Original Article

Individualized ventilation in influenza A (H1N1) infection:

The experience of a single intensive care unit

Evangelia Akoumianaki,[1]
Nektaria Xirouraki,[2]
Georgios Prinianakis,[3]
Evmorfia Kondyli,[4]
Eleni Apostolaki,[5]
Dimitris Georgopoulos[6]

[1]Pneumonologist, Intensive Care Physician, Intensive Care Unit, Heraklion University General Hospital
[2]Pneumonologist, Intensive Care Physician, ICU Registrar A, ICU, Heraklion University General Hospital
[3]Pneumonologist, Intensive Care Physician, ICU Registrar A, ICU, Heraklion University General Hospital
[4]Pneumonologist, Intensive Care Physician, Assistant Professor of Intensive Care Medicine, ICU, Heraklion University General Hospital, Medical School, University of Crete, Heraklion
[5]Physician-Intensive Care Physician, ICU Registrar B, ICU, Heraklion University General Hospital
[6]ICU Director, Professor of Intensive Care Medicine, ICU, Heraklion University General Hospital, Medical School, University of Crete, Heraklion, Crete

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Correspondence to:
Dimitris Georgopoulos
ICU, University General Hospital of Heraklion, University of Crete
P.O. Box 1352, 71110 Heraklion Greece
Tel.: +302810392636
E-mail: georgop@med.uoc.gr

SUMMARY. INTRODUCTION: Severe influenza A infection (H1N1) is associated with acute respiratory failure the management of which challenges intensive care unit (ICU) physicians. The clinical features and outcome of all patients with laboratory-confirmed H1N1 admitted to the Heraklion University Hospital adult ICU during the last two years are reported. **METHODS:** A retrospective observational single centre study was conducted at a tertiary ICU. The medical records of all patients admitted to the ICU with H1N1 infection 10th July 2009 - 1st May 2011 were reviewed. The data collected included demographic characteristics of the patients, the clinical manifestations and illness severity assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II, and interventions and complications during the ICU stay. The duration of mechanical ventilation, the length of ICU stay and the 60 day mortality were used as outcome indices. **RESULTS:** During the study period 23 patients with H1N1 were admitted to the ICU. They were relatively young (median age 39 yrs) with a median APACHE II on admission of 12 (range 5-22). In 7 patients (30.4%) there were no comorbidities on admission. In all cases the reason for admission was acute respiratory failure, with a median PaO_2/FiO_2 128 mmHg (range 83-376). Acute lung injury/ acute respiratory distress syndrome (ALI/ARDS) was the cause of respiratory failure in 21 patients (91.3%), while 2 presented with acute exacerbation of chronic obstructive pulmonary disease (COPD). Twenty patients (87%) required mechanical ventilation; 10 invasive, 5 non invasive and 5 both. Non conventional ventilator management, including oesophageal balloon insertion, high frequency oscillatory ventilation (HFOV), extracorporeal CO_2 removal ($ECCO_2$-R) and prone positioning were applied in 8 patients (34.8%). The median duration of mechanical ventilation and median length of ICU stay were 11.6 and 18.6 days, respectively. One patient died (4.3 % mortality). **CONCLUSION:** The necessity for non conventional ventilator strategies and the prolonged need for life support characterize the severity of

ARDS associated with H1N1 infection. An individualized ventilator approach, based on the principles of lung protective ventilation may have a significant influence on the course of the disease. *Pneumon 2012, 25(2):229-236.*

INTRODUCTION

Since the first outbreak of influenza A (H1N1) in Mexico, in March 2009[1] intensive care units (ICUs) worldwide came up against a unique phenomenon: relatively young, often previously healthy individuals presented with severe pneumonia rapidly progressing to acute respiratory distress syndrome (ARDS) necessitating intubation and long term mechanical ventilation. It was the first pandemic with such a demand for critical care services.

ICU mortality rates varied significantly among countries, possibly reflecting the availability, alertness and experience of critical care services. In Greece, the first laboratory confirmed case was reported in May 2009, followed by the first death attributed to the virus 4 months later. As of May 2011, 328 deaths had been attributed to laboratory confirmed influenza A (H1N1), with an overall ICU mortality rate ranging from 44% to 39% during the first and second outbreaks, respectively[2].

In this report, the demographic characteristics, clinical features, clinical course, treatment and outcome are described for all patients with laboratory-confirmed influenza A (H1N1) virus admitted to the Heraklion University Hospital adult ICU in the last 2 year period 10th July 2009 - 1st May 2011. In this specific patient population in whom acute respiratory failure was the major concern, the single centre character of the study is of specific interest as it offers a unique opportunity to study whether the management strategies applied to these patients might have had any impact on the outcome.

MATERIALS AND METHODS

This retrospective single-centre study was conducted in the 12-bed medical-surgical closed ICU of Heraklion University Hospital, a tertiary-referral teaching hospital. All consecutive adult patients admitted to the ICU with confirmed influenza A (H1N1) infection from July 10th 2009 through May 1st 2011 were enrolled. A 'confirmed case' of novel influenza A (H1N1) virus infection was defined as an individual with influenza-like illness and H1N1 virus infection laboratory confirmed by means of real-time reverse transcriptase polymerase chain reaction (rRT-PCR) assay performed on respiratory specimens.

The standardized notification and follow-up forms completed by the treating physicians were used retrospectively for data collection. Interventions and complications during the ICU stay were also recorded. Severity of the illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II within 24 hours of ICU admission[3]. The duration of mechanical ventilation, length of ICU stay, and 60 day mortality were used as outcome indices.

ARDS, nosocomial infections, including ventilator-associated pneumonia (VAP), and acute kidney injury (AKI) were defined using criteria established by the American-European Consensus Conference, Centers for Disease Control (CDC) and Acute Kidney Injury Network, respectively[4-6]. Hepatic dysfunction was defined as transaminase elevation 3 times above normal values. Shock and hypotension were defined as recommended elsewhere[7]. Obesity was defined as body mass index (BMI) equal or greater than 30 kg/m^2.

Data were summarized as percentages for categorical variables and as medians with 25% to 75% interquartile ranges for continuous variables. The Fisher exact and Mann-Whitney U tests were used as appropriate, and two-tailed $P<0.05$ was considered statistically significant.

Due to the retrospective nature of the study, with no interventions deviating from standard clinical practice and without the possibility of identification of individual patients from the anonymized collected data, the Ethics Committee of the University Hospital of Heraklion gave ethical approval for the study and waived the need for informed consent of the patients.

RESULTS

During the study period, a total of 23 patients with confirmed H1N1 infection were admitted to the ICU. The characteristics and survival outcome of the patients are shown in Table 1. The median time from illness onset to ICU admission was 5 days (range 2-7 days). The majority of patients (80%) were admitted to the ICU within 24hrs of hospital admission.

At ICU admission 10 patients were already intubated, 9 (39%) had thrombocytopenia (platelets, PLT <150,000/mm^3), 17 (74%) exhibited anaemia (Hb <12 g/dl), 9 (39%) had less than 3,500 leukocytes/mm^3 and only 2 (9%) had

TABLE 1. The characteristics and outcome of patients admitted to the intensive care unit (ICU) with Influenza A (H1N1)

No	Sex	Age (yrs)	Comorbidities	APACHE II	Admission Diagnosis	MV (Type)	ICU stay (days)	Outcome
1	M	33	None	11	ARDS	BiLevel	16	S
2	M	41	None	11	ARDS	VAC	21	S
3	M	31	None	8	ARDS	VAC	4	S
4	F	16	ALL	20	ARDS	NIMV / VAC	49	S
5	F	33	Pregnancy	14	ARDS	VAC	3	S
6	M	42	None	5	ARDS	NIMV	5	S
7	M	56	AF, MVD	17	ARDS	NIMV / VAC	25	S
8	F	58	Obesity	11	ARDS	NIMV	5	S
9	M	39	Psychosis, HC	6	ARDS	NIMV	4	S
10	F	43	None	16	ARDS	NIMV	6	S
11	F	51	Psychosis	10	ARDS	VAC	8	S
12	F	39	Obesity	10	ARDS	VAC	93	S
13	M	79	Lymhoma, CAD	18	ARDS	NIMV	2	S
14	F	39	None	9	ALI*	No	2	S
15	F	30	Pregnancy	12	ARDS	VAC / HFOV	13	S
16	M	62	MM	16	ARDS	NIMV / VAC/ HFOV	7	D
17	F	27	None	12	ALI*	No	2	S
18	F	47	DM, Obesity	20	ARDS	VAC / HFOV / $ECCO_2$-R	60	S
19	F	36	Obesity	16	ARDS	VAC / HFOV	16	S
20	F	34	Pregnancy	15	ARDS	NIMV / VAC	9	S
21	F	29	Pregnancy	10	ALI*	No	2	S
22	M	82	COPD, Malignancy	22	AECOPD	VAC	5	S
23	M	64	COPD	12	AECOPD	NIMV / VAC	41	S

Definition of abbreviations: ALI: Acute Lung Injury, ARDS: Acute Respiratory Distress Syndrome, APACHE II: Acute Physiology and Chronic Health Evaluation, ALL: Acute Lymphocyte Leukaemia, AF: Atrial Fibrillation, HC: Hypertrophic Cardiomyopathy, CAD: Coronary Artery Disease, DM: Diabetes mellitus, MM:Multiple Myeloma, MVD: Mitral Valve Disease, AECOPD: Acute Exacerbation of COPD, S: survived, D: died

*Patients without ventilatory support.

more than 10,000 leukocytes/mm^3. In 2 patients, viral infection was complicated with rhabdomyolysis, with creatine phosphokinase (CPK) values above 1,500 U/L leading, in both cases, to acute renal failure and renal replacement therapy; 8 patients developed liver dysfunction (reversible in all). In one patient, with a known history of coronary artery disease, the ICU stay was complicated by acute non ST elevation myocardial infarction.

Noradrenaline was the only vasopressor used: 16 patients (70%) were supported with noradrenaline, most of them during sedation. In 5 patients high doses of noradrenaline were required for the first 48 hours for management of vasodilatory shock.

AKI was developed by 13 patients (57%) at some point of their ICU stay; 2 patients had AKI of stage 2, 3 of stage 1 and 8 required renal replacement therapy. Compared to those without AKI, patients with AKI had a higher incidence of intubation (of the intubated patients 11 had AKI versus 4 who did not have AKI, p=0.04), and remained longer in the ICU (16 vs. 4.5 days, p=0.004).

Oseltamivir (150mg or 75mg b.i.d) was prescribed to all patients based on clinical suspicion while waiting for the results of rRT-PCR. This medication had been given before ICU admission to 6 patients and was administered within 2 days of admission to the rest. All patients received empirical broad-spectrum antibiotics for possible severe community-acquired pneumonia (CAP) in accordance with the consensus guidelines[8]. In 5 patients the antibiotics were

discontinued on diagnosis of the disease and in 7 patients who developed VAP the antimicrobial treatment was modified according to guidelines (9). In the remaining patients the antibiotics were continued for 10 days, because of either clinical suspicion of bacterial co-infection or pre-existing immunosuppression (2 patients). Ten patients received low dose intravenous steroids at some point during the ICU stay, for either critical illness-related corticosteroid insufficiency or an acute exacerbation of chronic obstructive pulmonary disease (COPD). High doses of prednisolone, equivalent to 1 mg/kg per day, were administered to one female patient late in the course of the disease (day 10) for the management of unresolving ARDS, complicated by pulmonary fibrosis (10). This patient underwent full recovery in terms of respiratory function.

The ventilator management of the patients is presented in Figure 1: 20 patients (87%) required mechanical ventilator support. Non invasive mechanical ventilation (NIMV) was applied in 10 patients (43%), in 5 of whom it was successful (BiPAP Vision, Respironics Inc., Murrysville, Pa., USA). (BiPAP Vision, Respironics Inc., Murrysville, Pa., USA). The patients were ventilated with full face mask, in lung protective ventilator strategy (PSV) and for a time period varying from a few hours to 5 days. NIMV failure was characterized by refractory hypoxaemia and worsening respiratory distress in 4 patients with ARDS and severe respiratory acidosis in a patient with acute exacerbation of COPD.

Overall, 15 patients were intubated, 13 of whom had ARDS and 2 acute exacerbation of COPD (Table 1). Two types of mechanical ventilators were used: Puritan-Bennett 840 (Nellcor Puritan Bennett LLC, Covidien, Boulder, CO) and Servo-i (Servo-i, Maquet Critical Care, Solna, Sweden). All patients with ARDS were managed with lung PSV. As part of the routine practice, lung protective ventilator strategy static end-inspiratory plateau pressure (Pplat) of less than 28 cmH_2O was aimed at. The positive end expiratory pressure (PEEP) was initially adjusted to obtain arterial oxygen saturation (SaO_2) of 90 ± 2% with $FiO_2 \leq 60\%$. If FiO_2 remained higher than 60% with a PEEP of 12-14 cm H_2O, a recruitment maneouvre was performed. During decremental PEEP trial after the recruitment maneouvre, the previously assessed lower inflection point, best static compliance, pressure-time shape curve during constant flow inflation and arterial oxygenation were all assessed for selection of the the optimum PEEP value.

In 4 patients with ARDS an oesophageal balloon was placed in order to measure oesophageal pressure and calculate transpulmonary pressures at end-expiration (Plend) and end-inspiration (Plin), aiming for Plin <20 cmH_2O and positive Plend (Figure 2). The decision to measure oesophageal pressure was made by the attending physician. Generally, the use of an oesophageal catheter was considered in patients with high PEEP (≥15 cmH_2O, all patients) and/or potentially harmful plateau pressures (>26-27 cmH_2O, 3 patients) or whenever there was skepticism about the contribution of chest wall compliance to estimated Pplat (i.e. due to obesity, 2 patients).

In 4 patients with ARDS high frequency oscillation ventilation (HFOV) was used. The decision to use HFOV was made early (in 3 patients within hours of intubation

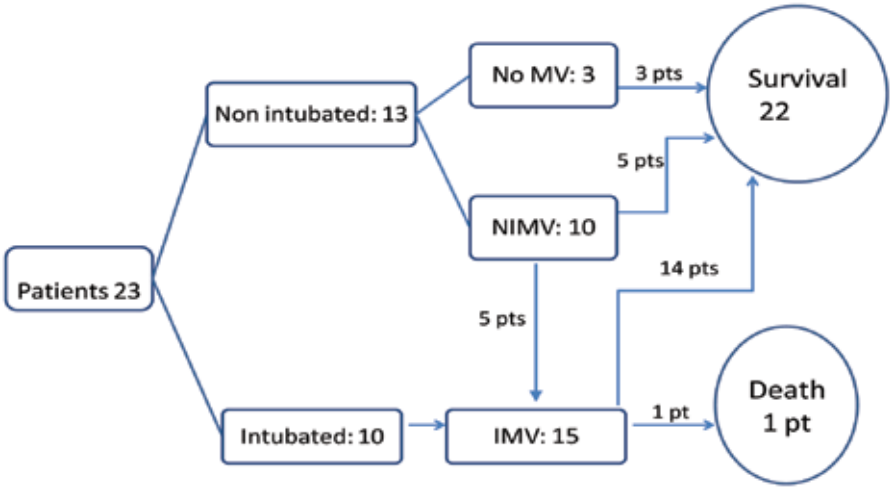

FIGURE 1. Flow chart of the ventilator management of 23 patients (pts) admitted to the intensive care unit with H1N1 infection. *Definition of abbreviations:* MV: Mechanical Ventilation, NIMV: Non Invasive Mechanical Ventilation, IMV: Invasive Mechanical Ventilation.

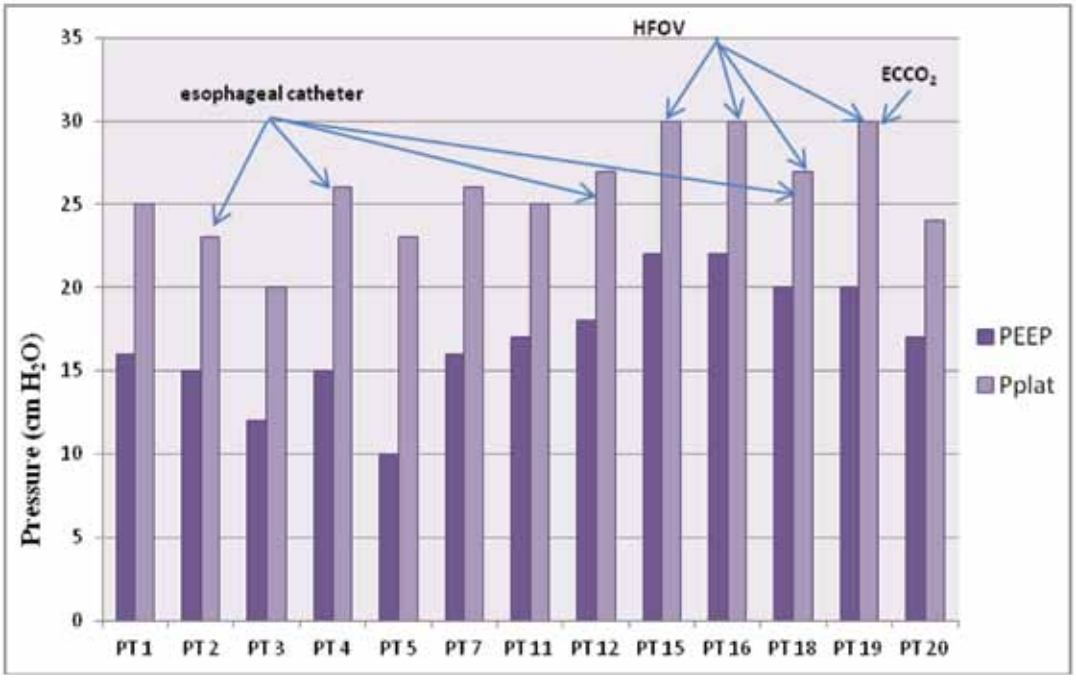

FIGURE 2. Maximum positive end expiratory pressure (PEEP) and static end-inspiratory plateau pressure (Pplat) during the 1st day of mechanical ventilation in 13 patients (PT) with H1N1 and acute respiratory distress. Arrows indicate patients (PT) in whom an oesophageal catheter was inserted and/or high frequency oscillation ventilation (HFOV) and extracorporeal CO2 removal (ECCO2-R) were applied at some point during the course of mechanical ventilation.

and in one on day 2), based on inability to follow a lung protective strategy without severe acidosis (pH < 7.20) and/or refractory hypoxaemia (PaO_2 < 60 mm Hg with FIO_2 >0.6 despite PEEP adjustment). One additional patient was placed prone, also early after intubation. During the second year of the study, extracorporeal CO_2 removal ($ECCO_2$-R) via a veno-venous haemofiltration system (Decap, Hemodec, Salerno, Italy) was available and it was used in one patient during HFOV for 12 hours. The HFOV settings over time are presented in Table 2. In one patient in whom $ECCO_2$-R was combined with HFOV, frequency in the latter was increased from 4 to 7 Hz within 4 hrs.

OUTCOMES

One patient died (4.3% mortality), a 62 year-old male with an underlying haematological malignancy. He presented with rapidly deteriorating ARDS, initially unresponsive to conventional mechanical ventilation despite recruitment manoeuvres and high levels of PEEP. The patient was placed on HFOV for 3 consecutive days, and subsequently on conventional mechanical ventilation, maintaining adequate gas exchange without injurious settings. The patient died unexpectedly on day 7 during a tracheostomy procedure, when the attempt to replace the endotracheal tube with the tracheostoma resulted in massive derecruitment, severe hypoxaemia, cardiac arrest (asystole) and death, despite prolonged resuscitation attempts.

The median duration of mechanical ventilation (invasive and non invasive) and median length of ICU stay were 12 days (range 1-41 days) and 19 days (range 2-93 days), respectively. The 3 patients who did not require mechanical ventilatory support improved rapidly and remained for only 2 days in the ICU.

DISCUSSION

Over a 2-year period, 23 patients were admitted to the single ICU with acute respiratory failure due to severe influenza A (H1N1) infection. The epidemiological characteristics of this population did not differ substantially from those described in previous reports[1,11-14]. Nearly two-thirds had at least one predisposing factor with malignancy, obesity, chronic respiratory disease and pregnancy being the most commonly encountered. Similarly to other documented studies, the patients presented with

TABLE 2. Settings of high frequency oscillation ventilation HFOV over time in 4 patients (Pt) with H1N1.

Pt. no	Settings	1 hr	3 hrs	6 hrs	12 hrs	24 hrs	36 hrs	48 hrs	60 hrs	Duration
16	mPaw	34	34	34	34	33	31	28	30	72 hrs
	ΔP	84	86	84	82	87	90	85	84	
	Fr	5	5	5	5	7	4	4	5	
	FiO2 (%)	70	65	60	60	80	65	55	65	
15	mPaw	34	34	34	33	34	30	26	-	48 hrs
	ΔP	88	86	86	84	76	86	86		
	Fr	6	7	8	9	11	11	10		
	FiO2 (%)	65	65	65	60	60	60	50		
18	mPaw	34	34	34	30	30	30	32	30	90 hrs
	ΔP	82	84	84	82	80	84	82	86	
	Fr	6	7	7	7	8	7	7	7	
	FiO2 (%)	70	70	65	65	65	65	65	60	
19	mPaw	33	34	34	35	30	24	-	-	40 hrs
	ΔP	90	90	90	92	92	70			
	Fr	7	8	8	8	8	9			
	FiO2 (%)	65	65	65	70	50	40			

Definition of abbreviations: mPaw: mean airway pressure (cm H_2O), ΔP: pressure amplitude (cm H_2O), Fr: oscillation frequency (Hz/min).

acute respiratory failure preceded by a short period of influenza-like illness[1,11-14]. Once the symptoms became severe enough to require hospitalization, the disease progressed rapidly, leading to ICU admission within 24 hours. This rapid evolution, probably a hallmark of disease severity, has been described repeatedly[15-17]. In this case series the bacterial infection rate at presentation was low (4%) compared to previous studies where the incidence of secondary super-infection ranged between 16-32%[9,17-20].

The 57% prevalence of AKI in this series of patients lies between the 51% and 67% reported by Nin *et al* and Sood *et al*, respectively[21-22]. Proposed explanations for the high incidence of AKI in patients with influenza A (H1N1) include glomerular deposition of immune complexes, virus-related rhabdomyolysis, hypoperfusion, sepsis-related multiple organ dysfunction and drug-related nephrotoxicity[19,21]. Renal replacement therapy (RRT) was necessary in 35% of these patients; the highest ever reported[12,15,19,21,22]. This may be explained, in part, by the earlier use of RRT in cases of renal acidosis in an effort to preserve low tidal volumes during mechanical ventilation.

In this case series the observed mortality of 4% is considered low with respect to the illness severity. In Greece, although official reports from each separate ICU are lacking, ICU mortality rates for influenza A (H1N1) infection were 44% and 39% respectively in the first and second years of the epidemic[2]. Mortality rates in studies published from other countries vary greatly from 77.7% to 14.3%[14,17,19,23-25]. It could be argued that a lower APACHE II score, compared to that documented in larger studies, indicates a less critically ill population[15-17,23]. The APACHE II score in the population under investigation, however, is similar to those reported by the SEMICYUC group in Spain[12,19]. The APACHE II may not accurately reflect the severity of ARDS but rather the young age of the study group, the presence of respiratory failure as single organ failure and the absence of chronic disabling diseases. On the other hand the PaO_2/FiO_2 ratio, the PEEP required and the end-inspiratory plateau pressure measured on the 1st day of intubation indicate that these patients suffered from severe hypoxaemic respiratory failure.

Since the ventilator management might have contributed, at least partly, to the observed low mortality, a more comprehensive description of the patients' ventilation is presented in the following paragraphs. Firstly, NIMV was considered as first line treatment in 43% of patients requiring mechanical ventilator support, and intubation was prevented in half of these. NIMV utilization has been also reported in other series, albeit with failure rates exceeding 70%[11-13,15-17,19]. The difference in success rate cannot be attributed to milder respiratory compromise, since in all patients severe derangement in gas exchange was observed, necessitating high PEEP. Specifically, a young female patient required PEEP as high as 15 cmH_2O and inspiratory assistance higher than 10 cmH_2O for 5 consecutive days. What might account for

the higher success rate observed in this case series is that patients were ventilated under the same principles that dictate invasive ventilation in ARDS: conservative use of pressure assist to keep the VT low, high PEEP, FiO_2 below 65% and minimal interruptions of NIMV to avoid de-recruitment. To date, bibliographic evidence for its usefulness in ARDS patients is considered vague[26,27], but Antonelli and co-workers showed that NIMV, when applied by experienced clinicians as a first-line intervention to treat early ARDS prevented intubation in 54% of cases and was associated with a lower incidence of septic complications and increased ICU survival[28].

Secondly, all intubated patients with ARDS were ventilated in the context of excessive stress and strain prevention, while in patients with acute exacerbation of COPD the reduction of dynamic hyperinflation was of paramount importance. Figure 2 shows a schematic description of the first day PEEP and Pplateau values and subsequent ventilator strategies in the 13 patients with ARDS. It is of interest that in patients with ARDS efforts were made to maintain Pplat at less than 27-28 cmH_2O using a VT as low as possible, whereas a high PEEP was implemented to minimize cyclic alveolar collapse. PEEP values in this patient population were significantly higher than those reported in most studies and in line with those used by Grasseli *et al*[15-18]. Even with high PEEP values, often exceeding 15 cmH_2O, Plat was not allowed to rise above 30 cm H_2O, as growing evidence indicates that there is no safe threshold for Pplat[29-31].

Whenever there was concern about the relationship between airway pressures and transpulmonary pressure (PL), oesophageal balloon catheters were inserted. Subsequently, airway-occlusion maneuovres were performed at end-inspiration and at end-expiration to obtain static measurements of PL and individualize ventilator settings. Ventilator settings were tailored according to PL estimation in 4 patients with severe ARDS, in all of whom PEEP was ≥15 cm H_2O, and 2 of whom were obese. The question to be answered was whether, based on PL, plateau pressures around 26 cm H_2O could be tolerated in the presence of obesity and if PEEP should be escalated or, conversely, decreased. A PEEP corresponding to an always positive end-expiratory PL was targeted, as proposed in the study of Talmor *et al*, to prevent alveolar collapse[32]. In that study, however, the upper threshold of 25 cm H_2O for end-inspiratory PL led to elevated plateau pressures in some cases of more than 30 cm H_2O. To avoid this, a lower target of 20 cm H_2O was adopted for the maximum value of end-inspiratory PL, in order for plateau pressures to be maintained within safer limits.

In cases where conventional ventilation was inadequate to maintain acceptable gas exchange without the risk of promoting lung injury, alternative strategies were applied. In 4 patients, in whom plateau pressures approached harmful limits, HFOV was implemented (Table 2). The triggering for changing conventional ventilation to HFOV was high airway pressures (PEEP ≥ 20 cm H_2O in all patients, plateau pressures of 30 cm H_2O in the first three and 27 cm H_2O in the fourth patient). HFOV was introduced early, within hours of intubation, eliminating the time wasted on injurious conventional ventilation. Initial settings and recruitment maneouvres were selected according to the protocol of Fessler *et al*[33], based on which an attempt was made to increase the frequency aiming at pH>7.25. This strategy avoids the delivery of VT that even with HFOV may be injurious. Indeed it has been demonstrated that VT delivered by HFOV at may be higher than previously thought and can approach values similar to those delivered by conventional ventilation, particularly when low frequency (<5 Hz) and high ΔP are set, both of which are commonly used in adult patients[34-36].

$ECCO_2$-R is continuously gaining acceptance for severe cases of ARDS. In a recent study of 22 patients with severe ARDS, $ECCO_2$-R combined with conventional invasive ventilation, produced a normal $PaCO_2$, despite significant reductions in tidal volume (from 6.3±0.2 to 4.2±0.2 ml/kg, predicted body weight), which resulted in a significant decrease in hyper-inflated, non-aerated or poorly aerated lung compartments on CT scan, and a decrease in the concentration of bronchoalveolar lavage (BAL) inflammatory cytokines[37]. In the present series, a young female patient, already on HFOV, received $ECCO_2$-Rremoval which, within hours after implementation allowed escalation of frequencies maximizing the lung protective properties of HFOV. Hence, the physiopathological framework beyond the use of $ECCO_2$-R during HFOV follows the same principles as during conventional ventilation: to provide the lung with maximum protection from ventilator induced lung injury (VILI). Further studies will confirm its possible role in this ventilation mode.

The main limitations of the study are its single centre character, which resulted in a small sample size, and its retrospective design, which was due to the fact that H1N1 infection was a disease with unpredictable incidence and clinical manifestations at the time of its first outbreak. On the other hand, single centre studies offer the opportunity to test the possible impact of relatively homogenously applied therapeutic strategies on the clinical course of

a specific disease. From this perspective, H1N1 infection is a representative example of a disease characterized mainly by the clinical manifestation of severe ALI/ARDS, the outcome of which is connected to the ventilator strategy followed.

CONCLUSIONS

Respiratory failure as a result of H1N1 infection is manifested as rapidly evolving ARDS, the treatment of which is similar to that of ARDS attributed to other causes. The adherence to the principles of lung protective ventilation, along with the appropriate general supportive management, might favourably influence the prognosis of severe ARDS due to H1N1 infection. To this direction, incorporation of the most recent knowledge regarding ALI/ARDS, supported in some patients by the application of non conventional ventilator techniques (such as oesophageal pressure measurements, HFOV and $ECCO_2$-R), is required to prevent the emergence of VILI and subsequent multiple organ dysfunction.

KEY MESSAGES

- Although ALI/ARDS associated with H1N1 infection usually affects young, previously healthy individuals, it is often severe leading to prolonged ICU stay
- Reported mortality rates in ICU patients differ substantially between centres
- Efforts to avoid the development of VILI appear to play an important role in the course of the disease
- Even in the most severe forms of ARDS, the application of non conventional strategies (oesophageal pressure measurement, HFOV, $ECCO_2$-R) to individualize treatment might lead to a favourable outcome

ABBREVIATIONS

APACHE, acute physiology and chronic health evaluation; **ALI,** acute lung injury; **ARDS,** acute respiratory distress syndrome; **COPD,** chronic obstructive pulmonary disease; **HFOV,** high frequency oscillatory ventilation; **$ECCO_2$-R,** extracorporeal CO_2 removal; **rRT-PCR,** real-time reverse transcriptase polymerase chain reaction; **AKI,** acute kidney injury; **CDC,** Centers for Disease Control and Prevention; **BMI,** body mass index; **NIMV,** non invasive mechanical ventilation; **Pplat,** static end-inspiratory plateau pressure; **PEEP,** positive end expiratory pressure; FiO_2, inspired fraction of oxygen; **Plend,** transpulmonary pressures at end-expiration; **Plins,** transpulmonary pressure at end-inspiration; **RRT,** renal replacement therapy; **PL,** transpulmonary pressure; **VT,** volume tidal; **ΔP,** delta pressure; **BAL,** bronchoalveolar lavage; **ALL,** acute lymphocyte leukemia; **AF,** atrial fibrillation; **HC,** hypertrophic cardiomyopathy; **CAD,** coronary artery disease; **MM,** multiple myeloma; **AECOPD,** acute exacerbation of chronic obstructive pulmonary disease; **VILI,** ventilator induced lung injury; **MV,** mechanical ventilation.

COMPETING INTEREST

The authors have no competing interest to disclose.

AUTHORS' CONTRIBUTIONS

EA developed the study design and carried out the data collection, data analysis, manuscript draft and revision. NX contributed with critical manuscript revisions. GP contributed with critical manuscript revisions. EK carried out data collection and manuscript revision. EA contributed with manuscript revision. DG brought up the study idea and carried out critical manuscript revision. All authors have read and approved the manuscript for publication.

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