Non-invasive ventilation in immunosuppressed patients with pneumonia and extrapulmonary sepsis

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Non-invasive ventilation; Immunosuppressed patients; SIRS and pneumonia

Summary

Purpose: International guidelines recommend the use of noninvasive ventilation in immunocompromised patients with acute respiratory failure (ARF). We analyzed failure rates and risk factors for NIV failure in immunocompromised patients.

Methods: We retrospectively analyzed 120 immunodeficient patients treated with NIV in our medical ICU from 2005 to 2011. We compared the clinical course and NIV failure rates. Furthermore, we compared patients with secondary respiratory failure due to those with Systemic Inflammatory Response Syndrome (SIRS) of other than pulmonary origin to those with primary pulmonary infiltrations.

Results: Regression analyses revealed high APACHE II score (p < 0.01), need for catecholamines (p < 0.05) and low paO2/FIO2 ratio (p < 0.05) as risk factors for NIV failure. Regarding the underlying diseases, we could not find differences in NIV duration (p = 0.07) and outcome (p = 0.44). 59.2% suffered from ARF due to lung infiltrations whereas 40.8% had secondary ARF caused by sepsis of extrapulmonary origin. Patients with lung infiltrations had a longer stay on ICU (16.3 vs 13.2 days; p = 0.047) and showed a trend toward longer NIV duration (87 ± 102 h vs 65.6 ± 97.8 h; p = 0.056). The SIRS patients compared to pneumonia patients showed a trend toward higher serum creatinine (1.63 mg/dL to 1.51 mg/dL; p = 0.059), a higher rate of renal failure (p < 0.01), higher APACHE II score (30.6–25.7, p < 0.01) and more frequently needed catecholamines (p < 0.01). NIV failure rate (overall 55%) was not different.

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Introduction

For several years, NIV has been used for treatment of neuromuscular diseases, chronic obstructive lung disease (COPD), pulmonary edema, in immunodeficient and postsurgical patients. Since invasive ventilation impedes the risk of severe complications such as ventilator associated pneumonia (VAP), barotrauma and lesions of the orotracheal and laryngeal regions, NIV is a preferred alternative in the therapy of acute respiratory failure (ARF).

Immunosuppressed patients have a high risk of dying from ARF. Due to rising numbers of bone marrow and solid organ transplantations, there is a growing cohort of immunosuppressed patients. Only few randomized studies assessed the benefit of NIV in immunosuppressed patients. Conti et al. showed in 1998, that NIV can be successfully applied to patients with hematological disorders and acute hypoxic respiratory failure. These findings were confirmed by Pancera et al., who demonstrated the successful use of NIV in immunocompromised children. Another small study proved the benefit of CPAP ventilation (continuous positive airway pressure) in neutropenic patients admitted to the ICU due to respiratory distress.

The cause of ARF might play an important prognostic role. In immunodeficient patients, infections and drug-related toxicity may lead to primary pulmonary infiltrations. In contrast, sepsis or SIRS of other than pulmonary origin often lead to secondary respiratory insufficiency due to capillary leak syndrome, disturbances of capillary perfusion, high oxygen consumption and elevated CO2 production. Studies comparing the outcome of immunocompromised NIV patients with regard to their underlying disease are rare. Gruson et al. showed a prognostic difference between bone marrow transplant recipients with proven infectious pneumonia compared to those with respiratory failure without proof of microbial origin.

We herein present a large observational study to assess the feasibility of NIV in immunocompromised patients with different underlying diseases. Assuming that secondary capillary leakage due to SIRS might potentially respond faster to NIV than solid pulmonary infiltrations, we compared outcome and failure rates of NIV in immunocompromised patients suffering from primary pulmonary infection or secondary respiratory failure due to SIRS of other than pulmonary origin.

Patients and methods

After approval by our ethical board, we performed a retrospective survey consecutively including all adult immunosuppressed patients admitted to our medical ICU between January 2005 and October 2011 and treated with NIV.

Inclusion/exclusion criteria

We enrolled patients with hematological disorders (leukemia, bone marrow infiltration), acquired immunodeficiency (e.g. AIDS), patients in leukocytopenia (due to chemotherapy or bone marrow deficiency) and patients receiving immunosuppressive drugs after bone marrow or solid organ transplantation as well as autoimmune diseases. Patients were eligible if they had respiratory distress despite application of oxygen (>50% FIO2) and respiratory rates >25–30/min and/or respiratory failure with a paO2/FIO2 ratio (Horowitz index) < 200.

For patients with sole hypoxemic ARF, non-invasive CPAP or bi-level positive airway pressure ventilation (BiPAP) was applied. If a respiratory exhaustion occurred during CPAP, we changed to BiPAP. Patients with primary hypercapnic ARF were directly treated with BiPAP. Facial masks (PerforaTrak SE, Philips Respironics) were used in all patients. For CPAP application we used the CF-800 (Dräger) device with high-flow gas application. For BiPAP we used either BiPAP Synchrony (Philips, Respironics), BiPAP Vision (Philips, Respironics) or V60 (Philips, Respironics).

Criteria for intubation or transfer to spontaneous breathing

Criteria for aborting NIV and indication for endotracheal intubation were an increase of hypoxemia despite NIV especially if paO2/FIO2 ratio decreased <200), severe tachypnea or exhaustion under NIV, respiratory distress under NIV despite mild analgo-sedation, progressive encephalopathy, lack of cooperation, a Glasgow coma scale (GCS) < 10, emesis or bleeding of the upper airways, a rising serum lactate, severe organ malfunction or failure leading to metabolic decompensation and progressive manifest shock.

Criteria for transfer to spontaneous breathing were stabilized clinical condition with reduced respiratory rate (<20–25/min), sufficient blood gases under spontaneous breathing with or without oxygen insufflations and subjective amelioration of respiratory distress.

Data analysis

We analyzed underlying diseases, kind of ARF (hypoxemic, hypercapnic respiratory failure, pneumonia, sepsis, structural lung diseases etc), NIV duration, blood gases and Horowitz index (paO2/FIO2) before, during and after NIV, failure rates, occurrence of organ failure, catecholamine dosages, APACHE II score, ICU days and outcome. Acute kidney injury (AKI) was defined according to the Acute
Kidney Injury Network (AKIN) as an abrupt (within 48 h) absolute increase in the serum creatinine concentration of \( \geq 0.3 \) mg/dL (26.4 mmol/L) from baseline, a percentage increase in serum creatinine concentration of \( \geq 50\% \), or oliguria of less than 0.5 mL/kg per hour for more than 6 h.\(^{11}\)

The differentiation between the groups (pneumonia vs sepsis) was done using a chest x-ray in all patients, a thoracic CT-scan (89 patients, 74\%) and bronchoalveolar lavage (BAL) results (65 patients, 54\%). Patients with known extrapulmonary focus (e.g. catheter sepsis, peritonitis, or urosepsis) and without relevant pulmonary infiltrations in x-ray were classified as "sepsis of extrapulmonary focus".

### Statistical analysis

To test for differences between the groups, we used Mann–Whitney U test for continuous parameters and Chi-square test for categorical parameters. For analysis of differences in continuous parameters between the underlying disease groups, we used the Kruskal–Wallis test. For statistical analysis of linked samples, the Wilcoxon test was applied. Univariate and multivariate regression analyses for identification of risk factors for NIV failure were assessed using a Cox regression analysis. The local significance level was set to 0.05. An adjustment to multiplicity is not performed. All analysis were performed using PASW\(^\text{TM}\) 20 software.

### Results

A total of 329 immunoincompetent patients were included in our analysis. Of them, 197 needed a primary endotracheal intubation and invasive ventilation during the observation period. They were not eligible for NIV due to severe neurologic impairment, cardiac arrest, pharyngeal or gastrointestinal bleeding or fulminant septic shock. Of the 132 immunocompromised patients treated with NIV, 12 were excluded before start of data processing because they were treated with NIV but due to bad prognosis or patient’s provision they were regarded not eligible for endotracheal intubation (Fig. 1).

Thus, we analyzed the data of 120 immunocompromised patients (16–83 years), who had been admitted to our ICU between 2005 and 2011 and were treated with NIV due to ARF. Most of them (75\%) suffered from hematological malignancies such as leukemia and aggressive lymphomas and underwent subsequent chemotherapy induced leukocytopenia. Furthermore, we included patients with other kinds of bone marrow failure (e.g. myelodysplastic syndrome), after solid organ transplantation, as well as those who received immunosuppressive drugs due to autoimmune diseases. One patient suffered from AIDS.

Seventy-one patients (59.2\%) were admitted with primary colonizing bacteria such as \( \text{Escherichia coli} \), \( \text{Pseudomonas} \), \( \text{Enterococcus} \), \( \text{Candida} \). These were followed by infections of intravasal catheters (e.g. with \( \text{Enterococcus} \), \( \text{Staph aureus} \)) and sepsis with primary colonizing bacteria such as \( \text{Streptococcus oralis} \). Several patients classified as "sepsis", lacked prove of sepsis source or causing microbiologic agents, but showed classical SIRS criteria, and were classified due to missing pulmonary infiltrations.

The mean APACHE II score of all study patients was 28, the mean Horowitz index at ICU admission was 179.

### Risk factors for NIV failure

High APACHE II score \( (p < 0.01) \), need for catecholamines \( (p < 0.05) \) and low Horowitz index at ICU admission \( (p < 0.05) \) were independent risk factors for NIV failure in the univariate and multivariate analyses (Table 1a and b).

We divided the patients into 4 groups regarding their \( \text{paO}_2/\text{FiO}_2 \) ratio at ICU admission (group 1: \(< 100 - 12.5\%\); group 2: \(100-200 - 48.3\%\); group 3: \(200-300 - 33.3\%\); group 4: \(> 300 - 5.8\%)\). We found a significant association between \( \text{paO}_2/\text{FiO}_2 \) group and NIV failure \( (p = 0.05) \) but not between \( \text{paO}_2/\text{FiO}_2 \) group and mortality \( (p = 0.681) \) (Fig. 2).

### Group comparison for underlying diseases

We found a remarkable difference in serum creatinine with regard to the underlying diseases \( (p = 0.002) \) with highest values in patients after solid organ transplantation \((3.3 \pm 1.9 \text{ mg/dL})\) and with autoimmune diseases \((2.7 \pm 3 \text{ mg/dL})\) compared to patients with bone marrow failure \((1.3 \pm 0.8 \text{ mg/dL})\) and hematologic patients \((1.3 \pm 0.8 \text{ mg/dL})\). ICU duration was shorter in hematologic patients \((12.5 \pm 15.7 \text{ days})\) than in other groups \( (p = 0.011) \). Relevant differences in patients count in the distinct diagnosis groups with most patients suffering from hematologic malignancies (75\%) have to be taken into account for interpretation of these results (Table 2).
Group analysis for pneumonia and SIRS patients

We compared patients with primary pulmonary infiltrations to those with secondary respiratory insufficiency due to SIRS of other than pulmonary origin (Table 3). Patients with primary lung infiltrations had a longer stay in the ICU (16.3 vs 13.2 days for SIRS patients; \( p < 0.047 \); Fig. 3a). The SIRS group showed a trend toward higher serum creatinine (1.63 mg/dL vs 1.51 mg/dL; \( p < 0.059 \)). Based on the AKIN definition, the SIRS patients had a higher rate of acute renal failure (\( p < 0.01 \)). They showed a higher APACHE II score (30.6 vs 25.7, \( p < 0.01 \)) and an elevated need for catecholamines (\( p < 0.01 \)). Comparison of NIV duration failed to reach statistical significance (\( p = 0.056 \)), but showed a trend toward longer NIV duration in pneumonia patients (87 ± 100 h compared to 65.6 ± 97.8 h).

Blood pressure, heart rate, \( \text{paO}_2/\text{FiO}_2 \) index at ICU admission as well as 1–2 h after stabilization under NIV, days of renal replacement therapy, survival rates and NIV failure rates did not differ significantly between both groups (Table 3, Fig. 3).

**Blood flow vs BiPAP ventilation**

A total of 34 (28.3%) patients were only treated with CPAP, 75 (62.5%) received BiPAP and in 11 (9.2%) cases, initial treatment with CPAP was changed to BiPAP due to muscular exhaustion. We found a significant higher rate of NIV failure in the group with primary (45/75, 60%) or secondary (8/11, 72.7%) need for BiPAP than in the CPAP group (13/34, 38.2%; \( p < 0.05 \)), what is most probably due to the fact, that BiPAP was used in patients with severe respiratory failure and additionally occurring respiratory exhaustion.

**Amelioration of respiratory parameters during NIV**

The \( \text{paO}_2/\text{FiO}_2 \) ratio approved significantly within the first 60–120 min after start of NIV (\( p = 0.022 \)) in all patients, but did not improve further until the end of NIV (\( p = 0.397 \)). Relevant differences with respect to cause for ARF (pneumonia vs SIRS) could not be observed. \( \text{PaCO}_2 \) did not improve significantly, but hypercapnic respiratory failure was extremely rare in our patients that mainly suffered from primary hypoxemic ARF.

**Outcome**

A total of 66 (55%) patients needed an endotracheal intubation during the treatment. Causes for intubation were respiratory exhaustion under NIV in 51 patients (77.3%), severe shock in 9 (13.6%), CPR in 4 (6.1%) and progressive neurological impairment in 2 (3%) of the patients. In 54 (45%) patients, a transfer from NIV to spontaneous breathing could be achieved. The mean ICU duration was 15.1 days, mean NIV duration was 78 h. The overall mortality was 52.5% (\( n = 63 \)), from these 48 patients died on ICU. In most of them (82.5%) the death was caused by progressive hemodynamic failure, 4.8% died from respiratory causes, in two patients, therapy was abandoned, in 6.3% cases, cerebral disorders lead to decease. Two deaths remained unclear. Four patients (6.3%) died during NIV, 44 (69.8%) under invasive ventilation and 15 (23.8%) suffered from fatal secondary complications after discharge from ICU.

The outcome of patients with regard to their underlying disease is shown in Table 2, that with regard to the cause of pulmonary failure (pulmonary infiltration vs SIRS) is displayed in Table 3.

**Discussion**

While plenty of reports describe the benefit of NIV for COPD patients and cardiogenic lung edema, studies investigating the use of NIV in immunosuppressed patients are rather rare. To our knowledge, this is one of the largest studies assessing the outcome of immunodeficient patients.
treated with NIV, and moreover the first study comparing NIV in immunoincompetent patients 1513
with pulmonary infiltrations to those with SIRS or sepsis of non-pulmonary origin. We showed in a large cohort
of patients admitted to ICU of other than pulmonary origin. We showed in a large cohort

Table 2  Patient’s characteristics and group comparison with regard to underlying diseases (values are presented as

mean ± SD, * = significant, ** = highly significant).

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Leukemia/lymphoma</th>
<th>Bone marrow</th>
<th>Solid organ</th>
<th>Autoimmune diseases</th>
<th>HIV</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>120</td>
<td>90 (75%)</td>
<td>12 (10%)</td>
<td>13 (10.8%)</td>
<td>4 (3.3%)</td>
<td>1</td>
<td>(0.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>36.7%</td>
<td>34 (37.8%)</td>
<td>5 (41.7%)</td>
<td>3 (23.1%)</td>
<td>2 (50%)</td>
<td>0</td>
<td>0.718</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53 ± 14.9</td>
<td>53.3 ± 14.2</td>
<td>47.3 ± 21.1</td>
<td>59.7 ± 10.4</td>
<td>41.2 ± 15.2</td>
<td>46</td>
<td>0.117</td>
</tr>
<tr>
<td>APACHE II</td>
<td>27.7 ± 7.5</td>
<td>28.2 ± 7.4</td>
<td>25.2 ± 6</td>
<td>26.8 ± 9</td>
<td>26.2 ± 7.3</td>
<td>32</td>
<td>0.650</td>
</tr>
<tr>
<td>PaO2/FIO2</td>
<td>179.3 ± 76.6</td>
<td>177.7 ± 68.9</td>
<td>207.6 ± 88.5</td>
<td>179.8 ± 112.3</td>
<td>102.2 ± 10.7</td>
<td>114.7</td>
<td>0.118</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>40.7 ± 14.5</td>
<td>40.3 ± 11.4</td>
<td>38.6 ± 6.8</td>
<td>30.4 ± 4.6</td>
<td>64.4 ± 47.4</td>
<td>44</td>
<td>0.230</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>37.1 ± 1.7</td>
<td>37.2 ± 1.7</td>
<td>37.2 ± 2</td>
<td>36 ± 1.5</td>
<td>37 ± 1.1</td>
<td>39.3</td>
<td>0.140</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.56 ± 1.27</td>
<td>1.3 ± 0.8</td>
<td>1.3 ± 0.8</td>
<td>3.3 ± 1.9</td>
<td>2.7 ± 3</td>
<td>0.6</td>
<td>0.002**</td>
</tr>
<tr>
<td>AKI</td>
<td>37 (30.8%)</td>
<td>28 (31.1%)</td>
<td>4 (33.3%)</td>
<td>4 (30.8%)</td>
<td>1 (25%)</td>
<td>0.96</td>
<td>0.856</td>
</tr>
<tr>
<td>RRT</td>
<td>19 (15.8%)</td>
<td>13 (14.4%)</td>
<td>3 (25%)</td>
<td>2 (15.4%)</td>
<td>1 (25%)</td>
<td>0</td>
<td>0.179</td>
</tr>
<tr>
<td>Duration of RRT (days)</td>
<td>0.4 ± 1.1</td>
<td>0.31 ± 0.96</td>
<td>2 ± 0.5</td>
<td>0.5 ± 0.1</td>
<td>1 ± 0.7</td>
<td>0.76</td>
<td>0.001**</td>
</tr>
<tr>
<td>ICU duration (days)</td>
<td>15.1 ± 18.2</td>
<td>12.5 ± 15.7</td>
<td>21.4 ± 16</td>
<td>21.7 ± 31</td>
<td>26 ± 9.3</td>
<td>43</td>
<td>0.011*</td>
</tr>
<tr>
<td>NIV duration (h)</td>
<td>78.2 ± 100</td>
<td>82.1 ± 99.8</td>
<td>116 ± 143.8</td>
<td>37.2 ± 42.9</td>
<td>28.8 ± 43.3</td>
<td>8.8</td>
<td>0.068</td>
</tr>
<tr>
<td>NIV failure rate</td>
<td>66 (55%)</td>
<td>48 (53.3%)</td>
<td>8 (66.7%)</td>
<td>5 (38.5%)</td>
<td>4 (100%)</td>
<td>1</td>
<td>0.179</td>
</tr>
<tr>
<td>Lethality</td>
<td>66 (55%)</td>
<td>47 (52.2%)</td>
<td>9 (75%)</td>
<td>7 (53.8%)</td>
<td>2 (50%)</td>
<td>0</td>
<td>0.442</td>
</tr>
<tr>
<td>Death at ICU</td>
<td>48 (40%)</td>
<td>35 (38.9%)</td>
<td>9 (75%)</td>
<td>2 (15.4%)</td>
<td>2 (50%)</td>
<td>0</td>
<td>0.186</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>56 (46.7%)</td>
<td>43 (47.8%)</td>
<td>3 (25%)</td>
<td>6 (46.2%)</td>
<td>2 (50%)</td>
<td>1</td>
<td>0.442</td>
</tr>
</tbody>
</table>

ICU = intensive care unit, AKI = acute kidney injury, RRT = renal replacement therapy.

Table 3  Comparison between patients with primary respiratory infiltrations and SIRS of extrapulmonary origin (values are presented as mean ± SD, * = significant, ** = highly significant; values marked with (*) were only borderline significant, showing a trend).

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Pneumonia</th>
<th>SIRS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>120</td>
<td>71 (59.2%)</td>
<td>49 (40.8%)</td>
<td>0.02*</td>
</tr>
<tr>
<td>% Female</td>
<td>36.7%</td>
<td>20 (28.2%)</td>
<td>24 (49%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53 ± 14.9</td>
<td>52.5 ± 15.7</td>
<td>53.6 ± 15.8</td>
<td>30.6 ± 7.2</td>
</tr>
<tr>
<td>APACHE II</td>
<td>27.7 ± 7.5</td>
<td>25.7 ± 7</td>
<td>30.6 ± 7.2</td>
<td>0.001**</td>
</tr>
<tr>
<td>PaO2/FIO2 admission</td>
<td>179.3 ± 76.6</td>
<td>172.4 ± 76.2</td>
<td>188.8 ± 77</td>
<td>0.189</td>
</tr>
<tr>
<td>PaO2/FIO2 after 1–2 h NIV</td>
<td>190.7 ± 86.6</td>
<td>181.2 ± 66.7</td>
<td>205.3 ± 109.8</td>
<td>0.297</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>40.7 ± 14.5</td>
<td>39.2 ± 9.3</td>
<td>43.1 ± 20.1</td>
<td>0.782</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 ± 0.16</td>
<td>7.38 ± 0.13</td>
<td>7.33 ± 0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>37.1 ± 1.7</td>
<td>37 ± 1.7</td>
<td>37.2 ± 1.7</td>
<td>0.41</td>
</tr>
<tr>
<td>MAP at admission (mmHg)</td>
<td>77.7 ± 31</td>
<td>80.1 ± 29.4</td>
<td>74.2 ± 32.8</td>
<td>0.119</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.56 ± 1.27</td>
<td>1.51 ± 1.38</td>
<td>1.63 ± 1.1</td>
<td>0.059(*)</td>
</tr>
<tr>
<td>AKI</td>
<td>37 (30.8%)</td>
<td>15 (21.1%)</td>
<td>22 (44.9%)</td>
<td>0.006**</td>
</tr>
<tr>
<td>RRT</td>
<td>19 (15.8%)</td>
<td>11 (15.5%)</td>
<td>8 (16.3%)</td>
<td>0.902</td>
</tr>
<tr>
<td>Duration of RRT (days)</td>
<td>0.4 ± 1.1</td>
<td>0.45 ± 1.25</td>
<td>0.27 ± 0.76</td>
<td>0.936</td>
</tr>
<tr>
<td>Need for catecholamines</td>
<td>38 (31.7%)</td>
<td>14 (19.7%)</td>
<td>24 (49%)</td>
<td>0.001**</td>
</tr>
<tr>
<td>ICU duration (days)</td>
<td>15.1 ± 18.2</td>
<td>16.3 ± 19.4</td>
<td>13.2 ± 16.5</td>
<td>0.047*</td>
</tr>
<tr>
<td>NIV duration (h)</td>
<td>78.2 ± 100</td>
<td>87 ± 102</td>
<td>65.6 ± 97.8</td>
<td>0.056(*)</td>
</tr>
<tr>
<td>% intubation = NIV failure</td>
<td>66 (55%)</td>
<td>38 (53.5%)</td>
<td>28 (57.1%)</td>
<td>0.695</td>
</tr>
<tr>
<td>Lethality</td>
<td>66 (55%)</td>
<td>41 (57.7%)</td>
<td>24 (59%)</td>
<td>0.418</td>
</tr>
<tr>
<td>Death at ICU</td>
<td>48 (40%)</td>
<td>28 (39.4%)</td>
<td>20 (40.8%)</td>
<td>0.642</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>56 (46.7%)</td>
<td>30 (42.3%)</td>
<td>25 (51%)</td>
<td>0.418</td>
</tr>
</tbody>
</table>

ICU = intensive care unit, AKI = acute kidney injury, RRT = renal replacement therapy, MAP = mean arterial blood pressure.
of 16 patients. In this study, a rapid improvement of gas exchange was reached in 15 of 16 patients. The rate of intubation was extraordinarily low (6%), this may be influenced by the relatively low SAPS II score of 13.4.

In our opinion, the present study clearly supports the use of NIV even in critically ill immunosuppressed patients with severe pneumonia and sepsis.

Anyhow, there are certain limitations of this report. Above all, it represents a retrospective observational analysis and not a prospective study with all limitations involved. With regard to pre-existing data about the good results of NIV in immunocompromised patients, a primary randomization seems questionable. A comparison to the immunosuppressed patients, that needed a primary intubation, seems not reasonable, because these patients suffered from different disorders (neurologic impairment, CPR and others) and not from ARF. Furthermore, during the long observation period, many different persons were involved in patients’ therapy, so individual decisions for or against NIV or disruption of NIV have to be taken in account.

**Use of NIV compared to oxygen insufflations only**

In 2001, Hilbert and colleagues showed that the outcome of immunosuppressed patients with fever, pulmonary infiltrations and ARF improved when NIV was used instead of oxygen application via mask. In this randomized study of 52 patients, a significant reduction of serious complications (13 vs 21, \( p = 0.02 \)) and death in hospital (10 vs 18, \( p = 0.03 \)) was observed in the NIV group. In accordance, patients after solid organ transplantation were reported to benefit from NIV compared to oxygen insufflations. Other reports displayed different results. Thus, a recent randomized study by Wermke et al. showed disappointing results in a defined group of patients with ARF after allogeneic stem cell transplantation, although a significant and rapid improvement of gas exchange was observed.

Although, the benefit of NIV compared to oxygen insufflations is discussed controversially, adverse events of NIV in immunocompromised patients have seldom been reported. In our study, we included only patients with severe respiratory failure under oxygen application and need for mechanical ventilation. A comparison to patients with sole oxygen insufflations was not done. Few further patients (approximately 10 per year) after bone marrow transplantation in our hospital received NIV instead of oxygen insufflations via mask at our bone marrow transplantation ward. They were not included due to a lack of continuous blood gas analysis and monitoring.

**Non-invasive and invasive ventilation**

Confalonieri et al. performed a study in 48 AIDS patients and found a significant better outcome in AIDS patients with *Pneumocystis carinii* pneumonia treated with NIV compared to invasive ventilation. Another recent retrospective analysis found an improved outcome in patients with hematologic malignancies treated with NIV compared to those with invasive mechanical ventilation. Limitation of this retrospective multicenter study was the fact, that patients who primarily needed invasive ventilation probably showed more co-morbidities. In contrast, a different trial failed to identify NIV compared to invasive ventilation to influence the overall patient’s outcome in hematologic patients with need for ventilator support. In this retrospective study only few patients (26 of 166) were treated with NIV, so the evaluation of the impact of NIV on clinical course is very limited. In addition, the 26 patients were included over a five years period, and 42% of them had DNR decisions.

Whether NIV might negatively influence the patient’s outcome by delaying necessary invasive ventilation is still under discussion. Gristina found unsuccessful NIV to be associated with 70% mortality in ALI/ARDS patients but also reported a similar overall mortality in the patient’s group with early compared to later endotracheal intubation. This report matches our results showing a lower \( \text{paO}_2/\text{FiO}_2 \) ratio being associated with a higher NIV failure rate. We found highest intubation rates in patients with low oxygenation index (\( \text{paO}_2/\text{FiO}_2 <100 \) and 100–200) but no association between severity of respiratory failure and mortality.

**NIV failure**

Our study revealed that co-morbidities defined by high ICU scores (APACHE II) and need for catecholamines were associated with higher risk for NIV failure in immunosuppressed patients, which is consistent with the previous
NIV in immunoincompetent patients

studies. In our opinion, the prove of higher NIV failure rates depending on severity of illness should not prevent the clinician from trying NIV in critically ill patients taking the contraindication into account.

In accordance with the recent study by Phua et al., in patients with bronchiectasis, we additionally found a low Horowitz index (paO₂/FiO₂) at ICU admission to be a predictor of NIV failure. The underlying disease did neither influence the course during NIV therapy, the NIV failure rate nor the patients’ outcome.

Compared to former studies as well as during the years in our own ICU (2005–2011) we found rising NIV success and overall survival rates which is most probably due to growing experiences with NIV as well as improvement of general ICU therapy and antimicrobial treatment.

NIV success rates dependent on the cause for respiratory failure

Assuming that sepsis and SIRS of other than pulmonary origin induce secondary respiratory insufficiency by capillary leak and enhanced need for oxygen as well as high CO₂ production, whereas primary respiratory failure is caused by direct lung infiltration, we examined the outcome of NIV in these different pathogenetic groups. ARF due to SIRS is caused by capillary leak as well as microcirculatory disorders, endothelial dysfunction and oxidative stress caused by cytokines, complement system and coagulatory disturbances. Pulmonary infiltrations are caused by inflammatory cell migration into the pulmonary tissue. Pneumonic infiltrations directly influence the alveolar gas exchange. In severe leukocytopenia, pulmonary infiltrations may go along without visible pulmonary infiltrations. Although these sepsis cases are of pulmonary origin, lack of leukocyte infiltrations also prevents disturbance of alveolar gas exchange.

These differences in pathogenesis of ARF are also associated with differences between the groups regarding other organ dysfunction, in our study being expressed by a higher serum creatinine and acute renal failure rate in the SIRS group.

Due to the pathogenesis, we assumed a different effect of non-invasive positive pressure ventilation on the pulmonary gas exchange knowing, that cardiac lung edema can be easily and quickly treated by NIV.

To our knowledge, this comparison has never been done. A single study by Fartoukh et al. has focussed on use of NIV in pulmonary capillary dysfunction by sickle cell anemia.

We could not detect significant differences in NIV failure and lethality rates dependent on the cause for respiratory failure. Patients with primary lung infiltrations showed a borderline-significant longer need for NIV and longer ICU stay compared to those with SIRS which might be ascribed to the assumed longer duration for healing of the cellular lung infiltrations.

Conflict of interest

No conflicts of interests have to be declared.

References


