

Management of severe respiratory failure following influenza A H1N1 pneumonia

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ABSTRACT

The use of non-invasive ventilation (NIV) in severe hypoxemic respiratory failure ($\text{PaO}_2/\text{FIO}_2 \leq 250$) due to H1N1 virus pneumonia is controversial. In this prospective study, we aimed to assess the efficacy of NIV in avoiding endotracheal intubation and to identify predictors of success or failure. Nineteen patients with H1N1 viral pneumonia had severe respiratory failure ($\text{PaO}_2/\text{FIO}_2$ ratio ≤ 250). Five patients with $\text{PaO}_2/\text{FIO}_2$ lower than 150 and simplified acute physiology score (SAPS II) lower than 34 underwent NIV and were admitted to the Intensive Care Unit and received NIV as first-line therapy. NIV failed in 2 of the 14 patients but had a good outcome in 12. None of the patients treated with NIV died. The duration of NIV was 5.0 ± 1.9 days and the hospital stay was 11.3 ± 1.2 days. The average $\text{PaO}_2/\text{FIO}_2$ ratio after 1 h of NIV was 239.1 ± 38.7 . No patient had multi-organ failure. $\text{PaO}_2/\text{FIO}_2$ ratio after 1 h and SAPS II at admission were independent variables correlated with the success of NIV. In our study, NIV was successful in 12 of the 14 patients (85.7%) and this is one of the highest success rates in the literature. In our opinion, the reason for these results is the strict selection of patients with severe respiratory failure ($\text{PaO}_2/\text{FIO}_2$ ratio ≥ 150) and the strict following of predictors of success for NIV such as SAPS II of 34 or lower and $\text{PaO}_2/\text{FIO}_2$ ratio of 175 or lower after 1 h of NIV. Clinicians should be aware of pulmonary complications of influenza A H1N1 and strictly select the patients to undergo NIV. NIV could have an effective and safe role in reducing the high demand for critical care beds, particularly during the pandemic.

Introduction

The use of non-invasive ventilation (NIV) in severe hypoxemic respiratory failure is still a subject of

controversy. However, in centers that have matured some years of experience, used early, NIV^{1,2} avoids the need for orotracheal intubation in 30-50% of patients.^{1,3} Non-invasive ventilation is not recommended in patients with influenza H1N1 virus complicated by pneumonia, acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). In fact, some Authors have shown that this method, although useful in improving oxygenation, is not necessarily capable of modifying the natural disease course.⁴⁻⁶ Given this, many Authors have reported high percentages of failure of NIV in cases of pneumonia in influenza H1N1 pandemics.⁵⁻⁹ Nevertheless, other Authors have more recently reported the efficacy of NIV in some cases of severe respiratory failure associated to H1N1 pneumonia.^{10,11} Estenssero *et al.*¹² presented a study of 337 patients with pneumonia from A H1N1 influenza who underwent mechanical ventilation. Data were collected from 35 Intensive Care Units (ICU) in Argentina. Sixty-four of them were treated with NIV and its use was associated with better outcome, perhaps due to the fact that this type of intervention was reserved for those patients with less severe hypoxemia.

In a recent study examining what was learnt from experiences in an ICU setting during an influenza A H1N1 pandemic, Rodriguez *et al.*¹³ reported a high failure rate with NIV (75%) and a recent meta-analysis suggested that NIV does not reduce the need for intubation. There is insufficient evidence to be able to support the routine use of NIV in severe hypoxemic

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Key words: influenza A H1N1, severe respiratory failure, non-invasive ventilation.

Contributions: MS and AN had access to data and are responsible for their soundness and the accuracy of the study and analysis.

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Conflicts of interest: the authors declare no potential conflicts of interest.

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respiratory failure.¹⁴ An opposite point of view concerns the use of NIV in women during pregnancy. Djibrè *et al.*¹⁰ reported the case of a pregnant woman with acute severe respiratory failure due to pneumonia associated with H1N1 infection successfully treated with NIV, but various other Authors, because of the risk of harming the fetus have suggested a more cautious approach, preferring to use tracheal intubation.¹⁵ Recently, the debate in the literature about the use of NIV in H1N1 pneumonia has been continued after the death of 4 Mexican patients who died while waiting for beds in the ICU to become available.¹⁶ Must NIV be considered a high-risk procedure? Does NIV represent an effective means of ventilation in this setting? Our study aims to help find an answer to these questions.

Materials and Methods

Inclusion and exclusion criteria

This prospective study was started in September 2009 and was completed in March 2012. The study was conducted at the General Hospital of Sestri Levante and Lavagna, in Liguria in northwestern Italy. Community-acquired pneumonia was diagnosed by the presence of a new infiltrate on chest X-ray associated with symptoms of infection of the lower respiratory tract. PaO₂/FIO₂ ratio of 250 or under with high-flow oxygen therapy administered via Venturi mask was considered index of acute severe respiratory failure. The two hospital centers share an Emergency Department where a special screening program was developed to allow for the quick diagnosis of H1N1 viral infection and prompt hospital admission in a protected environment (intensive therapy, semi-intensive respiratory therapy, and semi-intensive medical care) to avoid the infection spreading.¹⁷ Exclusion criteria were hospitalization within the previous ten days or concomitant pulmonary neoplasias or tuberculosis. Further exclusion criteria were: need for immediate intubation for cardiac-respiratory arrest, severe hemodynamic instability, organ failure in 2 or more organs, severe encephalopathy, and all conditions that do not allow NIV to be used, such as tracheostomy, facial deformity and recent maxilla-facial or gastro-enteric surgery.

Patients

Forty patients were seen in the Emergency Department with a diagnosis of H1N1 pneumonia confirmed by laboratory tests. Patients presented fever, influenza-like symptoms and had contracted viral A H1N1 influenza; the specific subtype was confirmed by a nasopharyngeal tampon using real-time transcriptase polymerase chain reaction. Twenty-seven of these patients presented a hypoxemic profile (PaO₂ ≤60 mm Hg) but only 19 were included in the study. Disease

severity was evaluated using the simplified acute physiology score (SAPS II) and the PaO₂/FIO₂ (ratio between partial pressure of O₂ arterial therapy and the fraction of O₂ inhaled at high-flow of oxygen with a mask) (P/F) calculated on admission. Five patients with PaO₂/FIO₂ ratio less than 150, SAPS II over 34 and multi-lobular pneumonia underwent invasive mechanical ventilation and were admitted to the ICU.^{1,19} Another 14 patients with PaO₂/FIO₂ ratio over 150, SAPS II below 34 and bilateral focal infiltrates were admitted to a sub-intensive care medical or pneumology unit and treated with NIV.

Care setting

The two semi-intensive medical and pneumology units are located on the two different hospital sites. The first is located in the Lavagna Hospital where the Emergency Department and general ICU are to be found, while the second is located in the Sestri Levante Hospital. The semi-intensive medical unit in Lavagna has 8 beds and the semi-intensive pneumology unit in Sestri Levante has 4 beds and is equipped with continuous non-invasive monitoring systems and intensive and semi-intensive care pulmonary ventilators, including NIV. A nurse specialized in the care of critical patients is available round the clock (24/7). Immediate availability of an Internal Medicine doctor is also available 24/7. In the Lavagna Hospital a reanimation specialist is also available. A pneumologist is available during the day (12 h) in the sub-intensive pneumology unit with additional on-call availability of the pneumologist and the reanimation specialist at night.

Data collection

The following parameters were recorded on admission: age, gender, any comorbidities, number of pulmonary lobes involved at chest X-ray or computerized tomography (CT) scan, PaO₂, PaCO₂, pH, PaO₂/FIO₂ ratio (P/F), SAPS II, ventilation approach, ventilator set-up and setting, and PaO₂/FIO₂ ratio after 1 h of NIV. Furthermore, all patients were evaluated on admission and daily during follow up, checking for hypotension (≤90 mmHg), confused mental state, intubation and invasive mechanical ventilation (IMV).

Each patient undergoing NIV who did not achieve an improvement in PaO₂/FIO₂ ratio over 175 after 1 h was re-evaluated, transferred to the ICU and underwent invasive ventilation. Ventilators with a special NIV platform were used with bilevel positive airway pressure (BIPAP) or pressure support ventilation (PSV) or in continuous positive airway pressure (CPAP). CPAP and aspiration with positive pressure of the airways (EPAP) were set to obtain PaO₂ ≥60 mmHg or spO₂ ≥90%. Inhalation pressure in airways (IPAP) was increased, starting with 10 cm H₂O, with

subsequent increases of 2-3 cm H₂O until obtaining 6-8 mL/kg volume and a respiratory frequency ≤30 breaths/min. NIV was considered efficient in cases of continuous improvement of oxygenation (P/F ratio) and when the patient did not feel the need for ventilation after at least 48 h of treatment, maintaining pI_{O₂ over 60 mmHg or a saturated O₂ over 90% with maximum FiO₂ 40%.}

Statistical analysis

Continuous variables were compared using univariate regression test (covariance analysis) with categorical variables as outcome (intubation). Logistical regression model was performed for categorical variable to predict risk factors related to NIV failure. Independent variables evaluated were: age, gender, any comorbidities, number of pulmonary lobes involved, SAPS II and P/F on admission and after 1 h of NIV, and length of hospital stay. All analyses were performed with R-Project software (version 2.13.2; R-Foundation, Vienna, Austria). P≤0.05 was considered statistically significant.

Ethics

This study was carried out according to the Declaration of Helsinki and was approved by the institutional ethics committee, Chiavari, Liguria, Italy. All patients provided informed consent.

Results

Among the 19 patients presenting acute respiratory failure, 5 patients (3 males and 2 patients) were immediately subjected to invasive ventilation while the remaining 14 were treated with NIV. Initial value of PaO₂ for patients undergoing NIV was 44.6±12.5 mmHg, PaCO₂ 38.2±5.06 mmHg, pH 7.41±4.8 mmHg, paO₂/FiO₂ 181.2±26.7, SAPS II 17.6±2.5 and PaO₂/FIO₂ after 1 h 239.1±38.7. Figure 1 shows changes over time in PaO₂/FIO₂ ratio during NIV. Number of lobes involved at X-ray and/or CT scan was 3.0±0.6, duration of NIV was 104.5±47.6, and hospital stay was 11.3±1.2 days. All patients were effectively treated with NIV except for 2 who were subsequently treated with IMV; both patients survived. Of these 2 patients who were subsequently intubated, one was treated with BIPAP and one with PSV. In both cases, new pulmonary infiltrates and a deterioration in the respiratory profile led to a general worsening of their condition.

The general characteristics of patients who underwent IMV and NIV are shown in Table 1. Twelve patients were successfully treated: 10 with BIPAP or PSV, 2 with CPAP. For the 10 patients treated with BIPAP or PSV, average IPAP was 18.4±2.4 cm H₂O (range 15-22 cm H₂O) and average EPAP was 6.0±0.9 cm H₂O (range 5-8 cm H₂O). For the 2 patients treated with CPAP, average value was 12.5±2.6 cm H₂O

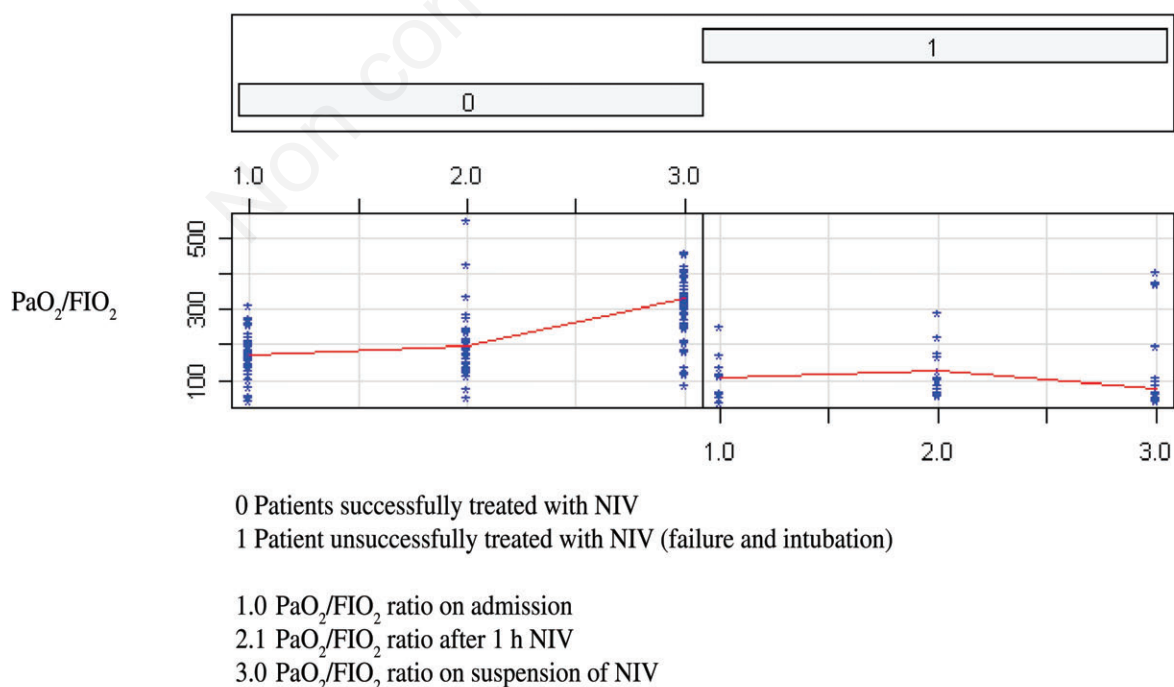


Figure 1. Changes over time in PaO₂/FiO₂ ratio during non-invasive ventilation (NIV).

(range 10-16 cm H₂O). Average oxygen fraction was 45.5±14.5 (range 30-60%). Non-invasive mechanical ventilation was only provided via an oro-nasal mask in patients undergoing BIPAP or PSV while other types of interface, total facemask or cap/helmet were used in patients undergoing CPAP. It must be emphasized that the CPAP approach was only used as an intrinsic method of pulmonary ventilation and at medium-high values that allowed oxygen saturation and flow volumes sufficient for the pathology; these were continuously monitored on the ventilator display.

Patients' characteristics, ventilation approaches and the ventilator settings used in patients treated with NIV who had a positive outcome are shown in Table 2. Statistically significant factors, according to logistical regression analyses and univariate regression analyses associated with successful NIV are shown in Table 3.

Table 1. General characteristics of patients who underwent invasive mechanical ventilation and non-invasive ventilation.

Patients	Intubation (5 patients)	NIV (14 patients)
Age	57.3±18.6	48.1±20.6
Gender (M/F)	3/2	9/5
Comorbidity	4/5	6/14
No. lobes	3.9±0.6	3.0±0.6
P/F on admission	155.0±21.5	181.2±26.7
P/F after 1 h NIV	166.5±42.2	239.1±38.7
SAPS II	38.5±19.6	18.3±3.0
Hours of ventilation	217.5±51.4	104.5±47.6
Length hospital stay	23.0±1.6	11.3±1.2

NIV, non-invasive ventilation; P/F, PaO₂/FIO₂ ratio; SAPS II, simplified acute physiology score.

Table 2. Patients' characteristics, ventilation approaches and the ventilator settings used in patients treated with non-invasive ventilation who had a positive outcome.

Age	Gender	Pulmonary lobes	PaO ₂ /FIO ₂ (on admission)	PaO ₂ /FIO ₂ (after 1 h)	SAPS II	Ventilator method	Ventilator parameters (cm H ₂ O)	Duration NIV (h)	Hospital stay (days)
35	M	3	185	310	18	BIPAP (I/E)	15/5 (I/E)	96	16
26	F	3	170	250	22	PSV	14/6	112	15
31	M	3	200	290	16	CPAP	15	64	12
35	M	4	170	220	20	PSV	15/5	118	15
63	M	4	150	200	26	BIPAP	20/6	172	19
38	M	3	185	235	16	BIPAP	14/6	86	7
62	F	3	170	190	18	BIPAP	21/7	211	12
53	F	4	150	170	18	BIPAP	20/7	151	11
30	M	3	200	240	18	CPAP	12	48	7
17	M	3	185	240	14	BIPAP	20/6	66	9
27	M	3	150	190	16	BIPAP	15/5	70	10
68	F	2	220	290	14	PSV	12/7	66	7

SAPS II, simplified acute physiology score; NIV, non-invasive ventilation; BIPAP, bilevel positive airway pressure; I, inspiratory positive airway pressure; E, expiratory positive airway pressure or PEEP positive end-expiratory pressure; PSV, pressure support ventilation; CPAP, continuous positive airway pressure.

Table 3. Statistically significant factors, according to logistical regression analyses and univariate regression analyses associated with successful non-invasive ventilation.

	Intubation	NIV	P
Gender (M/F)	3/2	9/5	0.42
Age	57.3±18.6	48.1±20.6	0.34
Pulmonary lobes	3.9±0.6	3.0±0.6	<0.01
P/F on admission	155.0±21.5	181.2±26.7	0.21
P/F after 1 h	166.4±42.2	239.1±38.7	<0.001
SAPS II on admission	38.7±3.0	18.3±2.9	<0.002
Hours of ventilation	217.5±51.4	104.5±47.6	<0.007
Length hospital stay	23.0±1.6	11.3±1.2	<0.009

NIV, non-invasive ventilation; P/F, PaO₂/FIO₂ ratio.

A smaller number of pulmonary lobes involved, lower SAPS II values on admission, P/F after 1 h of NIV ≥ 175 were the independent variables associated with a good outcome after NIV ($P < 0.001$).

A study flow diagram is provided in Figure 2.

Discussion

Non-invasive ventilation is often used in cases of acute respiratory failure in order to avoid intubation. Nevertheless, its use in cases of severe hypoxemic respiratory failure is still relatively new and some controversy still remains, with only a few studies available.^{1,20} Recently various studies have been published reporting success rates of 5-100%.^{8-10,12,21-45} At the beginning of the pandemic, the use of NIV was not recommended for lack of data supporting its safe use in treating patients with acute severe respiratory failure⁴⁶ and because of the high failure rate and the risk of possible consequence given that inappropriate and prolonged use of NIV had been suggested as a possible cause of death probably due to delayed intubation of these patients.⁴⁷ The situation is starting to change and the use of NIV during pandemics and a greater use in general in cases of acute pneumonia-associated respiratory failure is on the increase. But failure rates are still high. Various studies have already been carried out, most of which did not report the degree of respiratory failure (in particular, in cases in which there was NIV failure) understood as P/F ratio, the type of ventilator used, ventilation method and parameter settings, and, finally, the number of organs involved in the disease.

Different factors could play a role in NIV failure: number of organs involved,⁴⁸ the seriousness of the disease,¹ and the response to ventilation.^{1,49} In a recent study of children with ALI/ARDS, Piastra *et al.*⁴⁸ showed that the extent of organ failure on admission is a strong predictor of NIV failure and that patients with failure of only one organ have a 85.7% probability of success. The fact that information like this has not been available could be the reason behind the strong criticism concerning the poor efficacy of NIV in severe respiratory failure from H1N1 viral pneumonia. Furthermore, again in a recent study, Pelosi discussed a possible role for chest CT scan to identify patients with a lower possibility of selection for controlled mechanical ventilation. This Author declared that a $\text{PaO}_2/\text{FiO}_2$ ratio of less than 150 with FiO_2 100% and positive end-expiratory pressure (PEEP) 5-10 cm H_2O , associated with widespread opacity on CT scan, predicted greater suitability for controlled mechanical ventilation. In contrast, a patient with P/F over 150 and localized lobular opacity could have a low possibility of being assigned to controlled mechanical ventilation. This type of patient could be treated with

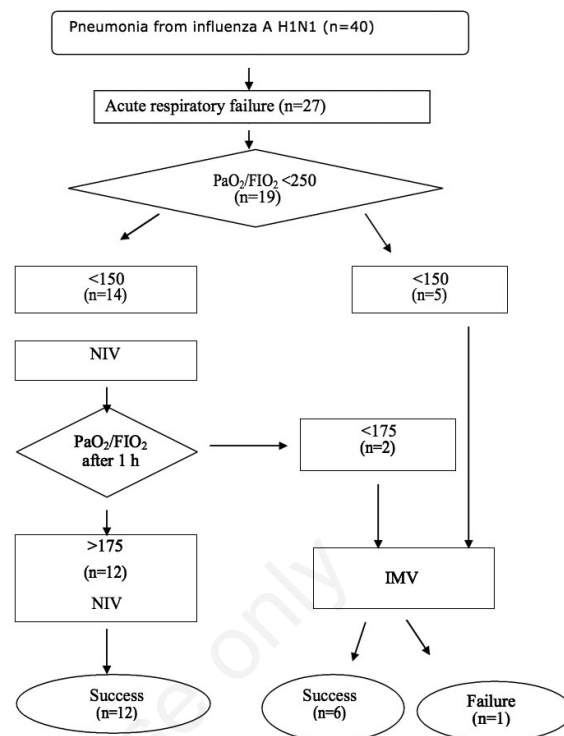


Figure 2. Study flow diagram.

assisted ventilation with flow volumes of 6-8 mL/kg and PEEP 5-10 cm H_2O .¹⁹ We used simplified criteria like this on admission to the Emergency Department to select our patients.

Admission to the sub-intensive care unit: lobular opacity, P/F ratio over 150 with FiO_2 60%, SAPS II 34 or below, no multi-organ failure.

Admission to ICU: widespread opacity, P/F ratio below 150, SAPS II over 34.

In our study, 73.68% of patients with severe respiratory failure were treated with NIV of whom 85.7% with a positive outcome, demonstrating one of the highest success rates for NIV ever reported.³¹ We believe that the reason for this was a rigorous selection procedure to choose patients to be treated, with no really severe cases of respiratory failure or distress ($\text{P/F} \leq 150$), the use of chest CT scan to evaluate pulmonary involvement, less serious disease status ($\text{SAPS} \leq 34$), failure of only one organ, rigorous monitoring or factors predicting NIV success such as P/F after 1 h ≥ 175 ¹ and any changes in indicators of disease in the hours and even days after admission.

Many Authors have expressed their concerns about the use of NIV during a pandemic because of the risk of infection through inhalation via the mask or via the ventilator tube, as these could infect doctors and nursing staff. No cases of contamination have been confirmed in our hospitals that have compromised the health of

our healthcare operators, even though most patients were treated with NIV. All patients with confirmed influenza A H1N1 infection were kept in isolation and in negative pressure rooms, and preventive measures against infection were adopted (masks, overalls, gloves and alcohol disinfectant gel for the hands). As far as the ventilators are concerned, unaided oro-nasal masks were preferred to limit the spread of infection.

This study has some limitations. Only 2 hospital centers are involved and there is only a small number of cases. It cannot, therefore, be considered to be representative of the situation in Liguria or northern Italy. Also our hospitals are not reference centers for children or pregnant women with H1N1 influenza infection so these patient populations are not included. Finally, mortality rates are extremely low and this makes it impossible to make a comparative analysis of mortality as outcome.

In conclusion, our success rates with NIV show that patients with severe pneumonia from H1N1 can benefit from this treatment, thus avoiding the need for invasive ventilation, reducing the incidence of complications, the length of hospital stay and hospital costs. All this can only be achieved if there is a careful selection of suitable patients. As reported above, this approach should be used with great caution and NIV should only be used with non-severe ALI/ARDS profiles (P/F 150) and all patients should be carefully monitored.^{49,50}

Physicians should be aware of the pulmonary complications of H1N1 influenza and carefully select patients suitable for NIV. They should also understand that an inappropriate use of NIV for too long (>24 h in cases of worsening clinical and hemogasanalytical profiles)⁵¹ could lead to death due to excessive delay in intubation.⁴⁶

A recent study by Masclans *et al.* did, however, show that failure of NIV in patients with severe respiratory failure caused by pneumonia from influenza A H1N1 virus has been associated with mortality rates similar to those reported for patients who underwent immediate intubation.⁴⁵ This finding, if confirmed further would change the idea that use of NIV could cause a delay in invasive treatment and worsen patient prognosis, as stated in the first studies on H1N1 influenza. Physicians expert in the use of NIV can avoid intubation, reduce the incidence of septic shock and improve survival with respect to only high-flow oxygenotherapy in acute respiratory failure caused by pneumonia.⁵² Given the evidence examined, the suggestion could be made to consider ventilation support as early as possible in the initial phase of acute pneumonia-related respiratory failure. Such an approach could have an effective and safe role in reducing the huge demand on beds in the ICU seen particularly during pandemics.

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