{-1}$, whereas in the present study a threshold of $<10^3$ CFU ml$^{-1}$ was applied to exclude BAL fluid samples with borderline quantitative culture results. The low culture threshold in the present study was combined to a threshold for infected cells of 2%, which is the lowest cited cutoff value (23). By using these stringent criteria, we aimed to minimise the diagnosis of false-negative infectious pneumonia but probably may have underestimated the number of non-infectious conditions.

Second, the authors of previous studies looked for alternative diagnoses in all non-infectious BAL fluid samples, irrespective of the BAL fluid cytological findings. In this way, their alternative diagnoses included more cases of atelectasis, pleural involvement and pulmonary oedema, which are conditions for which, to our knowledge, no specific cytological BAL fluid findings have been described. Although the present study did not intend to search an alternative diagnosis in Groups II and III, we assume that conditions such as atelectasis and pleural involvement may have been present in at least part of these episodes. The exact incidences and nature of the non-infectious conditions in this setting should however be addressed by a prospective study.

In contrast to previous studies, we added the findings of the cytological examination to direct the investigation to a non-infectious condition. Retrospectively, we were able to demonstrate an alternative diagnosis for infectious pneumonia in 20 (77%) out of the 26 patients that were selected based on well-defined cytological criteria. Most microbiological laboratories are reluctant to perform BAL differential cell counts as these counts are not always unequivocal (24) and cannot differentiate bronchial infection from lung infection (25). Moreover, performing BAL fluid differential cell counts requires skilled microscopists and is looked upon as labourious and time-consuming in times of limited sources and tendencies to automation. The cytological findings looked for in the present study are, however, easily discernable on MGG-stained cytocentrifuged preparations. The processes of cytocentrification, MGG staining and cell differentiation as described here can be achieved within a 2-h period, making the results of the BAL fluid cytology available within a very short delay. The MGG stain (or an equivalent one) with the differential cell count can be conveniently incorporated into the routine microbiological work-up of BAL fluid samples. Other advantages of the MGG stain are its ability to detect P. carinii (12) and its reliability for enumeration of intracellular organisms (13). The sensitivity of the cytological findings for the detection of a non-infectious origin,
together with the feasibility and the low turn-over time of the procedure, lead us to recommend BAL fluid cytology as part of the routine work-up in cases of ICU patients with suspected pneumonia.

One should note that the cytological findings under consideration are not pathognomonic. They point to the possibility of a non-infectious condition which has to be confirmed and identified by clinical, radiological or laboratory findings. In our experience, the above-listed cytological findings were not specific for the non-infectious BAL fluid samples. In this way, we also observed alveolar haemorrhage in seven of the 69 bacterial pneumonias, in agreement with the association between alveolar haemorrhage and infection reported by others (9). Moreover, seven of the patients in whom a non-infectious aetiology was diagnosed developed a pneumonia during their further ICU stay. In BAL fluid samples from patients with P. carinii pneumonia, we occasionally observed foamy macrophages and plasma cells similar to cases of drug-induced toxicity (unpublished observations) and we have noted elevated numbers of lymphocytes in BAL fluids obtained from patients with tuberculosis, in line with the findings of others (26,27). These observations emphasize the importance of a thorough microbiological investigation, even if BAL fluid cytology at first glance points to a non-infectious condition. Further, it should be noted that the presence of foamy macrophages in the case of amiodarone intake may represent amiodarone-impregnation and do not necessarily imply toxicity (6).

From Table 1, it is clear that, apart from malignancy, none of the cytological findings was confined to a particular non-infectious aetiology. This may partly be explained by an overlap between the distinct conditions, i.e., both lung contusion and aspiration of gastric contents are well-known risk factors for the development of ARDS (28) and non-infectious processes may co-exist with pneumonia (29). It is clear that the discriminatory power of the cytological findings will be augmented if the number of BAL fluid samples included for comparison increases. For this reason, we are presently conducting a prospective study that will investigate the predictive value of the different cytological parameters and their combinations.

In conclusion, the present study demonstrated the value of the BAL fluid cytological findings for the diagnosis of non-infectious conditions in ICU patients with suspected pneumonia. We recommend incorporating BAL fluid cytology as part of the routine work-up of BAL fluid samples obtained in the ICU setting. A prospective study should address the exact incidence and aetiologies of non-infectious pulmonary conditions in the ICU setting and allow refinement of the cytological description. In this way, cytology may further improve the diagnostic accuracy of BAL fluid analysis in ICU patients with suspected pneumonia.

Acknowledgement

The authors thank Dr J. Tjhie for performing the PCR analysis.

References