Dexamethasone in Patients with Acute Lung Injury from Acute Monocytic Leukemia

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Abstract

The use of steroids is not required in myeloid malignancies and remains controversial in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). We sought to evaluate dexamethasone in patients with ALI/ARDS caused by acute monocytic leukemia (AMLFAB-M5) via either leukostasis or leukemic infiltration. Dexamethasone (10 mg/6 hours until neutropenia) was added to chemotherapy and ICU management in 20 consecutive patients between 2005 and 2008, whose data were compared to those from 20 historical controls (1994-2002). ICU mortality was the primary criterion. We also compared respiratory deterioration rates, need for ventilation, and nosocomial infections. Seventeen (85%) patients had hyperleukocytosis, 19 (95%) had leukemic masses, and all 20 had severe pancytopenia. All patients presented with respiratory symptoms and pulmonary infiltrates prior to AMLFAB-M5 diagnosis. Compared to historical controls, dexamethasone-treated patients had a significantly lower ICU mortality rate (20% vs. 50%, $P=0.04$) and a trend for less respiratory deterioration (50% vs. 80%, $P=0.07$). There were no significant increases in the rates infections with dexamethasone. In conclusion, patients with ALI/ARDS related to AML FAB-M5, adding dexamethasone to conventional chemotherapy seemed effective and safe. These results warrant a controlled trial of dexamethasone versus placebo in AMLFAB-M5 patients with non-infectious pulmonary infiltrates.

Word count: 200

INTRODUCTION

Among patients with acute leukemia, up to half experience respiratory events early in the course of the disease [1,2]. In this situation, progression to acute respiratory failure requiring ventilatory support is a severe complication that is not only frequently fatal [3,4], but also delays the administration of optimal chemotherapy [5].

In patients with acute leukemia and pulmonary infiltrates, infection must be sought and treated empirically [3]. However, pulmonary involvement may be directly due to the malignancy. In patients with myelomonocytic or monocytic acute leukemia, leukemia-related pulmonary involvement is frequent and severe [6-8]. The diagnosis rests on negative findings from extensive tests for the main infectious and noninfectious causes. Leukemia-related pulmonary involvement includes pulmonary leukostasis, leukemic pulmonary infiltrates, and lysis pneumopathy [9-18]. We previously described 20 patients with acute monocyctic leukemia (FAB M5-AML) who presented with leukemic infiltrates or leukostasis at the earliest phase of the malignancy [8]. All patients experienced lysis pneumopathy within hours after chemotherapy initiation. Mechanical ventilation and mortality rates were high, indicating a need to develop better treatment strategies. In addition to early ICU management, best supportive care, and rapid cytoreduction via hydration and chemotherapy, antiinflammatory therapy would be expected to improve outcomes in these patients.

Steroid therapy has been used with variable results to prevent ARDS in high-risk patients [19], in short courses to treat early severe ARDS [20], and as rescue therapy in patients with persistent ARDS [21,22]. In AML FAB-M5 patients, steroids would be expected to decrease cytokine and oxidant release, blast adhesion to endothelial cells, and blast degeneration within the interstitium [15]. Steroids may both limit the extent of initial lung injury, as shown in patients with all-trans retinoic acid (ATRA) syndrome [23], and prevent lysis pneumopathy.
The objective of this study was to evaluate whether adding dexamethasone to the chemotherapy protocol in patients with acute monocytic leukemia (AML FAB-M5) and ALI/ARDS due to leukemic pulmonary involvement improved survival and decreased the incidence of respiratory deterioration and the need for ventilatory support.
PATIENTS AND METHODS

Consecutive patients with newly diagnosed and previously untreated M5-AML admitted to our ICU between January 1, 2005, and December 31, 2008 for acute respiratory failure were eligible for enrollment. The main inclusion criteria were as follows: i) cytologically documented M5-AML (according to the WHO classification, ≥20% leukemic blasts in the bone marrow with monocytic cells comprising more than 80% of non erythroids cells), ii) respiratory symptoms and pulmonary infiltrates at the earliest phase of M5-AML, iii) ICU admission for acute respiratory failure defined by respiratory rate > 30, oxygen saturation < 90% or signs of respiratory distress, iv) no chemotherapy before ICU admission, and v) no clinical or microbiological evidence of infection. Our institutional review board (Saint-Louis Teaching Hospital, Paris, France) approved the prospective data collection of AML cases, which was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization, and Guidelines for Good Clinical Practice. The protocol for treating AML FAB-M5 patients with non-infectious pulmonary manifestations at the earliest phase of the disease was amended by the addition of dexamethasone. All patients were informed of the diagnosis of AML FAB-M5, likelihood that the pulmonary manifestations were related to the leukemia, and use of dexamethasone added to conventional chemotherapy to limit the severity of ALI/ARDS severity and to prevent lysis pneumopathy.

ICU management was provided jointly by intensivists and hematologists. All patients underwent induction chemotherapy with an anthracycline plus cytarabine–based regimen. Based on previous experience in hyperleukocytic patients with acute promyelocytic leukemia, Dexamethasone has been preferred to methylprednisolone or hydrocortisone [24]. Dexamethasone (10 mg/6 hours intravenously) was given until leucopenia (<1G/L) occurred. ICU management included optimal ventilatory support with supplemental oxygen, noninvasive ventilation (NIV), and/or invasive mechanical ventilation (MV) as appropriate
and other life-sustaining therapies as required [8,26]. All patients underwent noninvasive tests for pathogens in sputum, induced sputum, nasopharyngeal aspirates, blood, and urine [25,27]. Echocardiography was normal in all patients. Patients requiring endotracheal intubation routinely underwent bronchoscopy and bronchoalveolar lavage (BAL). Antibiotics covering community-acquired pathogens (third-generation cephalosporin or piperacillin-tazobactam plus a macrolide/quinolone) were given to all patients for 7 days despite negative results of all tests for infection.

Variables listed in Tables 1 and 2 were collected prospectively. Vital status at ICU and hospital discharge was known for all study patients. Safety evaluation included mostly the proportion of patients presenting with hospital acquired bacterial or opportunistic infection.

Statistical analysis

Quantitative parameters are reported as median and interquartile range (IQR, 25th -75th percentile) and qualitative parameters as number and percentage. Comparisons were performed between the 20 patients given dexamethasone and 20 historical controls (previously published) who received the same treatment without steroids. ICU mortality was the primary evaluation criterion. Categorical variables were compared using the χ² test or Fisher’s exact test, as appropriate. Continuous variables were compared using the Mann-Whitney U test or the Wilcoxon test, as appropriate.

Associations between patient characteristics and hospital mortality were assessed using a logistic regression model. Multivariable analysis was performed using stepwise forward selection to introduce variables whose P values were smaller than 0.20 by univariate analysis. Then, the absence of a significant increase in the likelihood value after omission of each of the remaining variables was checked. Goodness of fit was evaluated using the Hosmer-
Lemeshow statistic. Odds ratios (OR) and their 95% confidence intervals (95%CI) were computed. $P$ values less than 0.05 were considered statistically significant. Analyses were done using the SAS 9.1 software package (SAS Institute, Cary, NC).
RESULTS

From January 2005 to December 2008, 450 patients with newly diagnosed acute myeloid leukemia were admitted to the Saint-Louis Teaching Hospital, including 45 (10%) with M5-AML, of whom 20 (44%) required ICU admission before chemotherapy initiation for respiratory manifestations with onset before the diagnosis of leukemia (Figure 1). Of these 20 patients, 11 were admitted directly to the ICU for acute respiratory failure and 9 were transferred from the hematological wards within 12 (6-36) hours after admission. In 14 patients, AML FAB-M5 was diagnosed during the ICU stay.

As reported in Table 1, there were 13 men and 7 women with a median age of 42 years (33-60). None had any co-morbidity. All patients had severe acute respiratory failure with tachypnea and profound hypoxemia. The chest radiographs consistently showed diffuse lung infiltrates. The SAPS II score was 39 (29-50). All 20 patients were febrile and all but 1 had physical evidence of leukemic masses. Laboratory findings included high WBC count in 17 patients, circulating blast cells in 16, and platelet count below 50 G/L in 12. The 3 patients without hyperleukocytosis had less than 10 G/L with no circulating blast cells. Disseminated intravascular coagulation was present in 7 patients.

As shown in Table 2, within a few hours after chemotherapy initiation, 10 patients had no respiratory status deterioration or increase in oxygen requirements and 10 had a deterioration in oxygenation requiring invasive MV. An additional patient required intubation and ventilation because of complex ventricular arrhythmia. Median length of ICU stay was 7 days (25th-75th, 3.5-14). ICU and hospital survival rates were both 80% (4 deaths). All 16 survivors were in remission after neutropenia recovery and received consolidation chemotherapy. One-year survival was 60% (8 deaths).

None of the baseline characteristics differed significantly between the historical controls and the dexamethasone-treated patients (Tables 1 and 2). In particular, the severity of
respiratory failure and characteristics of the leukemia were well balanced between the two groups.

In-ICU mortality was significantly lower in the dexamethasone group than in the control group (20% vs. 50%, $P=0.04$). In the dexamethasone-treated group, we found decreases in the occurrence of respiratory status deterioration, need for increased oxygen flow, and need for ventilatory support, compared to the controls (Figure 2). Chemotherapy initiation was followed by respiratory status deterioration in only 4 (20%) dexamethasone-treated patients compared to 20 (100%) controls.

Dexamethasone therapy was not associated with increased rates of hospital-acquired bacterial or invasive fungal infections.

Table 3 reports the results of the multivariate analysis for factors associated with ICU mortality. Higher respiratory rate and lower SpO$_2$ at ICU admission were independently associated with ICU mortality. Dexamethasone therapy was associated with a trend for a decrease in ICU mortality by multivariate analysis.
DISCUSSION

We evaluated the efficacy and safety of dexamethasone therapy in patients with AML FAB-M5 and noninfectious pulmonary infiltrates. Compared to historical controls who did not receive dexamethasone, patients given dexamethasone had a decrease in the severity of pulmonary involvement and a lower rate of respiratory status deterioration after chemotherapy initiation. ICU mortality was lower in the dexamethasone-treated patients than in the historical controls.

Pulmonary leukostasis occurs in patients with acute myeloid leukemia and rapidly increasing white blood cell count [10,11] and is consistently present when the count exceeds 200 G/L [12]. Pulmonary leukostasis leads to endothelial injury and activation from microvascular invasion, with hyperviscosity, leukocytic microthrombi, oxygen steal, and hypoxia [13-15]. Leukemic pulmonary infiltrates occur in patients with or without hyperleukocytosis. This fact suggests that both the type of the blasts and their affinity for the pulmonary endothelium may be responsible for lung injury [8,28]. Autopsy studies have shown blast aggregates within the vessel lumina [29]. The infiltrates typically follow the lymphatic routes along the bronchovascular bundles, interlobular septa, and pleural interstitial tissue [16-18]. Finally, lysis pneumopathy occurs immediately or early after chemotherapy initiation as a manifestation of acute tumor lysis syndrome. Lysis pneumopathy consists in diffuse alveolar damage [30] and is most common in patients with hyperleukocytic acute myeloid leukemia, particularly the myelomonocytic subtypes with abnormal marrow eosinophils [31].

Steroids have been used in early severe ARDS to improve oxygenation by decreasing lung collagen and edema formation [32,33]. However, steroid use in patients with persistent ARDS is controversial [21,22]. Steroids are a major component of the treatment regimen for acute lymphocytic leukemia but are not used in patients with acute myeloid leukemia [34].
patients with promyelocytic leukemia given ATRA, dexamethasone was very effective in
preventing or treating ATRA-related pulmonary toxicity [23,35].

Non-infectious pulmonary involvement is particularly common in patients with
hyperleukocytotic myeloid leukemia, particularly of the M4 and M5 subtypes [18]. In a
previous study, we described 20 AML FAB-M5 patients with acute respiratory failure from
pulmonary leukostasis and leukemic infiltration before the diagnosis of leukemia [8]. All 20
patients had postchemotherapy lysis pneumopathy. Ten patients died, indicating a need for an
intervention targeting the pathophysiological mechanisms responsible for the initial lung
injury and subsequent respiratory status deterioration. Steroid therapy was a good candidate,
as steroids are widely used in various subsets of ALI [33] and chemotherapy-related
pulmonary toxicity [23]. Our data suggest that steroid therapy may not only limit pulmonary
leukostasis and leukemic infiltration, but also prevent lysis pneumopathy. Compared to the
control group, the dexamethasone-treated group was characterized by lower rates of
respiratory status deterioration, mechanical ventilation, and death. We found no significant
increase in infections in the dexamethasone-treated group compared to the control group.

Our study has several limitations. We used historical controls, and the recruitment
period from the first control to the last dexamethasone-treated patient spans 15 years, during
which changes in the management of ALI/ARDS and increasing experience may have
affected patient outcomes [36]. However, the dexamethasone and control patients were not
different at baseline and received the same hematological and ICU management. Our data
suggest that a multicenter randomized controlled trial testing the risk/benefit ratio of
dexamethasone in patients with AML FAB-M5 and non-infectious pulmonary involvement
may be warranted. Whether such a trial should be extended to all patients with acute
leukemia-related non-infectious pulmonary involvement requires discussion. A second
limitation of the study is that we did not record non-infectious adverse effects of
dexamethasone therapy (e.g., poor glucose control). Future studies will need to record all possible adverse effects. Last, we assumed that all patients with AML FAB-M5, acute respiratory failure, pulmonary infiltrates, and negative tests for infection had leukemia-related pulmonary involvement. This reflects our standard diagnostic strategy, which is supported by five arguments. First, postmortem studies have established that the noninfectious pulmonary complications of acute leukemia include leukostasis, leukemic infiltration, and lysis pneumopathy [8], as well as alveolar proteinosis, which is extremely rare [37]. Second, opportunistic infections are not encountered at the earliest phase of AML [3]. In contrast to patients with acute lymphoid leukemia, patients with AML FAB-M5 and infection usually have community-acquired bacteria. All our patients received combination antibiotic therapy for 7 days starting at ICU admission. However, we cannot strictly rule out the diagnosis of infection, based on our data including post mortem biopsies in only two historical controls. Along this line, Confalonieri et al. reported benefits from steroids in patients with severe community-acquired pneumonia [38]. Third, our study was done in a homogeneous group of patients with AML FAB-M5 patients (monocytic subtype) and inaugural respiratory failure. Among the 20 historical controls, diffuse hemorrhage by BAL and post-mortem biopsies was a major finding. We believe this finding is sufficiently suggestive to maintain a high level of suspicion for leukemia-related pulmonary infiltrates in patients with untreated AML FAB-M5 and inaugural acute respiratory failure. However, overlap may occur between lysis pneumopathy and cytarabine-induced pulmonary toxicity. Such overlap would further support steroid therapy [39]. Fourth, all patients underwent noninvasive diagnostic tests to rule out infection [25,27]. Also, all intubated patients underwent bronchoscopy and BAL, which consistently showed diffuse alveolar hemorrhage. Fifth, the decrease in ICU mortality among dexamethasone patients in our study supports our presumptive diagnosis of leukemia-related pulmonary involvement without infection. Last, changes in mortality between historical
controls and Steroids-treated cases could have been ascribable to differences in ICU management and ventilatory strategies. However, median tidal volume was 9ml/kg (6-10) in historical controls and 9ml/kg (7-10) in steroids-treated cases (p=NS). Corresponding figures for PEEP were 7 (2-11) and 9 cmH2O (5-15) (p=NS).

In summary, adding dexamethasone to the chemotherapy regimen in AML FAB-M5 patients with acute respiratory failure from leukemia-related pulmonary involvement significantly diminished ICU mortality. In addition, the rate of postchemotherapy deterioration and the need for ventilatory support decreased with dexamethasone therapy. These results suggest that dexamethasone may be effective in decreasing leukemic pulmonary infiltration and leukostasis and in preventing lysis pneumopathy. We found no increase in infection rates with dexamethasone therapy. Although these data are not sufficient to make a recommendation about using dexamethasone, they warrant a trial of dexamethasone in patients with AML FAB-M5 presenting as acute respiratory failure without evidence of infection.
References


Table 1: Patient characteristics at ICU admission

<table>
<thead>
<tr>
<th></th>
<th>Historical controls, N=20</th>
<th>Dexamethasone group, N=20</th>
<th>P Value</th>
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<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>50 (36-65)</td>
<td>42 (33-60)</td>
<td>0.38</td>
</tr>
<tr>
<td>Male gender</td>
<td>13 (65)</td>
<td>13 (65)</td>
<td>0.99</td>
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<tr>
<td>Respiratory symptoms at presentation</td>
<td></td>
<td></td>
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<tr>
<td>Respiratory rate</td>
<td>33 (29-40)</td>
<td>31 (22-36)</td>
<td>0.11</td>
</tr>
<tr>
<td>Diffuse crackles at lung auscultation</td>
<td>11 (55)</td>
<td>10 (50)</td>
<td>0.88</td>
</tr>
<tr>
<td>PaO2 on room air at admission</td>
<td>44 (38-53)</td>
<td>44 (37-57)</td>
<td>0.67</td>
</tr>
<tr>
<td>Lower SpO2 on room air</td>
<td>80 (55-92)</td>
<td>77 (60-95)</td>
<td>0.44</td>
</tr>
<tr>
<td>Time from dyspnea onset</td>
<td>2 (1-5)</td>
<td>3 (0-19)</td>
<td>0.50</td>
</tr>
<tr>
<td>Clinical presentation of AML FAB-M5 at ICU admission</td>
<td></td>
<td></td>
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<tr>
<td>Headaches</td>
<td>4</td>
<td>4</td>
<td>0.99</td>
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<tr>
<td>Tonsil infiltration</td>
<td>7</td>
<td>6</td>
<td>0.45</td>
</tr>
<tr>
<td>Spleen and liver enlargement</td>
<td>14</td>
<td>17</td>
<td>0.14</td>
</tr>
<tr>
<td>Gingival infiltration</td>
<td>10</td>
<td>10</td>
<td>0.99</td>
</tr>
<tr>
<td>DIC</td>
<td>4</td>
<td>14</td>
<td>0.003</td>
</tr>
<tr>
<td>Temperature</td>
<td>38°C4 (37°C7-39°)</td>
<td>38°C7 (37°C7-39°5)</td>
<td>0.66</td>
</tr>
<tr>
<td>Leukocyte count (G/L)</td>
<td>98 (15-183)</td>
<td>149 (100-204)</td>
<td>0.08</td>
</tr>
<tr>
<td>Circulating blast cell count (G/L)</td>
<td>100 (65-169)</td>
<td>106 (83-180)</td>
<td>0.87</td>
</tr>
<tr>
<td>Platelet count (G/L)</td>
<td>32 (19-68)</td>
<td>52 (32-70)</td>
<td>0.20</td>
</tr>
<tr>
<td>Hemoglobin level (g/dL)</td>
<td>9.2 (7.2-19)</td>
<td>8.9 (7.1-9.8)</td>
<td>0.48</td>
</tr>
<tr>
<td>Radiographic findings</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Bilateral alveolar opacities</td>
<td>14 (60)</td>
<td>7 (35)</td>
<td></td>
</tr>
<tr>
<td>Bilateral interstitial opacities</td>
<td>5 (25)</td>
<td>10 (50)</td>
<td></td>
</tr>
<tr>
<td>Focal opacity</td>
<td>1 (5)</td>
<td>3 (15)</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>3 (15)</td>
<td>5 (25)</td>
<td></td>
</tr>
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</table>

IQR, interquartile range; PaO2, partial pressure of oxygen in arterial blood; SpO2, oxygen saturation by pulse oximetry; AML FAB-M5, acute myeloid leukaemia subtype 5; DIC, diffuse intravascular coagulation
Table 2: ICU management in historical control patients and in patients given dexamethasone

<table>
<thead>
<tr>
<th>N (%) or Median (IQR)</th>
<th>Historical controls, N=20</th>
<th>Dexamethasone group, N=20</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS II at ICU admission</td>
<td>44 (35-51)</td>
<td>39 (29-50)</td>
<td>0.54</td>
</tr>
<tr>
<td>Time from hospital to ICU admission</td>
<td>1 (0-3)</td>
<td>0.5 (0-3)</td>
<td>0.85</td>
</tr>
<tr>
<td>Bronchoscopy and BAL performed</td>
<td>20 (100)</td>
<td>5 (20)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Deterioration of respiratory status after chemotherapy initiation</strong></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>none</td>
<td>0 (0)</td>
<td>4 (20)</td>
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<tr>
<td>increased oxygen needs</td>
<td>4 (20)</td>
<td>6 (30)</td>
<td></td>
</tr>
<tr>
<td>invasive mechanical ventilation</td>
<td>15 (75)</td>
<td>10 (50)</td>
<td></td>
</tr>
<tr>
<td><strong>Use of NIV</strong></td>
<td>11 (55)</td>
<td>3 (15)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Need for NIV or MV</strong></td>
<td>15 (75)</td>
<td>11 (55)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Cardiac arrest after chemotherapy initiation</strong></td>
<td>3 (15)</td>
<td>1 (5)</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>ICU-acquired events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive fungal infection</td>
<td>3 (15)</td>
<td>1 (5)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hospital-acquired infection</td>
<td>7 (35)</td>
<td>2 (10)</td>
<td>0.05</td>
</tr>
<tr>
<td>Septic shock</td>
<td>11 (55)</td>
<td>6 (30)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Length of ICU stay</strong></td>
<td>8 (3.5-18.5)</td>
<td>7 (3.5-14)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>ICU mortality</strong></td>
<td>10 (50)</td>
<td>4 (20)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

IQR, interquartile range; SAPS II, Simplified Acute Physiology Score version II; ICU, intensive care unit; BAL, bronchoalveolar lavage; NIV, noninvasive mechanical ventilation; MV, invasive mechanical ventilation
Table 3: Factors independently associated with ICU mortality by multivariable analysis

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Respiratory rate at admission</td>
<td>1.22/ point</td>
<td>1.01-1.48</td>
<td>0.036</td>
</tr>
<tr>
<td>Dexamethasone (versus historical controls)</td>
<td>0.12</td>
<td>0.01-1.23</td>
<td>0.054</td>
</tr>
<tr>
<td>Time from hospital to ICU admission</td>
<td>1.17/ day</td>
<td>0.97-1.40</td>
<td>0.098</td>
</tr>
<tr>
<td>SAPS II score at ICU admission</td>
<td>1.06/point</td>
<td>0.96-1.17</td>
<td>0.216</td>
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</table>

SAPS II, Simplified Acute Physiology Score version II; ICU, intensive care unit
Figure legends

Figure 1: Patient flow chart.
‡ the study periods ran from January 1994 to July 2002 and from January 2005 to December 2008.

Figure 2: Impact of dexamethasone therapy on clinical outcomes. Columns in gray refer to dexamethasone-treated patients and columns in black to historical controls. An additional patient from the dexamethasone group received ventilation for complex arrhythmia.
1079 patients admitted to the hospital for Acute Myeloid Leukemia during the study period, including 75 (7%) patients with Acute Monoblastic Leukemia (AML5).

40 (53%) AML5 patients with Acute Respiratory Failure from Leukemic Pulmonary Infiltration at the earliest phase of AML5.

20 historical controls receiving Urgent chemotherapy alone.
- 20 (100%) respiratory worsening after chemotherapy, including 16 (80%) patients needing ventilatory support.
- 10 (50%) patients died in the ICU.

20 Patients receiving Dexamethasone along with urgent chemotherapy.
- 16 (80%) respiratory worsening after chemotherapy, including 10 (50%) patients needing ventilatory support.
- 4 (20%) patients died in the ICU.
Figure 2

![Bar chart showing respiratory deterioration, increase in oxygen flow, need for ventilatory support, and ICU mortality.](image-url)