

Comparison of high flow and standard oxygen therapy in patients with acute hypoxemic respiratory failure in emergency department. A randomized controlled cross over superiority trial

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Abstract

The aim of our study was to determine whether high flow oxygen therapy reduced the rate of endotracheal intubation and improve pulmonary outcome score. A total of 300 consecutive patients were enrolled in the study. The etiologies of acute respiratory failure were classified into trauma, lung diseases, fluid overload states and undifferentiated. Patients were randomized by block randomization method into two groups. First group received HFNC while the second received conventional oxygen therapy. Patients in both the groups were escalated to either NIV or invasive

mechanical ventilator support if there were any signs of respiratory distress noted. Pulmonary outcome scoring done at 2 hours was designed to see if there was any improvement in patient's condition in both the groups. SPSS (version 21.0, Illinois, Chicago) was used for the statistical analysis. The partial pressures of oxygen improved significantly in the HFNC group as compared to the COT group irrespective of the etiology. The partial pressures of CO₂ on ABG were similar in both the groups until 12 hrs. However, pCO₂ was earlier reduced in the HFNC group as compared to the COT group. Steady decrease in serum lactate levels were observed in HFNC group. The base deficit was corrected between 6-12 hours in patients of HFNC group which could not be seen in patients of COT group. There was a statistically significant difference noted at 12 and 24 hours between the two groups. The mean length of stay in HFNC group was around 4 days which was less compared to the length of hospital stay in COT which was an average of 7 days. The mortality in HFNC group was 4% and in COT group was 7.33% in our study. The study demonstrated that the use of HFNC in ED patients presenting with AHRF was associated with a greater reduction in need for escalation of ventilation requirements and improves pulmonary outcomes compared with standard oxygen therapy.

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Introduction

Acute Hypoxemic Respiratory Failure (AHRF) is a common life-threatening medical emergency in patients admitted to hospitals.¹ The devices for oxygen therapy include unassisted oxygen delivery devices and assisted ventilation devices. Unassisted oxygen therapy, also called Conventional Oxygen Therapy (COT) is the main supportive treatment administered to patients with AHRF. It is usually delivered with nasal prongs or face masks. Assisted ventilation devices include Non-Invasive Ventilation (NIV) and invasive mechanical ventilation (IMV). NIV was increasingly used in the ED settings in the last decade. But the outcome of NIV is highly dependent on the patient's cooperation along with many other factors like interface and leaks.²

The high-flow nasal cannula (HFNC) is a recently developed oxygen therapy device that can deliver a humidified and heated mixture of air and oxygen at a high flow rate. It can provide a maximal flow rate of up to 60 L/min with a FiO₂ of 100%.³ The use of HFNC has been demonstrated to generate positive airway pressure at end expiration, ameliorate oxygenation and dyspnea,⁴ reduce the work of breathing and the respiratory rate,⁵ and be more comfortable for patients.⁶ These benefits are attributed to the mechanisms of HFNC, including their ability to more adequately meet the peak flow of inspiration,⁷ flush the anatomical dead space and deliver warm and humidified gas,⁸ thereby promoting muco-ciliary function.⁹

Materials and Methods

This prospective, randomized study was conducted in the emergency medicine department of a tertiary care teaching institute in India over a period of 15 months. The department has an annual intake of approximately 15,000 patients. Acute respiratory failure (ARF) is the third most common emergency presenting to our department. The sample size of our study was calculated based on the study published by Frat JP et al which compared the effect of HFNC to standard oxygen therapy.¹⁰⁻¹² 300 consecutive patients older than 18 years of age were enrolled if they met any of the five following criteria: i) A respiratory rate of more than 25 breaths per min; ii) Peripheral capillary oxygen saturation (SpO₂) < 92% on room air; iii) A ratio of the partial pressure of arterial oxygen (PaO₂) to the fraction of (FiO₂) less than or equal 200 mmHg on room air; iv) A partial pressure of arterial carbon dioxide (PaCO₂) not higher than 45 mmHg; v) An absence of clinical history of underlying chronic respiratory failure. Patients with acute exacerbations of asthma and chronic respiratory failure, reduced level of consciousness, urgent need for mechanical ventilation, do not intubate orders and lack of consent were excluded from the study.

The etiologies of acute respiratory failure in our study was classified into 5 categories including trauma, lung diseases – predominantly hypoxic, lung diseases – hypoxic with additional hypocapnia/ mild hypercapnia, fluid overload states and undifferentiated.

The selected patients were randomized by block randomization method into two groups with sealed envelope technique. Group 1 [HFNC]: Patients received oxygen at a flow rate of 50 L/min and FiO₂ of 0.6 at the start of therapy. The fraction of oxygen in the system was subsequently adjusted to maintain SpO₂ of ≥ 95% after two hours of therapy. High flow oxygen was applied for at least 20 hours in a day. Group 2 [COT]: Patients received oxygen by venturi-mask (green-coded) at a flow rate of 15 L/min. This was also equal to FiO₂ of 0.6 theoretically. After two hours of therapy, O₂ flows were titrated to maintain SpO₂ > 95%. The statistician was blinded to the nature of interventional group.

The arterial blood gas parameters, haemodynamics and signs of worsening respiratory function were studied at 0, 2, 6, 12 and 24 hrs. Later, intra and inter group comparisons were done and analyzed. Patients in both the groups were crossed over/escalated to either NIV or IMV if there were any signs of respiratory distress (increase in HR, increase in RR, thoraco-abdominal asynchrony, low/falling arterial oxygen saturation and decrease in sensorium with a GCS of <12). Pulmonary outcome scoring done at 2 hrs was designed to see if there was any improvement in patient's condition in both the groups. The parameters included >20% decrease in RR from baseline, no further worsening of acidosis pH <7.25 and improvement in SpO₂ >90%. For the ease of study, improvement in each parameter was compared individually between both the groups.

Patients in both the groups who have continued the same intervention till the end of 24 hrs were assessed for the comfort level of the therapy and adverse effects (dryness of mouth and increased thirst), if any. The length of hospital stay, history of repeated hospitalization and number of patients with all cause mortality at 90 days were compared between both the groups. The duration of study was 24 hours. Post study, patients were managed by the admitting unit till discharge from the hospital.

Categorical variables were described by frequency and percentage, while normally-distributed continuous variables were described by mean and standard deviation and statistically evaluated using the t-test. The Chi-square test was used for comparisons and defining association between categorical variables. Odds ratio and Relative risk were calculated for calculating the probabilities of disease progression. Similarly, means for continuous variables were tested using the T-test. A p value of less than and equal to 0.05 was considered as statistically significant. SPSS (version 21.0, Illinois, Chicago) was used for the statistical analysis.

Results

The patients enrolled in the study were coded as medical (M) or surgical (S) at the time of entry to the ED depending upon their presenting complaint. All trauma cases were considered under surgical code. 300 patients enrolled were equally divided into two arms - HFNC and COT arms. Among 150 cases in the HFNC arm, 30 were surgical (20%) and remaining 120 (80%) were medical cases. Similarly among 150 cases of COT arm, 27 (18%) were surgical and 123 (72%) were medical cases. The primary diagnosis causing respiratory failure was similar in both the groups. Based on the presentation of patients, both the intervention groups were analyzed among 5 subgroups (Table 1). A small number of cases were clubbed as undifferentiated since patients had multiple differential diagnoses and were under further evaluation for dyspnea till the end of 24 hrs (*i.e.*, the end point of study). Baseline characteristics of both the groups were compared in Table 2.

The improvement in PO₂ was significantly higher in the HFNC group (56.03±9.8 to 140±38.1 mmHg) than the COT group (50.06±10.4 to 91.83±25 mmHg, p0.001). Maximum increase in pO₂ in HFNC group was noted very early at 2 hours and was later maintained at the same level. In COT group, there was persistent improvement in PO₂ over a period of time. Overall, there was a statistically significant improvement in PO₂ in the HFNC group (Table 3).

The partial pressures of CO₂ on ABG were similar in both the groups until 12 hrs. However, PCO₂ was earlier reduced in the HFNC group, which shows that high flow therapy produces significant pressure gradient leading to CO₂ wash out. The patients in COT group slowly started building up the PCO₂ which was the major reason for intubation and invasive mechanical ventilation

Table 1. Etiology of acute respiratory failure in both groups.

Cause	HFNC n (%)	COT n (%)
Trauma	30 (20)	27 (18)
Lung disease – primarily hypoxemic	42 (28)	45 (30)
Lung diseases with additional hypocapnia or mild hypercapnia	21 (14)	24 (16)
Fluid overload states	48 (32)	39 (26)
Undifferentiated	9 (6)	15 (10)

(Table 4).

Serum lactates were higher at baseline in HFNC group than COT group. Two hours of HFNC therapy decreased the lactate levels below 2.0 mg/dL. Steady decrease in lactates were observed in HFNC group. However, in COT group, few patients had a high lactate level even beyond 12 hours (Figure 1). These patients also required escalation of respiratory support in terms of IMV.

Bicarbonate deficit is a relatively new concept in critically ill patients. It guides resuscitation protocols. In our study, the base deficit was corrected between 6-12 hours in majority of patients in HFNC group. As the deficit was not corrected in patients of COT group, there was a statistically significant difference noted at 12 and 24 hours between the two groups (Figure 2).

It was observed that in HFNC group, the heart rate settled earlier around 100 beats/min than in group where COT was used. Even at the end of 24 hours, statistically significant higher HR were observed in COT group. Patients with primarily hypoxemic respiratory failures had earlier response to HFNC in terms of decrease in HR towards normal baseline.

Tachypnea was observed in both groups at the start of study.

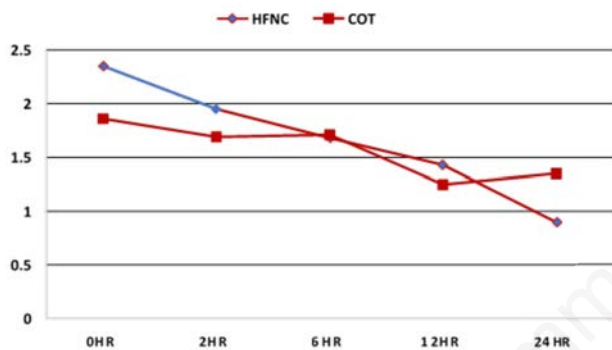


Figure 1. Line diagram delineating the trend of lactates in both groups.

Patients benefited with oxygen supplementation in both the groups. As time of therapeutic intervention passed by, the RR settled below the cut off value of 25 breaths per min. The inter-group comparisons were statistically significant and favored HFNC at 2, 6 and 12 hour time points. Clinical comparison from start to 24 hours of intervention in HFNC group showed a 35% improvement. The mean RR at the time of presentation was 26.3±6.43. 78 patients among 150 cases of HFNC showed decrease in RR, among whom 51 cases showed >20% decrease in RR within 2 hours of initiation of high flow therapy. Compared to COT where 88 patients showed decrease in RR and among them 33 cases showed >20% decrease in RR within 2 hours.

The mean SpO₂ at the time of presentation was 79.7±2.4. Among 150 cases of HFNC 126 cases achieved more than 95% SpO₂ at the end of 2 hours. The mean SpO₂ became 99.2% from 78.26% with mode of 100%. Among COT group 123 cases achieved more than 95% SpO₂ at the completion of 2hrs but the mean was 95.81% from 81.4% which is lesser compared to COT with mode of 98%.

The mean pH at start of the study was 7.37±0.05. The acidotic

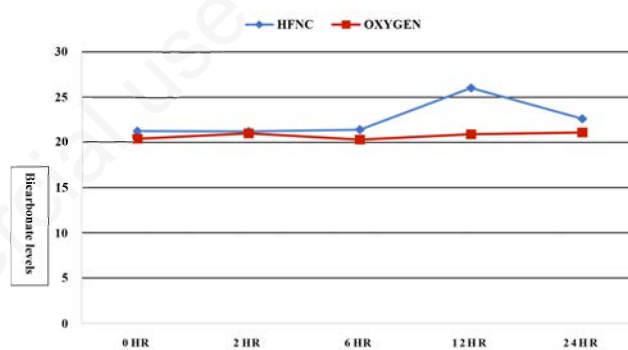


Figure 2. Line diagram showing trend of Bicarbonates at different intervals.

Table 2. Comparison of baseline characteristics in both groups.

Category	Variable	COT n=150	HFNC n=150
Demography	Age (mean, SD)		
	Male	44.8±15.8	46.1±16.8
	Female	52.76±12.98	54.2±14.48
	Gender		
	Male (%)	34	36
	Female (%)	16	14
	Medical (%)	72	80
	Surgical (%)	18	20
Respiratory	RR	27.65 ± 6.86	28.18± 7.74
	Oxygen saturation	80.14±9.32	78.26±11.0
Cardiovascular	HR	116.02 ± 11.81	117.22 ± 16.67
	Blood pressure:		
	SBP	115.8± 26.3	119.4± 23.4
	DBP	64.2±12.6	66.6± 13.9
Arterial blood gas	Pco2	34.5±5.44	34.46±5.80
	Po2	50.16±10.4	56.03±9.83
	Bicarbonate	20.45 ± 4.52	21.23 ± 5.34
	Lactates	1.86± 1.21	2.35± 1.69

pH at the start of study was noted in 9% of cases in HFNC and 6% of COT group. The further deterioration was seen in 6 patients in COT group. However, no patient had shown severe acidosis developing (pH<7.2) over 2 hours. At the end of 6 hours in HFNC, 10 patients still had pH below 7.25. A pH between 7.1-7.3 was highly significant for step up in respiratory support in both the groups. This observation was noticed from 6 hours onwards.

The blood pressures were monitored in both groups during the study. They were comparable at the onset of randomization, however there was statistically significant inter group difference in mean value of SBP and DBP at the end of 2 hours of intervention. Patients in HFNC intervention group had stable blood pressures

earlier and this is a major advantage of HFNC over COT.

Among the total 150 cases started on HFNC, 32 patients (21%) had to be switched over to mechanical ventilatory support either in the form of NIV (n=8) or endotracheal intubation (n=24). In COT group, 48 patients (32%) needed escalation of ventilatory support in the form of NIV (n=14) or intubation (n=34).

Compared to the surgical cases, more of the medical cases were intubated in both the groups. Among COT group, 12% cases were having diagnosis of pneumonia/sepsis, where as in HFNC group, 10% of cases were having diagnosis of acute lung injury/sepsis. Among surgical cases, chest trauma with bilateral lung contusion required mechanical ventilatory support in both the

Table 3. Inter group comparison of pO₂ at various intervals.

Intervention	pO ₂ (0hr) Mean± SD	pO ₂ (2hr)	pO ₂ (6hr) Mean± SD	pO ₂ (12hr) Mean± SD	pO ₂ (24hr) Mean± SD
HFNC	56.03±9.83	123.42±80.6	120.31±54.7	125.80±48.50	140±38.10
COT	50.16±10.4	62.19±15.59	74.41±21.90	90.25±26.20	91.83±25.00
P	0.88	0.0001	0.0001	0.0001	0.0001

Table 4. Inter group comparison of pCO₂ at various intervals.

Intervention	pCO ₂ (0hr) Mean± SD	pCO ₂ (2hr)	pCO ₂ (6hr) Mean± SD	pCO ₂ (12hr) Mean± SD	pCO ₂ (24hr) Mean± SD
HFNC	34.46±5.80	33.3±6.45	34±7.17	32.2±6.22	33.2±4.8
COT	34.5±5.44	33.29±5.43	33.9±6.22	34.8±5.74	34.9±5.62
P	0.95	0.98	0.89	0.0002	0.0052

Table 5. Study outcome in both groups.

Outcome	COT group n=150	HFNC group n=150	P-value
Primary outcome			
Escalation in therapy % (NIV,MV) (Respiratory distress index)	48(32%)	32(21%)	0.03
Pulmonary outcome score at 2hrs			
1.>20% decrease RR	33	51	
2.Delta change in SpO ₂	14.40	20.04	0.02
3.No further worsening of acidosis below pH <7.25	6 (4%)	None	
Changes in ABG parameters at 24hrs			
Po ₂	91.83±25.00	140±38.10	0.0001
pCO ₂ ,	34.9±5.62	33.2±4.8	0.0052
HCO ₃ ,	21.1 ± 3.70	22.6 ± 4.32	0.001
Lactates	1.35 ± 0.8	0.9 ± 0.43	0.0001
Secondary outcome			
Haemodynamics -changes at 24hrs			
HR	106.6 ± 12.94	90.4 ± 12.7	0.0001
SBP	113.4 ± 11.9	118.4 ± 12.7	0.0005
DBP	63.4 ± 5.34	67.6 ± 12.3	0.0002
Comfort score at the end of 24hrs (%)	16%	6%	0.01
Length of hospital stay (days)	7	4	
Repeated hospitalization	50 (33%)	30 (20%)	
Mortality	18 (7.33%)	6 (4%)	

groups. The use of accessory muscles, persistence of high RR and thoraco-abdominal asynchrony are indicative of an unsatisfactory response to HFNC. The outcome in terms of patients getting switched over to mechanical ventilatory support was found to be significantly lower in the HFNC group than the COT group with an odds ratio of 0.57 with 95% CI (0.54-0.67).

The adverse effects were subjectively assessed. Patients were assessed at the end of 24 hours with regards to tolerance of therapy and comfort levels with either of the intervention. Among total of 150 patients in HFNC arm, 6% had adverse effects in the form of dryness of mouth and increased thirst, whereas in COT arm 16% had mask discomfort ($P=0.01$).

The mean length of stay in HFNC group was around an average of 4 days which was less compared to the length of hospital stay in COT which was an average of 7 days. The mortality in HFNC group was 4% and in COT group was 7.33% in our study. This included death during primary hospitalization and up to 90 days of first day of arrival to our ED. 5 patients in COT group were discharged against medical advice. The study outcome in both the groups is summarized in Table 5.

Discussion

The patients we enrolled in our study had acute hypoxemic respiratory failure - AHRF (Type-I) without any history of chronic lung infection. The mean age of patients in our study was 45.93 ± 15.9 years. The age group between 40-60 years is second most vulnerable group after childhood for the incidence of pneumonias.¹⁰

A retrospective study on 558 COVID-19 patients reported a 48.2% success rate of HFNC in covid pneumonias.¹¹ Internationally, a multi-centric trial by Frat JP et al on efficacy of initiating HFNC therapy in AHRF included 310 patients with mean age group of 61 ± 16 years.¹²

It included adult patients with no prior history of lung disease who presented with a respiratory rate greater than 25 breaths per minute, a $\text{PaO}_2/\text{FiO}_2$ ratio less than 300 on 10 L/min or more of oxygen and a PaCO_2 below 45 mm of Hg. In our study, patients were less sick in comparison to the above study, as we had included patients with $\text{PaO}_2/\text{FiO}_2$ ratio less than or equal to 200 on room air.

Different studies have evaluated the role of HFNC in specific etiologies of AHRF like PTE¹³ and Covid 19 pneumonias.¹⁴ Similarly HFNC have proven to be extremely beneficial in infants and children.¹⁵ Our study is unique in experimenting HFNC therapy for treating AHRF associated with diverse etiologies like first episodes of acute decompensated heart failures, traumatic chest injuries and respiratory distress secondary to various fluid overload states. Post-hoc subgroup analysis has shown encouraging results in chest trauma patients. A particular observation in our study is clearing of infiltrates from chest radiograph after application of HFNC. This observation can be explained by the fact that HFNC therapy produced increase in end expiratory volumes which is a reflection of functional residual capacity. This leads to increased alveolar recruitment and thus more lung units are open and available to participate in gas exchange.¹⁶ Warm and humid gas reduces the work of breathing and improves muco-ciliary function, there by facilitating secretion clearance and decreasing the risk of atelectasis.¹⁷

HOT-ER study by Jones *et al.*¹⁸ included subjects with heart failure, COPD and mild asthma. HFNC was provided at a flow rate

of 40 L/min. A significance of $p=0.053$ was obtained favoring HFNC to lower the rates of intubation after 24 hours of therapy in their study. We have similarly initiated HFNC at 40-50 L/min with FiO_2 of 0.6 (titrated to $\text{SpO}_2 > 96\%$). Flows $< 40\text{L/min}$ do not show better pulmonary outcomes. In another study, Zhu *et al.*¹⁹ concluded that HFNC should be given for at least 24 hours as therapy to prevent bias in outcome. In our study, we provided HFNC for at least 24 hours. However, beyond this, the oxygen therapy was decided by the admitting unit.

Though majority of studies on HFNC have not commented directly on HR and SBP variability with application of HFNC but good over all outcomes with HFNC indirectly suggested stable haemodynamics. We have observed a statistically significant HR within 2 hours of application of HFNC therapy. Roca *et al.*²⁰ examined IVC collapse during inspiratory pause by echocardiography in subjects with NYHA class III heart failure. HFNC decreased the inspiratory collapse of IVC, and it suggested that HFNC was supportive for subjects with severe heart failure.

Our results in context of decrease in RR was similar to study by Nerida Bell *et al.*²¹ who randomised 100 patients presenting to ED with acute undifferentiated shortness of breath. They concluded that a reduction in respiratory rate $> 20\%$ from baseline was noticed in 66.7% patients in HFNC arm vs 38.5% patients in control group.

Similar results were obtained in 75 patients recruited by Zhang *et al.*²² who concluded that during the first 24 hours HFNC therapy improved a number of respiratory parameters including PaO_2 , SpO_2 , RR and HR. These observations collectively indicate that patients with AHRF can be safely managed with HFNC therapy during the initial stages of Type I respiratory failure.

In a study by Messika *et al.*²³ in 2017, a retrospective analysis on patients suffering from severe pulmonary thrombo-embolism managed with HFNC was conducted. Patients showed rapid improvement in oxygenation within 2 hours of high flow oxygen use, without any significant variation in hemodynamic parameters. SpO_2 increased from 93% (80-98) to 100% (99-100) with $p < 0.00001$.

ROX index was devised by Roca *et al.*²⁴ to predict outcomes of patients with hypoxemic respiratory failures resulting from pneumonia/ARDS treated with HFNC. The score is likely to be useful clinically because it requires few data points and is simple to calculate at the bedside. It has a positive predictive value for success of HFNC of $> 80\%$ between 12 to 20 hours post initiation, when most of intubations occur. The cut off values of 2.85 (2 hours), 3.47 (6 hours) and 3.85 (12 hours) has 98%-99% specificity. Subgroup analysis in our patients also revealed a ROX score between 3.9-4.4 for patients in whom the respiratory support had to be escalated.

The most important change in ABG seen with HFNC therapy is a significant increase in arterial PaO_2 levels explained by the positive pressure which distends the lungs, ensures lung recruitment and decreases the ventilation-perfusion mismatch in the lungs as explained by Papazian *et al.*²⁵

The initial fear with starting HFNC was the misconception of increasing arterial PaCO_2 levels due to decreased hypoxic drive. However, it is not so. It has been hypothesized that the continuous administration of a very high flow of gas flushes the CO_2 out of the upper respiratory airway, avoiding the re-inhalation of the previous exhaled gas.

In our study, among the total 150 patients in HFNC group, 6% ($n=9$) had adverse effects in the form of dryness of mouth and increased thirst. Among the total 150 patients in COT group 16% ($n=24$) had mask discomfort. These adverse effects were similar to

most of the other studies. 21% patients in HFNC arm and 32% in COT arm needed mechanical ventilatory support in our study. The relative risk was 0.66 (95% CI- 0.45 to 0.98) with a z statistic of 5.41 and p value < 0.035. This implies that there was a significant decrease in the intubation rate in HFNC group when treated with HFNC therapy for ≥ 24 h as compared with COT. There was a mortality of 4% in HFNC group and 12% in COT group. The relative risk was 0.33 (95% CI- 0.13 to 0.81) with a z statistic of 2.40 and p value = 0.016. This means that there is no decrease in mortality when HFNC therapy is used compared to COT.

The important causes of HFNC failure in our study include low P/F ratio at the time of initiation, refractory shock, bilateral pneumonia, sepsis and severe contusions in chest trauma. One of the limitations of our study was a wide variability in inclusion criteria which creates considerable heterogeneity in results. Though all patients had AHRF at the onset, however combining pulmonary with non pulmonary etiology could have introduced a statistical bias. The primary end points used in our study were improvements in physiological variables which do not always translate in to better clinical outcomes like reduced respiratory distress, lesser intubation rates or better survival.

Conclusions

The study demonstrated that the use of HFNC in ED patients presenting with AHRF was associated with a greater reduction in the need for escalation of ventilatory requirements and improves pulmonary outcomes compared with standard oxygen therapy. These results suggest that HFNC should be considered first line therapy for patients with moderate hypoxemia presenting to emergency department. However, a major limitation of our study was that the etiology of acute hypoxemic respiratory failure was very varied. As the study was carried out in a busy emergency department, patients could not be followed beyond 24 hours to ascertain the proper etiological diagnoses. Further studies with extended follow up in the intensive care units would be warranted for better understanding.

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