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Review article

The use of non-invasive ventilation during acute respiratory failure due to pneumonia[☆]

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ABSTRACT

The use of non-invasive ventilation in patients with community-acquired pneumonia is controversial since this is associated with high rates of treatment failure, compared with other causes of severe acute respiratory failure. The populations of patients with community-acquired pneumonia who have demonstrated better response to non-invasive ventilation are those with previous cardiac or respiratory disease, particularly chronic obstructive pulmonary disease. By contrast, the use of non-invasive ventilation in patients with community-acquired pneumonia without these pre-existing diseases should be very cautious and under strict monitoring conditions, since there are increasing evidences that the unnecessary delay in intubation of those patients who fail treatment with non-invasive ventilation is associated with lower survival.

Pulmonary complications of immunosuppressed patients are associated with high rates of intubation and mortality. The use of non-invasive ventilation in these patients may decrease the need for intubation and improve the poor outcome associated with these complications.

Continuous positive airway pressure has been used to treat acute respiratory failure in several conditions characterised by alveolar collapse. While this is extremely useful in patients with acute cardiogenic pulmonary oedema, the efficacy in pneumonia seems limited to immunosuppressed patients with pulmonary complications. Conversely, there are no sufficient evidences on the efficacy of continuous positive airway pressure in immunocompetent patients with pneumonia and severe acute respiratory failure.

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1. Introduction

Based on controlled clinical trials that demonstrate a marked decrease in the needs for intubation, as well as improved morbidity and mortality, non-invasive ventilation (NIV) is now considered as a first-line ventilatory treatment in selected patients with severe exacerbation of chronic obstructive pulmonary disease (COPD) and hypercapnic respiratory failure [1–4]. Other patients who show benefit from the use of NIV are those affected of acute cardiogenic pulmonary oedema (CPO). Both NIV and continuous positive airway pressure (CPAP) are equally effective in decreasing the needs of intubation and improving mortality in these patients [5–7]. Finally, immunosuppressed patients have poor outcome when they develop pulmonary infiltrates and acute hypoxemic respiratory failure (AHRF); in these

patients, NIV seems to decrease the needs of intubation and the related morbidity and mortality [8,9].

The benefits of NIV appear to be the consequence of avoiding tracheal intubation and the associated morbidity and mortality. Morbidity includes an increased risk for ventilator-associated pneumonia (VAP) [10], ventilator-induced lung injury [11], increased needs of sedation that contribute to prolonged ventilation, and complications of the upper airway related with prolonged translaryngeal intubation.

However, the role of NIV in other type of patients is still under debate. It is possible that other populations at risk for complications related to invasive mechanical ventilation may benefit from the use of NIV. However, the efficacy of NIV in patients with different types of AHRF is less evident from controlled clinical trials. Although patients with AHRF were less likely to require tracheal intubation when NIV was added to standard therapy, a systematic review of the literature did not support the routine use of NIV in all patients with AHRF due to a less clear effect on mortality and the heterogeneity found among studies, suggesting that effectiveness varies among different populations [12].

The first problem in addressing patients with AHRF is the heterogeneity of this condition. Studies assessing the outcome of patients with AHRF treated with NIV in the intensive care unit (ICU) identified

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up to 9 different groups of patients, with substantial differences in outcomes among them (Fig. 1) [13]. Moreover, a majority of clinical trials that assessed the efficacy of NIV in patients with AHRF studied mixed populations of patients, with controversial results when all these trials are analysed together. By contrast, few studies have assessed specifically the usefulness of NIV in patients with pneumonia [14] and it is even considered controversial due to a major variability in failure rates [14–17], which are generally higher than those observed in COPD [4] or acute CPO [18].

Studies on NIV often include pneumonia in the heterogeneous condition of AHRF, which was independently associated with NIV failure in a multicentre study [19]. However, large published series of hospitalised patients with community-acquired pneumonia (CAP) report high rates of chronic respiratory or cardiac co-morbidities [20,21]. Hence, a recent report on patients with CAP treated with NIV in the ICU reported a substantial proportion of patients with previous cardiac or respiratory disease, resulting in a high proportion of hypercapnic respiratory failure among them [22]. Hence, the outcome of NIV in patients with CAP from studies that have excluded COPD or hypercapnic patients [13,15,16,23] should not be extrapolated to general CAP populations treated with NIV.

2. Non-invasive ventilation in severe community-acquired pneumonia

Community-acquired pneumonia is a significant cause of morbidity and mortality [24,25]. Severe CAP is conceptually pneumonia requiring admission to the ICU or carrying a high risk of death [25,26]. Direct admission to an ICU is required for patients with septic shock or acute respiratory failure (ARF) requiring invasive mechanical ventilation, defined as major severity criteria in the current Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS) guidelines used to define severe CAP [24]. Admission to an ICU is also recommended for patients with other minor severity criteria (Table 1). The IDSA/ATS guidelines recommended that patients with three or more minor severity criteria, in the absence of major criteria, be admitted to an ICU. Among all criteria that define severe CAP, the need for invasive ventilation, severe arterial hypoxemic, and increased respiratory rate are related with ARF.

The cornerstone in the treatment of pneumonia is antibiotic therapy, and ventilatory support in patients with severe respiratory

Table 1

Criteria for severe CAP according to the IDSA/ATS guidelines (adapted from [24]).

Minor criteria
Respiratory rate ≥ 30 breaths/min ^a
PaO ₂ /FiO ₂ ≤ 250 ^a
Multilobar infiltrates
Confusion-disorientation
Uraemia (BUN level ≥ 20 mg/dL)
Leucopenia (WBC count $< 4 \times 10^9/L$)
Thrombocytopenia (platelet count $< 100 \times 10^9/L$)
Hypothermia (core temperature $< 36^\circ C$)
Hypotension requiring aggressive fluid resuscitation
Major criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors

Definition of abbreviations: PaO₂/FiO₂ = ratio of arterial oxygen tension to inspired oxygen fraction; BUN = blood urea nitrogen; WBC = white blood cells.

^a The need for non-invasive ventilation can substitute for respiratory rate ≥ 30 breaths/min or PaO₂/FiO₂ ≤ 250 .

failure [27]. The most important rationale for using NIV is to overcome an episode of severe acute respiratory failure (ARF) without the need for invasive mechanical ventilation. The background for the use of NIV in severe CAP is related to the presence of severe ARF. Invasive ventilation is indicated in case of life-threatening respiratory failure; however, invasive ventilation is associated to increased risk of severe complications. Since the main objective of NIV in severe ARF in general is help in overcoming the acute episode without the need for invasive mechanical ventilation, by avoiding tracheal intubation, morbidity and mortality would decrease in these patients.

2.1. Non-invasive ventilation and outcome of pneumonia

Pneumonia in patients treated with NIV is persistently associated with poor outcome in the literature. The first study that found this association was a retrospective analysis of 59 episodes of ARF in 47 patients with COPD exacerbations. In 46 of them NIV was effective and in 13 failed and patients needed tracheal intubation and invasive mechanical ventilation [28]. Among others, a univariate analysis assessing predictors of NIV failure found pneumonia as the cause of exacerbation associated with higher failure of NIV. In this study pneumonia was the cause of 38% unsuccessful episodes and 9% successful episodes of ARF. While the failure rate of patients with other causes of exacerbation was 16%, the failure rate of patients with pneumonia was 56%.

A multinational study in 8 ICUs analysed the evolution of 356 patients who received NIV for an episode of severe AHRF in relation with the aetiology of the episode [13]. Among the different causes of AHRF, the highest rates of tracheal intubation corresponded to patients with acute respiratory distress syndrome (ARDS, 51%) and CAP (50%) (Fig. 1). A multivariate analysis of predictors of NIV failure found the presence of ARDS or CAP a significant and independent predictor of NIV failure, with an adjusted odds-ratio of 3.75. Other independent predictors of NIV failure were age older than 40 years, higher scores of severity at ICU admission, and worse hypoxemia after 1 h of NIV treatment.

Another prospective study analysed 24 patients without underlying chronic respiratory disease who were treated with NIV because of severe CAP and ARF [15]. In general, the use of NIV was followed by a decrease in respiratory rate and increase in arterial hypoxemia after 30 min, with return to the baseline values after NIV was removed. However, the overall intubation rate was 67% in these patients. Among others, advanced age and lower levels of arterial oxygenation were predictors for intubation. Likewise, intubation was associated with higher mortality and longer length of hospital stay. By contrast, those patients in whom NIV avoided intubation had a very favourable

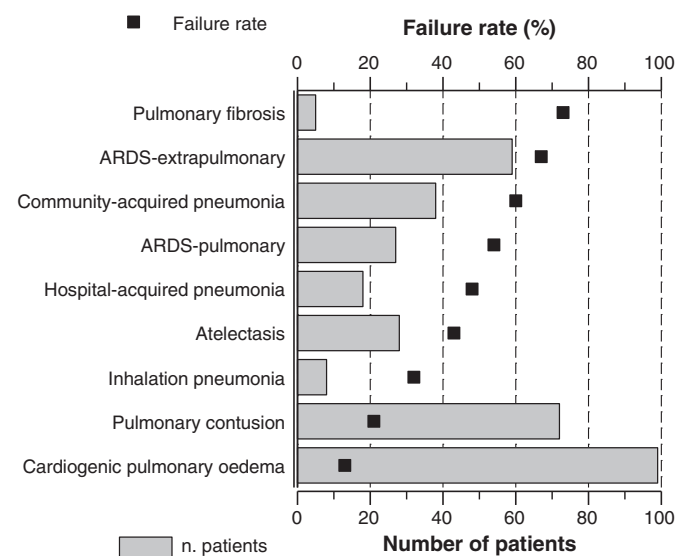


Fig. 1. Causes of acute hypoxemic respiratory failure and frequency of NIV failure. ARDS patients are divided into pulmonary and extra pulmonary origin. For each subset of patients, grey columns represent the number of patients, and the black dots represent the percentage of patients that required intubation. Adapted from [13].

outcome. Due to the good outcome in these patients when tracheal intubation was avoided and the fact that the assessment of the efficacy of NIV resulted in minimal delay in intubation, the authors of this study suggested that these patients may undergo a trial of NIV with appropriate monitoring in order to avoid unnecessary delay in intubation.

This conflict between a favourable physiological response to NIV and a poor clinical evolution of patients with severe CAP was observed in another study in patients with severe AHRF, 18 with severe CAP and 15 with CPO [16]. Both groups had similar baseline levels of arterial hypoxemia, respiratory rate and heart rate. The improvement in arterial hypoxemia and heart rate was similar in both groups of patients, while respiratory frequency improved only in patients with CPO when NIV was applied. Likewise, the intubation rate was higher and the hospital length of stay was longer in patients with pneumonia. As expected, the hospital mortality rate was substantially higher in intubated than in non-intubated patients.

In the light of these results we can conclude that, in patients with severe AHRF who need NIV, those whose cause of respiratory failure is pneumonia are among those with worse outcome, even with similar levels of arterial hypoxemia. However, prospective randomised clinical trials are needed in order to assess whether NIV is effective in patients with severe CAP.

2.2. The use of non-invasive ventilation in community-acquired pneumonia

Few controlled trials have assessed the efficacy of NIV in patients with severe pneumonia. The only prospective randomised controlled trial in patients with severe CAP included 56 patients, who were allocated to receive conventional treatment with or without NIV [14]. This study demonstrated that patients who had received NIV together with conventional treatment had lower rate of tracheal intubation (21 vs. 50%, $p < 0.03$) and a shorter stay in the intermediate care unit than those who received conventional treatment only, although the length of hospital stay and hospital mortality were similar between both groups. This study also showed, in a subset analysis, that the significant benefits of NIV occurred in patients with COPD and hypercapnic respiratory failure only; this subset of patients had also a lower mortality after two months (11 vs. 63%, $p = 0.05$). By contrast, patients without COPD nor hypercapnic respiratory failure did not

benefit from NIV. Although these results were promising, the routine use of NIV in patients with CAP and without COPD has not been clearly established.

A more recent prospective randomised controlled trial in patients with severe AHRF demonstrated that NIV decreased the need for tracheal intubation and ICU mortality, compared with high-concentration oxygen therapy [17]. Moreover, a subgroup analysis observed that patients with pneumonia as the cause of the episode of AHRF were those in whom NIV showed significant benefits; in this subset of patients, the benefits in decreasing tracheal intubation and ICU mortality remained. As regards to the other subsets of patients, there was a non-significant trend to a lower rate of NIV failure in patients with thoracic trauma, and NIV failure in patients from this study with CPO and ARDS was very low and high, respectively, without differences between patients treated with NIV and those from the control group [17]. In this study, the use of NIV resulted in a faster improvement of arterial hypoxemia and tachypnea, compared with high-concentration oxygen therapy (Fig. 2). Likewise NIV was also associated with a lower rate of septic shock and a trend to a lower incidence of hospital-acquired pneumonia.

Concerns have been raised due to the high mortality rate of patients who fail NIV treatment, particularly in those with AHRF and without previous cardiac or respiratory disease (“de novo” ARF), and the possibility that unnecessary delay of intubation results in excess mortality [19,29]. Particularly, an actual mortality of patients intubated after NIV failure higher than mortality predicted by severity scores has been reported [29]. However, these comparisons may be misleading, since severity scores often underestimate hospital mortality in ICU patients [30,31]. A recent preliminary report on the use of NIV in patients with CAP and severe ARF found for the first time a consistent association between delayed intubation and increased mortality in patients with CAP and “de novo” ARF [22]. Longer duration of NIV before intubation was not related with severity of patients at admission in this study. Moreover, patients with shock who needed intubation failed NIV earlier than those without shock. Therefore, this excess of mortality was attributed by the authors to delayed intubation rather than a more severely-ill selected population. By contrast, no relationship was found between delayed intubation and mortality in patients with CAP and previous cardiac or respiratory disease from this study [22].

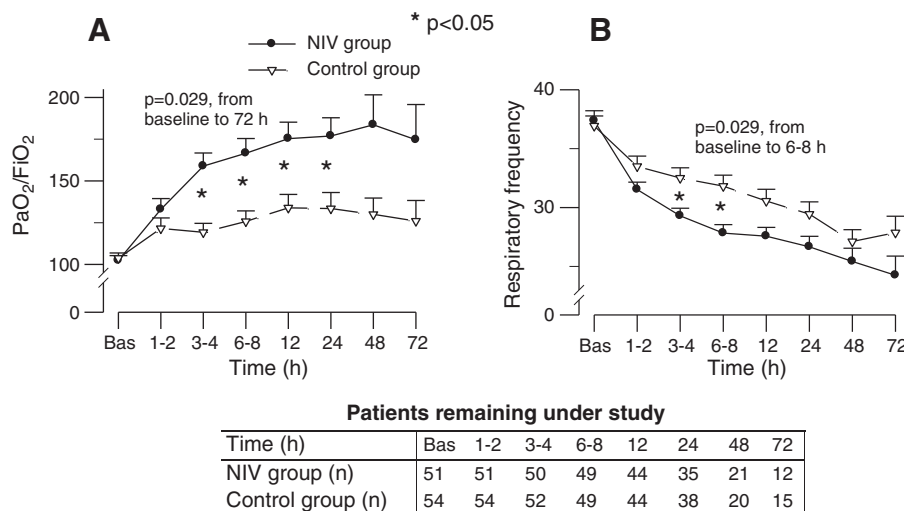


Fig. 2. Time-course evolution (mean \pm SEM) of arterial hypoxemia, as assessed by the $\text{PaO}_2/\text{FiO}_2$ ratio (panel A), and respiratory frequency (panel B), in the two groups. Both variables improved with time in the two groups. Asterisks denote significant differences between the two groups at individual time-points. After Bonferroni correction, the improvement of the two variables was significantly greater in the NIV group after 3–4 h of randomization, and remained significantly greater 24 and 6–8 h after randomization for $\text{PaO}_2/\text{FiO}_2$ ratio and respiratory frequency, respectively. The table below the graph denotes the number of patients remaining under study at each time-point in the two groups. The time-course decrease of patients corresponds to those meeting criteria to terminate the protocol. Adapted from [17].

In summary, patients with severe CAP who receive NIV as a support for severe AHRF are among those with the highest rate of NIV failure. For this reason, when NIV is indicated in these patients, they should be managed in setting with appropriate resources in staff and equipment for a correct monitoring in order to early detect evidences of NIV failure and therefore avoid unnecessary delay in the intubation of patients. However, an appropriate selection of patients with severe CAP and the addition of NIV to the standard treatment may decrease the likelihood to need intubation.

3. Non-invasive ventilation in immunosuppressed patients with pulmonary complications

The early application of NIV may be extremely helpful in immunosuppressed patients with pulmonary infiltrates not necessarily associated with ALI, in whom intubation dramatically increases the risk of pneumonia, infections, and ICU mortality.

Two trials evaluated NIV, as opposed to standard treatment alone, in immunosuppressed patients characterised by a respiratory rate >30 breaths/min and $\text{PaO}_2/\text{FiO}_2 <200$ mmHg. Antonelli et al. [8] compared NIV vs. standard therapy in solid organ transplant recipients with AHRF. Within the first hour of treatment, $\text{PaO}_2/\text{FiO}_2$ improved in 70% of patients in the NIV group and in only 25% of patients receiving medical therapy alone. NIV was associated with a significant reduction in the rate of intubation, complications, mortality, and duration of ICU stay among survivors. In patients with immunosuppression secondary to haematological malignancies, transplantation or human immunodeficiency virus infection, Hilbert et al. [9] compared early NIV with standard treatment. All patients had fever, bilateral pulmonary infiltrates and hypoxemia. Fewer patients in the NIV group required intubation, had serious complications, or died in the ICU or in the hospital. It has been shown that NIV, especially when applied early, can significantly ameliorate the conditions of these patients, reduce need for intubation and overall mortality.

In 1998 the first report of the use of NIV outside the ICU in a patient with respiratory failure after hematopoietic progenitor transplantation was published [32]. More recently, Principi et al. [33], described the use of NIV directly in the haematological unit of a university hospital in a prospective clinical study with historical matched controls. They compared the efficacy of early administration of non-invasive CPAP delivered by the helmet vs. face mask to treat haematological malignancy patients with fever, pulmonary infiltrates, and hypoxemic acute respiratory failure ($\text{PaO}_2/\text{FiO}_2 <200$ mmHg). A total of 34 patients were enrolled with a mean $\text{PaO}_2/\text{FiO}_2$ around 140. Oxygenation improved in all patients after non-invasive CPAP. No patient failed helmet CPAP because of intolerance while eight patients in the mask group did so. CPAP could be applied continuously for a longer period of time in the helmet group. The authors concluded that early CPAP with helmet improves oxygenation in selected immunosuppressed patients with hypoxemic acute respiratory failure even outside the ICU. Indeed the tolerance of helmet CPAP seems better than that of CPAP delivered by mask.

There are several new information from the Principi's study [33]. First, they assess the safety and feasibility of NIV outside the ICU in haematological patients with severe ARF. Second they have applied a particular interface such as the helmet, that is probably the simplest and easiest way to apply CPAP outside a protected unit, since it does not require any electrical power and/or need of a ventilator. The helmet should however be used with caution, especially in hypercapnic patients, when applying pressure support ventilation, with a commonly used ventilator, due to the possibility of CO_2 rebreathing and of poor patient/ventilator interaction [34,35]. Third, this study indirectly highlighted that interdisciplinary collaboration between haematologists and intensivists appears crucial for achieving an early implementation of NIV and improving the quality of care. One year later, Rabbitsh et al. [36] analysed retrospectively the efficacy of NIV

in 35 patients with AHRF after autologous or allogeneic stem cell transplantation, directly ventilated in the bone marrow transplant unit. NIV was delivered by a standard face mask or helmet. Of the eighty-two patients who developed respiratory failure, 47 patients were initially intubated and mechanically ventilated. None of these patients survived. Thirty-five patients initially underwent NIV. Seven of these patients survived and were discharged from the hospital (20%). Eleven of the 35 (31%) patients improved within the first 4 h of NIV with respect to oxygenation and were regarded as responders. In all survivors, the partial pressure of arterial oxygen (PaO_2) improved after the initiation of NIV while in non-survivors, PaO_2 improved in only 4/28 patients (17%, $p < 0.0001$). The authors concluded that in patients with ARF after stem cell transplantation, NIV could improve prognosis when compared to a group of patients who constantly die if they receive mechanical ventilation.

The use of NIV for Severe Acute Respiratory Syndrome (SARS) and other airborne diseases has generated debate. Based on the Toronto experience with SARS, in which a certain number of caregivers contracted SARS when a patient was intubated following failure of NIV, the use of NIV was discouraged for these patients [37]. Two subsequent observational studies from China, however, found no evidence of viral spread to caregivers who took appropriate precautions [38,39]. In the event of a bird flu pandemic, ventilator resources are likely to be severely strained, and NIV may offer a means of supporting some of the afflicted, mainly those with initial respiratory failure. However, NIV is often considered contraindicated in respiratory failure from communicable respiratory airborne diseases unless it is used within a negative pressure isolation room and strict precautions are taken. Several experimental studies have shown substantial exposure to exhaled air within 0.5 to 1 m radius from patients receiving NIV with different facial masks, especially at higher levels of positive pressure [40,41].

4. Continuous positive airway pressure

4.1. Effects of continuous positive airway pressure on the respiratory system

Continuous positive airway pressure has been used to treat ARF in several conditions where alveoli collapse due to increase of transpulmonary pressure over airway closing pressure. Collapsed alveoli do not participate in gas exchange, representing a common example of intrathoracic shunt mechanism of hypoxemia that typically does not respond to oxygen administration. In this case, the only way to improve gas exchange is alveolar recruitment induced by CPAP. Patients breathe against a constant resistance to a supra-atmospheric pressure. This increase of airway pressure is present during the whole breathing cycle; in particular, the positive end-expiratory pressure (PEEP) allows the collapsed alveoli to remain open also during expiration. This means that more alveoli participate to gas exchange, thus leading to improved oxygenation due to shunt effect decrease with improved ventilation/perfusion ratio. This leads to an increase of functional residual capacity (FRC) with compliance increase and decrease of work of breathing.

The effects of CPAP on the respiratory system have been demonstrated many years ago by Räsänen et al. in another model of patients with acute parenchymal respiratory failure such as subject admitted to an ICU with acute CPO [42,43]. The application of higher levels of PEEP yielded a decrease in transpulmonary pressure and a parallel decrease in pulmonary pressure. Similarly, higher PEEP values were associated with greater levels of oxygenation and decrease of intrapulmonary shunt.

More recently, l'Her et al. evaluated the effect of PEEP in 10 patients with acute lung injury, 7 of whom had pneumonia [44]. This study compared the short-term effect of CPAP at 10 cmH_2O (CPAP-10) and 2 combinations of NIV with pressure-support ventilation

(PSV): an inspiratory support level of 10 cmH₂O with positive end-expiratory pressure (PEEP) of 10 cmH₂O (PSV 10–10) and an inspiratory support level of 15 cmH₂O with PEEP of 5 cmH₂O (PSV 15–5) [44]. Compared with spontaneous breathing, the respiratory frequency decreased with the highest levels of inspiratory support (PSV 15–5). By contrast, arterial oxygenation improved similarly with CPAP-10 and PSV 10–10, while this increase failed to reach statistical significance for PSV 15–5. Finally, the work of breathing decreased with both modalities of NIV but not with CPAP (Fig. 3), although the highest reduction in dyspnoea was achieved with PSV 15–5. However, the authors discuss as a major limitation their specific CPAP experimental setting. They state that the disappointing results observed with CPAP may be explained in part by the type of patient, the interface, and the ventilator used to deliver CPAP. Moreover, the authors point out that a low level of PSV was applied during the initial and final periods to compensate for the dead space imposed by the circuit and the measurement apparatus. However, no PSV level was added during CPAP trial. Although designed to compensate for the load imposed by the circuit during spontaneous breathing, one cannot exclude that the absence of this low PSV level during the CPAP trial could explain part of the tidal volume decrease noted after switching from initial baseline to CPAP.

According to the observed variations in airway pressure in some patients, it could be considered that CPAP was not fairly administered by the ventilator. The authors conclude that whether a different system or type of administration (high-flow CPAP vs. ventilator; helmet vs. face-mask) would give different results may warrant further investigation.

The effects of helmet CPAP in pneumonia were evaluated by Cosentini et al. in a recent study on patients with pneumonia [45]. The effects on oxygenation of helmet CPAP were compared with Venturi mask in patients with moderate-to-severe hypoxemia (PaO₂/FiO₂ ratio ≥ 210 and ≤ 285). The primary endpoint was the time to reach a PaO₂/FiO₂ ratio > 315 . Forty-seven patients were recruited: 20 randomised to CPAP and 27 controls received oxygen. Patients randomised

to CPAP reached the end-point in a median of 1.5 h, whereas controls reached the end point in 48 h ($p < 0.001$). The proportion of patients who reached the primary end-point was 95% (19/20) among the CPAP group and 30% (8/27) among controls ($p < 0.001$). However, 1 h after reaching the primary end-point, only 2/14 patients in the CPAP group maintained a PaO₂/FiO₂ value > 315 , suggesting that PEEP is rapidly effective but should be applied for longer period to obtain clinically relevant effect. However, the effect on oxygenation was not applied for a longer period of time, therefore, the possible decreasing efficacy of CPAP with time, as observed in the study of Delclaux, was not tested. The authors conclude that CPAP delivered by helmet rapidly improves oxygenation in patients with CAP suffering from a moderate hypoxemic ARF. Therefore, this study may represent a proof-of-concept evaluation of the potential usefulness of CPAP in patients with CAP, since the similar effect on oxygenation observed in Delclaux' study was obtained in a mixed population including patients with acute cardiogenic pulmonary edema.

4.2. Effects of continuous positive airway pressure on circulation

The circulatory effects of CPAP application have been effectively studied and applied mainly in patients with ARF of cardiac origin, such as congestive heart failure and acute CPO. Indeed, the increased intrathoracic pressure induced by the application of PEEP decreases venous return that is usually elevated in patients with heart failure, especially in those with reduced ejection fraction. Moreover, the increase of intrathoracic pressure reduces transmural left ventricular systolic pressure and consequently decreases ventricular afterload [46]. This may produce an increase in cardiac output. In patients with acute CPO with diastolic dysfunction, the increase of intrathoracic pressure induced by PEEP application benefit of CPAP results from a decreased left ventricular end-diastolic volume, i.e. preload [46].

The cardiovascular effects of CPAP in patients with pneumonia are less known. The venous return decrease induced by PEEP application

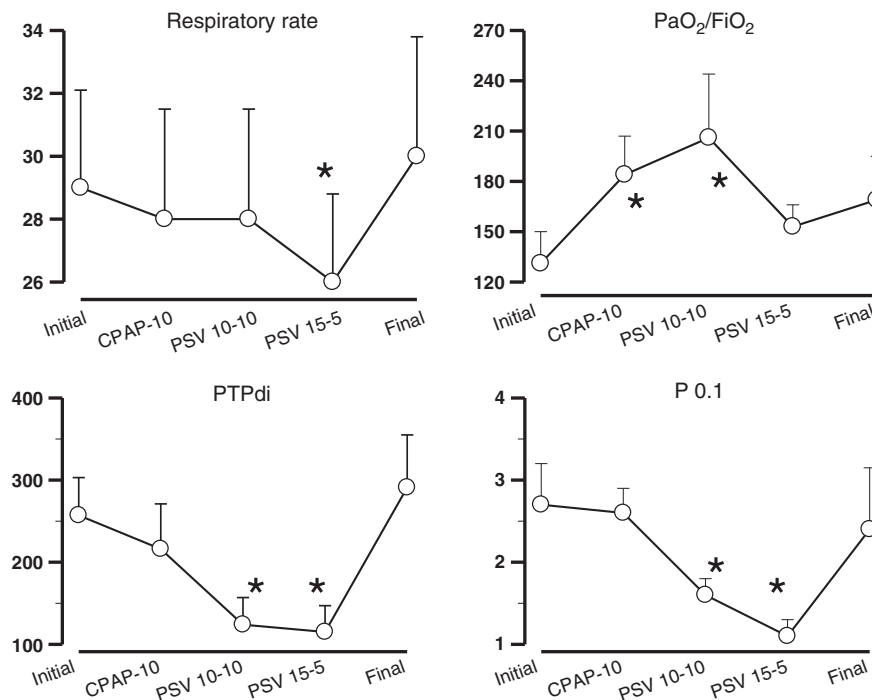


Fig. 3. Average changes in respiratory variables (respiratory frequency, arterial hypoxemia, assessed by the arterial oxygen tension to inspired oxygen fraction ratio, work of breathing, assessed by the pressure–time product of the diaphragm (PTPdi), and the respiratory drive, assessed by the occlusion pressure ($P_{0.1}$)) comparing the initial and final values during spontaneous breathing with the three ventilatory modalities: CPAP 10 cmH₂O, pressure-support ventilation (PSV) 10 cmH₂O with PEEP 10 cmH₂O, and PSV 15 cmH₂O with PEEP 5 cmH₂O. Asterisks denote significant differences between initial values and the specific ventilatory modality. Adapted from [44].

may impair stroke volume in patients who are frequently febrile and relatively or absolutely hypovolemic. This may lead to a net unfavourable effect on the balance between blood oxygenation and tissue oxygen delivery (DO_2).

The cardiovascular effects have been studied by Cosentini et al. Systolic and diastolic blood pressure, together with heart rate, were not significantly modified after 1 h of CPAP application. Similarly, haemodynamic data were unchanged after 1 h of Venturi mask oxygen administration, and were comparable to 1-hour cardiovascular findings observed in the CPAP group (Table 2) [45].

Data on systolic blood pressure and heart rate were analysed by Delclaux et al. [47]. Unfortunately, the 123 hypoxemic patients randomised to CPAP (62) vs. oxygen alone (61) belong to a very heterogeneous group of diseases, ranging from acute heart failure to near-drowning and SIRS/shock, making it impossible to draw a conclusion on haemodynamic effect on the subset of patients with pneumonia (67/123 cases). Overall, heart rate significantly decreased in both groups at 1 h in ICU, without differences between CPAP and oxygen therapy. Conversely, systolic blood pressure was unchanged after 1 h in ICU in both groups.

In conclusion, the scarce data on haemodynamic effects of CPAP application in patients with pneumonia are insufficient to make an evidence-based suggestion. However, the demonstrated effect of venous return decrease with PEEP application should alert physicians to monitor the haemodynamic effects when CPAP is considered an option to treat a patient with ARF secondary to pneumonia; patient's volume should always be assessed before CPAP application, and fluids should be reasonably administered to counterbalance the expected effects of PEEP on intrathoracic and circulating volume.

4.3. Continuous positive airway pressure in immunosuppressed patients

The first attempts to apply positive pressure ventilation in immunosuppressed patients, although not those with haematological disorders, were made in the late 1980s and early 1990s using CPAP, mainly on patients with acquired immunodeficiency syndrome and with acute respiratory failure due to *Pneumocystis jirovecii* infection, formerly known as *P. carinii* pneumonia (PCP).

In 1988, Kesten et al. applied nasal CPAP to 9 subjects with PCP. All patients showed oxygen improvement; after 20 min of nasal CPAP without supplemental oxygen; the mean PaO_2 increased from 55.9 to 68.4 mmHg, and the calculated alveolar-arterial oxygen gradient decreased from 48.3 to 34.3 mm Hg [48]. Two years later, Gregg et al. treated 18 AIDS patients with PCP with mask CPAP. The mean PaO_2 rose from 62 to 158 mmHg, the respiratory rate decreased from 51 to 32 breaths/min, and the $PaCO_2$ was unchanged. The mean duration of treatment was 4.5 days. Only one patient developed a pneumothorax, there were no other major complications, and the mortality rate was 55% [49]. Later, other authors reported the use of CPAP in ARF due to PCP in more than 60 patients, with a mortality rate ranging from 12 to 22% [50–52].

All these studies, although uncontrolled, concluded that CPAP delivered via a nasal or face mask was an effective supportive therapy in these acutely ill patients, although the authors highlighted that attention should be paid to the possible occurrence of pneumothorax.

Table 2

Cardiovascular effects of CPAP in patients with community-acquired pneumonia, compared with control patients treated with oxygen therapy. Modified from [45].

Cardiovascular findings	Time	CPAP (patients)	Controls (patients)	p value
Systolic BP, mmHg	Baseline	132 ± 26 [18]	135 ± 22 [25]	.407
	1 h	127 ± 13 [9]	127 ± 16 [11]	
Diastolic BP, mmHg	Baseline	78 ± 14 [18]	73 ± 12 [25]	.794
	1 h	74 ± 7.4 [9]	75 ± 8.9 [11]	
Heart rate, beats/min	Baseline	89 ± 15 [20]	94 ± 16 [25]	.189
	1 h	84 ± 12 [12]	93 ± 18 [13]	

Acute lung injury is very common during the course of haematological malignancy. Hilbert et al. [53] published in 2000 a 5-year prospective study on CPAP efficacy in the treatment of febrile neutropenic patients with ARF. 64 patients with fever and normocapnic ARF defined as PaO_2/FiO_2 ratio <200 mmHg were treated with CPAP with a facial mask. CPAP was administered for a mean period of 6 h during the first 24 h, and the mean duration of CPAP was 7 days. A reduction in respiratory rate to less than 25 breaths/min was achieved in 53% patients, and the mean PaO_2/FiO_2 ratio increased from 128 to 218 mmHg. CPAP was successful in avoiding endotracheal intubation in 16/64 patients. A total of 16 responders and four non-responders survived. In the multivariate analysis, the Simplified Acute Physiology Score (SAPS)-II and hepatic failure at the entry into the study were predictive of CPAP failure. The authors concluded that CPAP was efficient in 25% of cases, all of whom survived, and that further controlled studies are needed to confirm the efficacy of non-invasive CPAP and to evaluate the most appropriate selection of immunosuppressed patients.

More recently, the efficacy of early CPAP vs. oxygen alone was evaluated in a prospective randomised controlled study by Squadrone et al. [54]. The authors enrolled 40 consecutive neutropenic patients with radiological evidence of bilateral pulmonary infiltrates, SpO_2 <90% while breathing room air, and respiratory rate >25 breaths/min. They were randomised to control (oxygen through Venturi mask at FiO_2 0.50) or helmet CPAP (FiO_2 0.50 plus PEEP 10 cmH₂O). Patients who received CPAP had less need of ICU admission for mechanical ventilation (4 vs. 16 patients; $p=0.0002$). CPAP reduced the relative risk for developing need of ventilatory support to 0.25, with a 95% confidence interval 0.10–0.62. Among patients admitted to the ICU, the intubation rate was lower in the CPAP than in the control group (2 vs. 14 patients; $p=0.0001$). CPAP reduced the relative risk for intubation to 0.46, with a 95% confidence interval 0.27–0.78. The authors suggested that the early use of CPAP on the haematological ward in patients with early changes in respiratory variables prevents evolution to acute lung injury requiring mechanical ventilation and ICU admission.

In conclusion, CPAP application for the treatment of ARF in immunosuppressed patients seems effective not only in terms of gas exchange and physiologic variables, but also in the reduction of endotracheal intubation and mortality. The effect on mortality reduction is probably driven by the decrease of ETI rate, since endotracheal intubation in this subpopulation is associated with a disproportionate high mortality rate due to immunodeficiency and risk of tube-associated fatal infections.

4.4. Continuous positive airway pressure in immunocompetent patients

The first reports on the application of CPAP in the treatment of ARF in the immunocompetent population date back to the 1970s [55]. Three patients with severe hypoxemia (PaO_2/FiO_2 ratio <50 with and right-to-left pulmonary shunts greater than 45%) secondary to influenza were treated with incremental PEEP values until the PaO_2 was above 200 mmHg and the right-to-left shunting had fallen to less than 25%. Two of the three patients did not require mechanical ventilation and survived. One died of a neurologic complication after a cardiopulmonary arrest, despite clearing on the chest X-ray film and improved gas exchange. The authors concluded that treatment with CPAP can be safely used in adults and has practical as well as theoretic benefits over CPAP. Other authors reported 6 years later a patient with chicken-pox pneumonia successfully treated with CPAP [56].

The first randomised controlled study comparing CPAP with oxygen alone was published in 2000 [47]. Delclaux et al. enrolled 123 consecutive patients admitted to 6 ICUs with severe ARF (PaO_2/FiO_2 ratio ≤300 mmHg). This population consisted of patients with pneumonia in 54% and acute pulmonary oedema in the remaining cases.

Despite an initial physiologic improvement in patients treated with CPAP (after 1 h of treatment the median $\text{PaO}_2/\text{FiO}_2$ ratio was greater with CPAP than patients with oxygen alone, Fig. 4), the final outcomes were not significantly different between the two treatments. The application of CPAP failed to reduce the endotracheal intubation rate (34% vs. 39% in the standard therapy group, $p=0.53$), hospital mortality (31% vs. 30%, $p=0.89$), or ICU length of stay. A higher number of adverse events occurred with CPAP treatment (18 vs. 6; $p=0.01$). The authors concluded that despite an early physiologic improvement, CPAP neither reduced the need for intubation nor improved outcomes in patients with acute hypoxemic, non-hypercapnic respiratory insufficiency primarily due to acute lung injury. However, several concerns have been raised on this study. First, the title of the study states that hypoxemic non-hypercapnic patients were enrolled. However, exclusion criteria were acute respiratory acidosis defined as a $\text{pH} < 7.30$ and a $\text{PaCO}_2 > 50$ mmHg and COPD. This means that patients with ALI/ARDS may have been enrolled with an initial acute respiratory acidosis with $\text{pH} \geq 7.30$ and $\text{PaCO}_2 \leq 50$ mmHg. Indeed, patients treated with CPAP had a median respiratory rate of 34 breaths/min (95th percentiles = 20–60) with a median pH of 7.42 (7.21–7.62) and PaCO_2 37 mmHg (23–61). Second, this hypothesis is indirectly confirmed by the authors when they state that a large proportion of patients enrolled met the definition of ARDS that has been demonstrated a negative prognostic factor of hypoxemic ARF together with pneumonia [13]. Third, among patients enrolled, only 54% had pneumonia. Hence, it is hard to conclude from this study that CPAP is not effective in pneumonia, since results are not described according to subgroups of diseases such as acute CPO, near-drowning and SIRS/shock. Fourth, among the 61 patients randomised to oxygen alone, 5 (8%) were switched to CPAP but the authors did not indicate whether their outcome was attributed to the initial treatment arm. Finally, pneumonia is an infectious disease and survival is associated to a correct antibiotic therapy and supportive measures which are not discussed in the paper. In conclusion, since this trial was not conducted on strictly hypoxemic patients with pneumonia but rather on heterogeneous hypoxemic/hypoxemic–hypercapnic subjects mainly suffering from ARDS, these data add limited evidence-based information on the efficacy of CPAP in pneumonia.

Another randomised controlled trial on the use of CPAP vs. oxygen alone has been published in 2010 [45]. This study was focused to the evaluation of the efficacy of CPAP application in terms of oxygenation specifically in a population of patients with pneumonia and moderately severe non-hypercapnic hypoxemia. The inclusion criteria were moderate acute respiratory failure ($\text{PaO}_2/\text{FiO}_2$ ratio ≥ 210 and ≤ 285 mmHg, and respiratory rate ≤ 35 breaths/min). Patients were randomised to receive helmet CPAP or standard oxygen therapy (control group). The primary end-point was the time to reach a $\text{PaO}_2/\text{FiO}_2$ ratio ≥ 315 mmHg. Patients who did not reach this threshold level before the last planned arterial blood gas measurement at 48 h were considered as failures. Forty-seven patients were recruited: 20

randomised to CPAP and 27 to controls. Patients randomised to CPAP reached the end-point in a median of 1.5 h, whereas controls reached the end-point in 48 h ($p < 0.001$). The proportion of patients who reached the primary end-point was 19 (95%) in the CPAP group and 8 (30%) among controls ($p < 0.001$). One hour after reaching the primary end-point, 2/14 patients in the CPAP group maintained a $\text{PaO}_2/\text{FiO}_2$ value ≥ 315 . The authors concluded that CPAP application in patients with moderate hypoxemic ARF due to CAP improves oxygenation. Moreover, the most impressive finding was the rapid effect of CPAP in comparison with standard oxygen therapy. Another interesting finding is the vanishing of the oxygenation improvement once CPAP was discontinued. This phenomenon has been defined by the authors as the “on-off” effect of CPAP on pneumonia, as already seen in patients with pneumonia treated with NIV [15]. Therefore, in order to obtain not only a physiologic but also a significant clinical effect, it could be necessary to open and keep open the lungs of patients with pneumonia through the application of CPAP while waiting for the antibiotic effect. In conclusion, this study proved the effect of CPAP in improving gas exchange in a well-defined model of hypoxemic ARF, such as CAP. The authors conclude that their study represents a proof-of-concept study that could sustain the development of future trials analysing clinical outcomes and possible adverse events in a population of patients with more severe CAP treated with CPAP. These trials would be needed to evaluate the possible role of CPAP as a valid and a safe tool in the management of patients with CAP. Until further randomised controlled trials define this issue, we do not recommend the use of this technique in patients with CAP with severe respiratory failure.

For these reasons, a new randomised controlled study to compare helmet CPAP application to oxygen alone in patients with pneumonia with severe acute respiratory failure is ongoing (www.clinicaltrials.gov NCT01383213). The inclusion criteria are: 1) ARF defined as dyspnoea at rest with respiratory rate ≥ 30 breaths/min or signs of respiratory distress; and 2) $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 250 evaluated during oxygen therapy supplied at least 1 h through a Venturi mask with FiO_2 0.50. This is a multicentre international study still enrolling patients to reach the sample size of 80 patients divided into two balanced groups of treatment. The primary end-point is the development of endotracheal intubation criteria maintained for at least 1 h. This study will be the first randomised controlled trial on the comparison of CPAP vs. oxygen alone in a cohort of patients with the diagnosis of pneumonia as unique cause of severe acute respiratory failure.

Finally, observational retrospective data on the efficacy of CPAP and NIV application in pneumonia have been published very recently in patients with ARF from H1N1 pneumonia. The authors describe a case-series of 5 out of 10 patients with ARF due to H1N1 pneumonia treated with Boussignac CPAP, Helmet system and BiPAP Vision. Both CPAP and NIV were effective in all patients in terms of clinical and arterial blood gas improvement, and avoiding intubation. There were no patient deaths in the ICU or in hospital, and the median duration

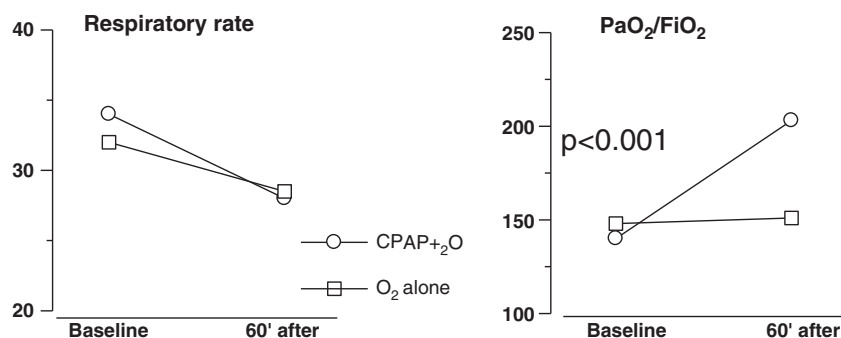


Fig. 4. Initial evolution of respiratory rate (left panel) and arterial hypoxemia, assessed by the arterial oxygen tension to inspired oxygen fraction ratio (right panel) for patients treated with CPAP plus oxygen as compared with those treated with oxygen alone, from baseline to 60 min after the initiation of treatment. Adapted from [47].

of ventilation was 6 days [57]. However, these favourable results have to be considered in view of the study limitations, since this is a small retrospective case series of patients with pneumonia without other serious organ involvement.

In summary, the evidence based data provided by the literature on CPAP application in pneumonia is relatively robust in the immunosuppressed population, where the application of NIV is also generally strongly recommended. However, in the immunocompetent population, prospective randomised controlled trials on CPAP use are very few and the design, results and conclusions of some of them are debatable. The only data where all trials are concordant regards to the common observation that CPAP application improves gas exchange and physiologic variables. However, until reliable well-designed controlled studies will be available the question whether CPAP is useful in patients with pneumonia is still open.

4.5. The grey zone: is oxygenation enough?

Unlike CPAP application in acute CPO, PEEP in pneumonia may improve oxygenation but may impair stroke volume that may counterbalance its beneficial effect. Moreover, oxygenation is only one of the variables involved in DO_2 . Conversely, PEEP application in acute CPO is part of the treatment since its beneficial effects include respiratory and circulatory performance. Alveolar recruitment leads not only to oxygenation improvement, but also to increase in FRC and compliance. On the other hand, heart performance is favoured by two phenomena, the decreased transmural LV pressure determined by the respiratory effort decrease induced by CPAP application, and the decreased venous return.

The lack of improvement in the work of breathing with the application of CPAP observed by L'Her et al. in their physiologic study on patients with acute lung injury mainly caused by pneumonia, in contrast with the marked improvement observed with the application of NIV [44], may also explain the lack of clinical benefits of CPAP in immunocompetent patients. Indeed, a randomised controlled trial on the use of NIV in patients with severe AHRF found that the most frequent indications for intubation or relevant feature at the time of intubation was the presence of signs of exhaustion [17].

In summary, the peculiarity of the relationship between CPAP application and clinical effects in the acute CPO model is profoundly different from that of pneumonia in two fundamental aspects. First, in acute CPO, PEEP application induces favourable physiological effects on the cardiopulmonary compartment on both sides, respiratory and cardiocirculatory, whereas in pneumonia the effects on heart may be detrimental. This means that in acute CPO, DO_2 and tissue perfusion are favoured by CPAP application. Second, in pneumonia, the beneficial respiratory effect on oxygenation through alveolar recruitment represents only a part of the strategy to improve tissue perfusion and oxygenation. Indeed, tissue perfusion depends on both mean arterial pressure and DO_2 ; the latter is related only in part to arterial blood oxygenation, but also to haemoglobin and cardiac output. Hence, it is easy to understand that a unique improvement in arterial oxygenation is not sufficient to assure an optimal tissue perfusion. Therefore, in pneumonia it is crucial always focusing on the triad concurring to DO_2 , i.e. arterial oxygenation, cardiac output, and haemoglobin, as recommended in the approach to severe sepsis, mainly represented by pneumonia.

As a clinical example, we know that normal DO_2 in a healthy man of 75 kg is about 1000 mL/min. If a patient with pneumonia has a PaO_2 of 45 mmHg in room air, Hb 7 g/dL, and cardiac output 5.3 L/min, the DO_2 is around 300 mL/min [58]. If we increase the PaO_2 to 124 mmHg by increasing FiO_2 and/or applying a PEEP, the DO_2 will increase only to around 400 mL/min (a 31% increase), still less than half the normal. However, if the patient is transfused to reach a haemoglobin level of 10.5 g/dL, the DO_2 will be increased by a further 48% to almost 600 mL/min. Finally, if cardiac output is optimised to 6.0 L/

min, the DO_2 will be increased of a further 50% to exceed 800 mL/min, thus approaching the normal values.

We can conclude, therefore, that non-invasive ventilation and CPAP in particular, has a role in the management of ARF in the immunosuppressed population, but evidence-based data are insufficient to recommend its use in the immunocompetent population. In any case, CPAP alone should only be considered a support measure to increase oxygenation that is only a part of the approach to optimise tissue perfusion which is always the aim of the treatment of pneumonia, while NIV may be also used as a “true” support of the failing respiratory pump.

Conflict of interest statement

The authors declare no conflicts of interest regarding to this subject.

Learning points

- The use of non-invasive ventilation in patients with community-acquired pneumonia is controversial since this is associated with high rates of treatment failure, compared with other causes of severe acute respiratory failure.
- The populations of patients with community-acquired pneumonia who have demonstrated better response to non-invasive ventilation are those with previous cardiac or respiratory disease, particularly chronic obstructive pulmonary disease.
- By contrast, the use of non-invasive ventilation in patients with community-acquired pneumonia without these pre-existing diseases should be very cautious and under strict monitoring conditions, since there are increasing evidences that the unnecessary delay in intubation of those patients who fail treatment with non-invasive ventilation is associated with lower survival.
- Pulmonary complications of immunosuppressed patients are associated with high rates of intubation and mortality. The use of non-invasive ventilation in these patients may decrease the need for intubation and improve the poor outcome associated with these complications.
- Continuous positive airway pressure has been used to treat acute respiratory failure in several conditions characterised by alveolar collapse. While this is extremely useful in patients with acute cardiogenic pulmonary oedema, the efficacy in pneumonia seems limited to immunosuppressed patients with pulmonary complications.
- Conversely, there are no sufficient evidences on the efficacy of continuous positive airway pressure in immunocompetent patients with pneumonia and severe acute respiratory failure.

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