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Systematic approach for severe respiratory failure due to novel A (H1N1) influenza

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ABSTRACT

Aim. In April 2009, a novel influenza A (H1N1) virus appeared in Mexico. It rapidly acquired the characteristics of a pandemic disease. Our objective is to present a case series of mechanically ventilated patients with severe influenza, treated with a systematic approach.

Methods. Prospective, observational, single-center study in a University Hospital. A (H1N1) virus was confirmed by rRT-PCR. In this report, we only considered patients that required mechanical ventilation (MV). All patients received antibiotics, steroids and oseltamivir from the time of admission. The main strategies incorporated in the systematic approach were a lung-protective strategy, PEEP adjusted for each patient, protocol-guided sedoanalgesia, restrictive fluid management, weaning protocol, and prolonged prone ventilation and extracorporeal membrane oxygenation (ECMO) as rescue therapies.

Results. We studied 19 patients: age 41±13 years old, APACHE II 16±7 and SOFA 8±4. All patients presented $PaO_2/FiO_2 \leq 200$ before connection to MV. Their worst values within the first 24 hours for oxygenation index, PaO_2/FiO_2, and $PaCO_2$ on MV were 21.8±13, 98±39, and 48±16 mmHg, respectively. Sixteen patients achieved ARDS; three exhibited acute lung injury criteria. Ten required a prone position, and two required ECMO (one patient required both therapies). Time on MV was 16±13 days. Length of stay in the ICU and in hospital was 18±12 and 28±17 days, respectively. Mortality was 21%.

Conclusion. Severe hypoxemia and a high rate of rescue therapies were observed among our patients. Nevertheless, mortality was lower than previously reported in comparable populations, which may be related to the management by a critical care team and the use of a systematic approach for ventilatory and non-ventilatory therapeutic strategies. *(Minerva Anestesiol 2011;77:510-21)*

Key words: Respiratory distress syndrome, adult - Respiration, artificial - Influenza, human.

In April 2009, a novel influenza A(H1N1) virus appeared in Mexico, causing an outbreak of respiratory disease.[1] It rapidly spread widely around the world, acquiring the characteristics of pandemic disease. During 2009, 12302 cases were confirmed in Chile. Nevertheless, 368129 patients met criteria of suspicious cases and 1622 developed severe illness, resulting in one of the highest rates of infection worldwide.[2]

Despite the low lethality among the global population, the high transmissibility of the virus caused serious difficulties in health care systems around the globe.[3] Among the critically ill influenza patients, a high incidence of severe hypoxemia, early development of multiple organ dysfunction syndrome (MODS), and frequent necessity of rescue therapies were observed from the beginning of the pandemic.[1, 4-11] The mortal-

ity rate in mechanically ventilated adult patients ranged from 20% to 46%.[1, 4-10] Most ICUs adopted a lung-protective strategy similar to that recommended for acute respiratory distress syndrome (ARDS) from other causes, maintaining low tidal volumes and plateau pressures <30-35 cmH_2O. Nevertheless, A(H1N1) can result in rapidly progressive respiratory failure refractory to conventional mechanical ventilation (MV). This forced intensivists to employ sophisticated MV support and different adjunct therapies, among them: airway pressure released ventilation (APRV), high frequency oscillatory ventilation (HFOV), prone position and extracorporeal membrane oxygenation (ECMO).[6-11] However, these therapies can potentially cause harm if not implemented in a coordinated manner by a critical care team with adequate expertise and institutional support to facilitate timely treatment.

Bundles applied to different areas of intensive care have demonstrated that systematic approaches can minimize bias and medical errors, and improve clinical outcomes.[11-16] This concept prompted our critical care team to assess a strict multifaceted management protocol, incorporating evidence-based strategies in the form of ventilatory and non-ventilatory strategies, to treat the most severely ill subset of patients with influenza A(H1N1) virus infection. In this manuscript, we report our experience.

Materials and methods

This observational study was conducted in our critical care service which includes 55 beds, 12 in ICU and 43 in intermediate care units. All influenza patients requiring MV were transferred to ICU for management and isolation. The study was approved by the institutional review board and surrogates signed their informed consent.

Patients

Patients were classified as suspicious cases according to the case definition adopted by the Ministry of Health of Chile,[2] as confirmed by testing respiratory specimens with real-time reverse transcription-polymerase chain reaction (rRT-PCR).[17] Between June 13 and August 27, 2009, 68 confirmed adult cases were admitted to our hospital, 36 of whom were sent to the critical care service. Among these 36 patients, 19 required MV (Figure 1**).** For the purpose of this report, we only considered those patients that required MV. Patients' medical records were collected for the analysis of demographics, clinical findings, and outcomes. Septic shock was defined according to the survival sepsis campaign definitions.[18] Acute Physiology and Chronic Health Evaluation II score (APACHE II) and Sequential Organ Failure Assessment score (SOFA) were calculated at ICU admission.[19, 20]

From the time of hospital admission, all patients received oseltamivir (75 mg BID for 7-10 days), ceftriaxone plus levofloxacin (as treatment for severe community-acquired pneumonia), and corticosteroids (hydrocortisone 300 mg per day, for 7-10 days).

Microbiologic studies

Nasopharyngeal-swab specimens were collected at hospital admission, and bronchial-aspirate samples were obtained after tracheal intubation once patients had entered the ICU. In addition to specific rRT-PCR testing for A(H1N1), respiratory specimens were tested with DFI (DNA fragmentation index) assay or viral panel. Blood and urinary cultures, as well as measurement of urinary antigens of Legionella pneumophila and Streptococcus pneumoniae were performed upon admission to the hospital.

Oxygen exchange, respiratory mechanics and mechanical ventilator settings

The partial pressure of oxygen in arterial blood/fraction of inspired oxygen ratio (PaO_2/FiO_2) was measured at the time of connection to MV (T0), which corresponds to the beginning of the systematic approach, and at 48 and 72 hours after (T48 and T72, respectively). In addition, the worst PaO_2:FiO_2 at 12 to 24 hours after initiating the systematic approach was included (T12-24). Tidal volume (TV), positive end-expiratory pressure (PEEP), plateau pressure, static compliance of the respiratory system (Crs), and

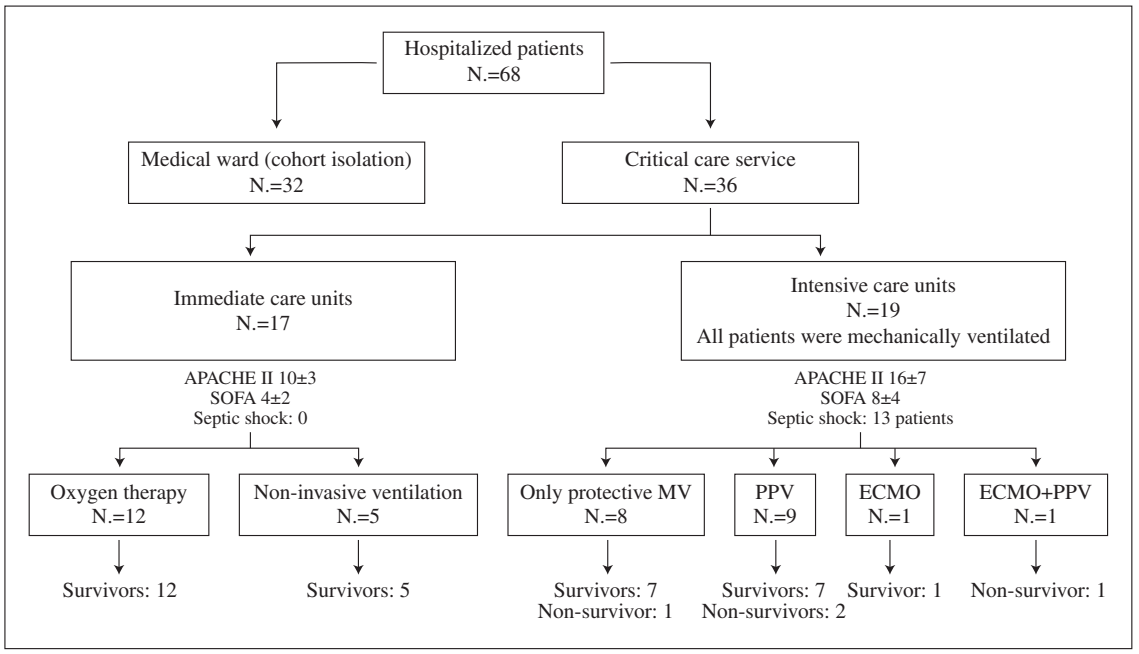

Figure 1.—Flow chart. APACHE II: Acute Physiology and Chronic Health Evaluation II score;[8] SOFA: Sequential Organ Failure Assessment score.[9] Septic shock was defined according to the Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock.[23] MV: mechanical ventilation; PPV: prolonged prone ventilation; ECMO: extracorporeal membrane oxygenation. Non-invasive ventilation was used in cases of chronic obstructive pulmonary disease exacerbation (2 patients), congestive heart failure (2 patients), and human immunodeficiency virus (HIV) in stage C3 (1 patient).

oxygenation index (OI) were registered periodically. OI was calculated as mean airway pressure (Paw)×FiO_2×100/PaO_2.

ARDS was defined according to the American-European Consensus Conference,[21] and Severe ARDS was defined as persistence of an OI≥15 and PaO_2/FiO_2≤100 mmHg, after recruitment maneuvers and PEEP adjustment.[22, 37, 38]

Ventilatory management

A lung-protective strategy including low tidal volume and low plateau pressures was applied, according to standard recommendations.[23] All patients were ventilated with a Puritan-Bennett 840 Ventilator System (Nellcor Puritan Bennett, CA). A closed tracheal suction system was used. FiO_2 and respiratory rate (RR) were adjusted to maintain oxygen saturation ≥90% and pH>7.2.

Recruitment maneuvers (RM) were performed before a decremental PEEP trial, using the pressure-controlled mode. For RM, we used 45 cmH_2O as total inspiratory pressure (PEEP 20 cmH_2O+delta-inspiratory pressure 25 cmH_2O), I:E ratio 1:1, RR 15 per minute, for 1 min. RM were applied predominantly within the first 48 hours of MV, after hemodynamic stabilization, before each PEEP change, after every disconnection from the ventilator, and after every postural change (supine – prone).

The PEEP trial was performed by setting PEEP according to a Hickling's modified strategy,[24] applying a constant TV and decreasing levels of PEEP. PEEP was reduced progressively from 20 cmH_2O, in steps of 2 cmH_2O. A 2 second-inspiratory pause was applied with each reduction of PEEP, and Crs was calculated. PEEP level was set (after a new RM) at 2 cmH_2O above the reduction in PEEP that generated a fall in Crs during the decremental PEEP trial.

Rescue therapies: prolonged prone ventilation and ECMO were used as rescue therapies, each applied following established criteria.[22, 25] Patients were maintained in the prone position for 48 hours or until they reached an OI≤10 on two consecutive measurements. A specific nurs-

ing care protocol was applied while patients were in the prone position.[22] ECMO was applied through a veno-venous system, and the CESAR guidelines for management and care of patients in ECMO were followed.[25]

Non-ventilatory management

Analgesia-based sedation was guided by protocol: this protocol is based on fentanyl and midazolam. Daily goals of sedation based were defined based on the sedation agitation scale (SAS),[26] and doses were adjusted accordingly. Neuromuscular blockage was used only for severe ARDS patients. A validated Spanish Confusion Assessment Method in the Intensive Care Unit (CAM-ICU) was applied for delirium diagnosis when patients achieved a SAS level 3.[27]

Restrictive fluid management: once hemodynamic stability was achieved and hypoperfusion was excluded, we used restrictive fluid management, similar to the ARDS-network strategy.[28] If furosemide was indicated, and plasma albumin was lower than 2.5 mg/dL, we added albumin (20 g QID).

A weaning protocol guided by respiratory therapists was systematically applied.[29] If the patient satisfied goals of oxygen exchange, respiratory rate, blood pressure, heart rate and consciousness, a spontaneous breathing trial was performed. If the trial was successful, the patient was extubated.

Early physical and occupational therapy in mechanically ventilated patients: once clinical stability was achieved, early exercise and mobilization were used in accordance with a recently published strategy.[30] Unresponsive patients underwent passive range of motion exercises for all limbs. For interactive patients, active assisted (with manual assistance) and active (independent) range of motion exercises were applied in the supine position. If these exercises were tolerated, treatment was advanced to bed mobility activities, including transfer to upright sitting. Critical illness neuromuscular abnormalities (CINMAs) were periodically evaluated.[31]

Early percutaneous tracheostomy using the fiberoptic bronchoscopy-assisted Ciaglia Blue Rhino technique (Cook Critical Care, Bloomington, IN) [32] was considered when the predicted time on MV was more than 7 days. This protocol also included the semirecumbent position, early enteral feeding, thrombosis prophylaxis, and ulcer prevention.

Although the assessment of potentially recruitable lung was not included as part of this protocol, four severe ARDS patients underwent whole-lung computed tomography (CT) during breath-holding sessions at consecutive airway pressures of 5 and 45 cmH_2O, as in the Gattinoni *et al.* trial.[33] Images were analyzed manually with Pulmo® software (Siemens). The percentage of potentially recruitable lung was defined as: (nonaerated tissue [NAT] at 5 - NAT at 45 cmH_2O)/total weight. In the same patients, we evaluated the effect of increasing PEEP from 5 to 15 cmH_2O, with and without interposed RM, while measuring arterial blood gases 20 minutes after increasing PEEP.

Follow-up and outcomes

Time on MV, infectious complications, incidence of delirium and CINMAs, use of tracheostomy and continuous renal replacement therapies (CRRT), length of stay at ICU and at hospital, mortality, and one-year follow-up, were recorded.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 software for Windows. The Kolmogorov-Smirnov test was used to test the normality of data distributions. Results are expressed as mean±SD, median (IQR), or percentage. Numerical variables were compared by Student's t-test or Mann-Whitney rank sum test, and categorical variables were compared by Fisher's exact test. A two-sided p value <0.05 was considered statistically significant.

Results

Characteristics of the 19 patients are shown in Table I. The mean age was 41±13 years old; 10 patients were female. Fifteen patients had preexisting medical conditions, and in four patients,

Table I.—*Individual characteristics of the 19 patients at ICU admission.*

Case (N.)	Age (years)	Gender M / F	Comorbidities Yes/No	Chest X-ray	APACHE II	SOFA	SS Yes/NO	ARDS/ ALI*
1	39	M	Yes [8]	Mixed	16	8	No	ARDS
2	35	F	No *	Mixed	24	8	Yes	ARDS
3	58	M	Yes [1, 3]	Mixed	19	10	Yes	ARDS
4	36	M	Yes [4]	Mixed	6	5	Yes	ARDS
5	18	F	Yes [2]	Mixed	26	15	Yes	ARDS
6	49	M	Yes [1]	Mixed	12	5	No	ARDS
7	24	F	Yes [5]	Interstitial	8	3	No	ARDS
8	36	F	No	Patchy	10	7	Yes	ARDS
9	51	M	No	Patchy	22	9	Yes	ARDS
10	26	M	Yes [8]	Mixed	8	4	No	ARDS
11	42	M	Yes [8]	Mixed	11	7	Yes	ARDS
12	54	M	Yes [1, 8]	Mixed	16	7	Yes	ARDS
13	52	F	Yes [1, 8]	Mixed	18	9	Yes	ARDS
14	63	F	Yes [1, 2, 4]	Interstitial	27	13	No	ALI
15	41	F	No	Patchy	12	7	Yes	ALI
16	53	M	Yes [1, 6, 7]	Patchy	11	11	Yes	ARDS
17	32	M	Yes [5]	Interstitial	11	5	No	ALI
18	23	F	Yes [2]	Interstitial	25	16	Yes	ARDS
19	45	F	Yes [8]	Interstitial	24	11	Yes	ARDS

Comorbidities:[1]hypertension, [2]chronic liver disease, [3]orthothopic liver transplant under immunosuppressive therapy, [4]diabetes mellitus, [5]asthma, [6]chronic renal failure, [7]connective tissue disease, [8]obesity.

Postpartum women. APACHE II: Acute Physiology and Chronic Health Evaluation II score;[8] SOFA: Sequential Organ Failure Assessment score.[9] SS: Septic shock. Septic shock was defined according to Surviving Sepsis Campaign:International guidelines for management of severe sepsis and septic shock.[23] ARDS: acute respiratory distress syndrome criteria, according to the American-European Consensus Conference,[10] were evaluated after connection to mechanical ventilation.

these were severe comorbidities. Six patients were obese. Three patients were transferred from other ICUs because of severe ARDS; one was a woman in her fourth postpartum day. At ICU admission, eighteen patients satisfied the case definition criteria,[2] and 16 fulfilled the criteria for ARDS.[21] The APACHE II score was 16±7; SOFA score was 8±4. Fifteen patients required vasopressor drugs (13 developed septic shock). Time from illness onset to initiation of antiviral treatment was 5.1±2.6 days.

Microbiologic studies

Six patients had evidence of influenza A infection, as determined either by viral panel or by immunofluorescence. Bacterial lung coinfection by *Streptococcus pneumoniae* was identified in three patients.

Chest X-ray and CT findings

All patients had abnormalities on their chest radiographs at admission (Table I). One patient who had asthma presented a spontaneous pneumomediastinum. High-resolution CT confirmed the findings revealed by chest X-ray and revealed scarring and fibrosis in 4 patients at later stages (Figure 2). Pulmonary embolism was identified in one patient 12 days after admission.

Oxygen exchange, respiratory mechanics and mechanical ventilation settings

Time between illness onset and connection to MV was 6.2±2.6 days. Individual values of PaO_2/FiO_2 for the 19 patients at T0, T12-24, T48 and T72, as well as other variables of oxygenation and respiratory mechanics are shown in Table II. The worst values for PaO_2/FiO_2, OI, and $PaCO_2$ within the first 12 to 24 hours after initiating the systematic approach were 98±39, 21.8±13, and 48±16 mmHg, respectively. The PaO_2/FiO_2 of patients who required and those who did not require rescue therapies was 93±28 and 122±33 mmHg, respectively, at T0 (P=0.079); 77±23 and 128±37 mmHg at T12-24 (P=0.002); 154±64 and 242±59 mmHg at

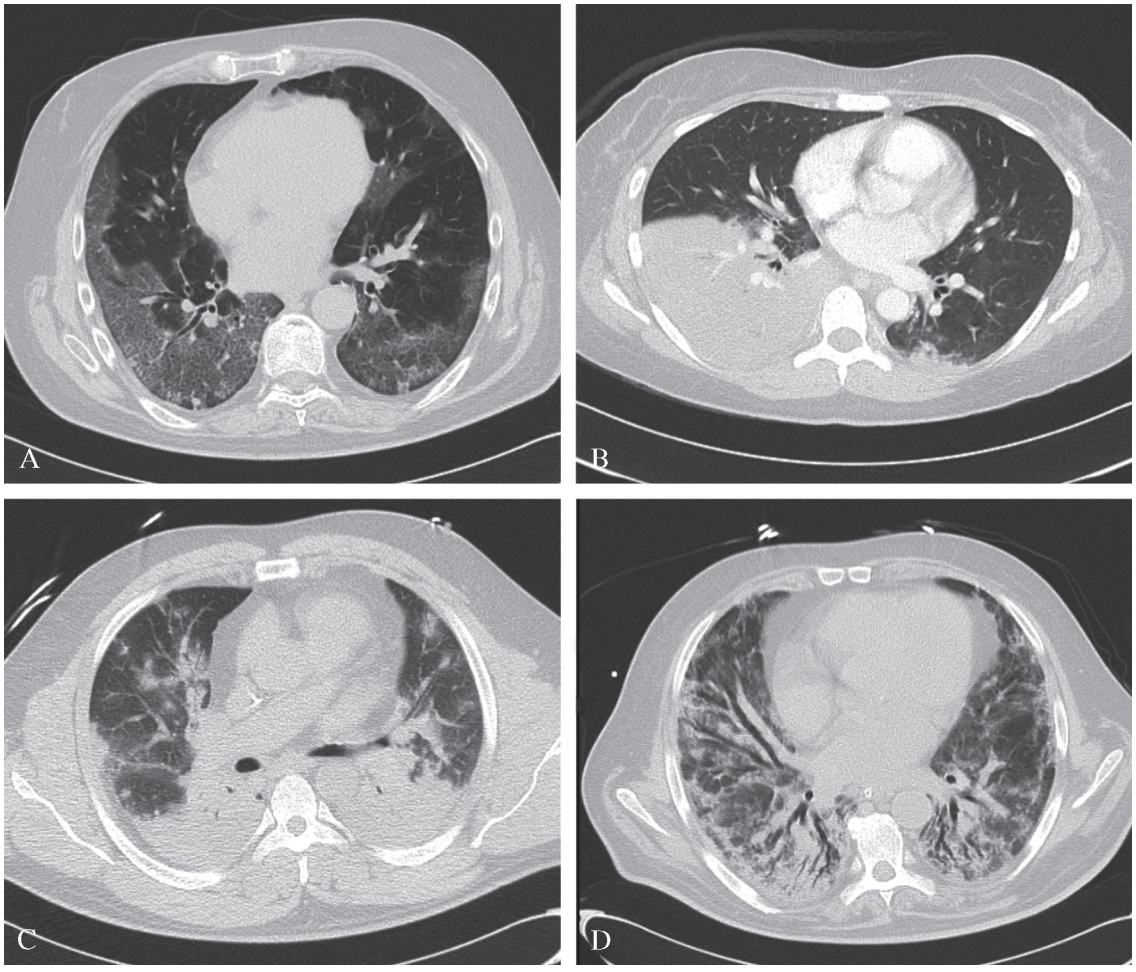

Figure 2.—Radiological patterns of patients with severe respiratory failure due to novel A (H1N1) virus infection. CT slices of the thorax obtained from 4 patients with severe respiratory failure exclusively due to the novel influenza, showing different radiological patterns: focal and scattered ground-glass (A, case 3), unilateral consolidation (B, case 8), bilateral patchy alveolar opacities plus areas with mixed interstitial-alveolar pattern consistent with ARDS (C, case 1), and interstitial thickening with pleural reaction and bronchial dilatation from a patient who evolved to fibrosis (D, case 12).

T48 (P=0.008); and 180±75 and 242±59 mmHg at T72 (P=0.011). In addition, patients treated with rescue therapies had higher PEEP (14±3 *vs.* 10±3 cmH_2O, P=0.042); higher plateau pressures (28±4 *vs.* 25±2 cmH_2O, P=0.035), and higher OI (32±12 *vs.* 13±7, P=0.001), compared to patients who did not require rescue therapies (Table II).

The percentage of potentially recruitable lung obtained from 4 patients was 30±7% (Figure 3). In these patients, performing an RM before increasing PEEP to 15 cmH_2O resulted in higher PaO_2 (168±4 *vs.* 109±7 mmHg, P=0.027), higher PaO_2:FiO_2 (159±3 *vs.* 104±2, P=0.015) and lower OI (12±3 *vs.* 18.5 P=0.006) than when the increase in PEEP was not preceded by an RM.

Rescue therapies

Eleven patients required rescue therapies: ten required prolonged prone position and two required ECMO, with one patient requiring both therapies. The time between onset of MV and pronation was 26±27 hours. Patients remained in the prone position for 82±49 straight hours. Three patients required a second period in the

Table II.—*Clinical variables before and after rescue therapies, and outcome of the 19 patients.*

Cases (N.)	PaO_2/FiO_2 (mmHg)				TV€ (ml/kg)	PEEP* (cmH_2O)	Plateau¶ (cmH_2O)	Crs# (ml/cm/ cmH_2O)	OI∞	NE dose& (µg/kg/ min)	RT (Yes/No)	VM (days)	UCI (days)	Outcome (S/NS)
	T 0	T 12-24	T 48	T 72										
1	116	60	274	327	6.5	17	29	46	36	-	Yes (1)	25	27	S
2	NA	52	85	102	6.3	18	30	29	42	0.32	Yes (2)	21	21	S
3	60	83	116	176	6.4	10	20	45	18	0.1	Yes (1)	15	15	NS
4	131	119	158	144	6.7	16	28	40	16.9	0.12	Yes (1)	31	33	S
5	101	49	64	86	5.1	14	31	15	51.4	0.35	Yes (1.2)	11	11	NS
6	70	101	124	145	6.2	11	29	30	18.8	-	Yes (1)	9	10	NS
7	120	90	161	134	6.7	8	26	20	8.9	-	No	7	6	S
8	110	129	341	330	7.2	12	28	28	11.6	0.08	No	7	12	S
9	148	98	217	266	6.7	10	22	41	12.2	0.28	No	14	14	S
10	93	81	173	218	6.9	10	21	54	18.7	-	Yes (1)	11	13	S
11	117	102	186	228	5.9	14	28	31	21	0.08	Yes (1)	9	12	S
12	NA	84	165	145	5.7	16	31	27	20.3	0.1	Yes (1)	50	51	S
13	48	65	105	132	6.5	18	30	32	35.5	0.1	Yes (1)	38	39	S
14	NA	200	254	380	7.1	13	28	28	7.5	0.05	No	8	9	S
15	148	159	215	340	6.6	11	25	37	8.1	0.1	No	3	8	S
16	68	99	215	222	6.3	14	26	40	18.1	0.12	No	3	12	S
17	165	138	315	348	7.1	6	22	33	8	0.05	No	4	5	S
18	99	115	221	258	6.3	13	26	24	18	0.1	No	8	8	NS
19	104	49	247	285	5.7	10	33	13	43	0.4	Yes (1)	24	28	S
Mean±SD	106±33	98±39	191±75	224±92	6.5±0,5	12.7±3	27±3	32±10	21.8±13	0.15±0.1		16±13	18±12	

PaO_2/FiO_2: partial pressure of oxygen in arterial blood/inspired oxygen fraction ratio was measured at the time of connection to mechanical ventilation and initiation the systematic approach (T 0) and at 48 and 72 hours after initiation of the systematic approach (T 48 and T 72. respectively). In addition: the worst PaO_2/FiO_2. between the first 12 to 24 hours after initiating the systematic approach was included (T 12-24). TV: mean tidal volume employed in the first 72 hours; PEEP: highest positive end-expiratory pressure; Plateau: highest plateau pressure; OI: highest oxygenation index; Crs: lowest compliance of the respiratory system; NE dose: highest norepinephrine dose; RT: rescue therapies, 1: prolonged prone ventilation, 2:extracorporeal membrane oxygenation; MV: time on mechanical ventilation; ICU: length at intensive care unit; S: survivors. NS: non-survivors. NA: Data from three patients were not available: two of them were transferred from others centers.

prone position. Only minor complications were observed during prone positioning: four patients developed grade II pressure ulcers, and one patient developed a grade III pressure ulcer. ECMO was started 6 hours after admission in one case, and on day 3 of MV in the other. These patients remained on ECMO for 10 and 9 days, respectively. Only the second patient died due to multiple organ failure.

Follow-up and outcomes

Five patients acquired respiratory infections during the hospital stay. One patient developed candidemia. Two patients developed organizing pneumonia, confirmed by lung biopsy, and were successfully treated with high-dose corticosteroids.[34] Eleven patients presented delirium, seven developed CINMAs, six were tracheostomized, and four patients required CRRT for acute renal failure.

The mean time on MV was 16±13 days. Length of stay at ICU and hospital was 18±12 and 28±17 days, respectively. Four patients died, and fifteen were discharged in good condition. On the follow-up at one year, one patient had committed suicide. The rest of the patients remained in good condition. Among all registered parameters, severe comorbidities and SOFA score at admission were the only factors associated with mortality (Table III).

Discussion

A high frequency of severe ARDS with novel influenza A(H1N1) virus infection was observed in this case series. More than half of mechanically ventilated patients required rescue therapies due

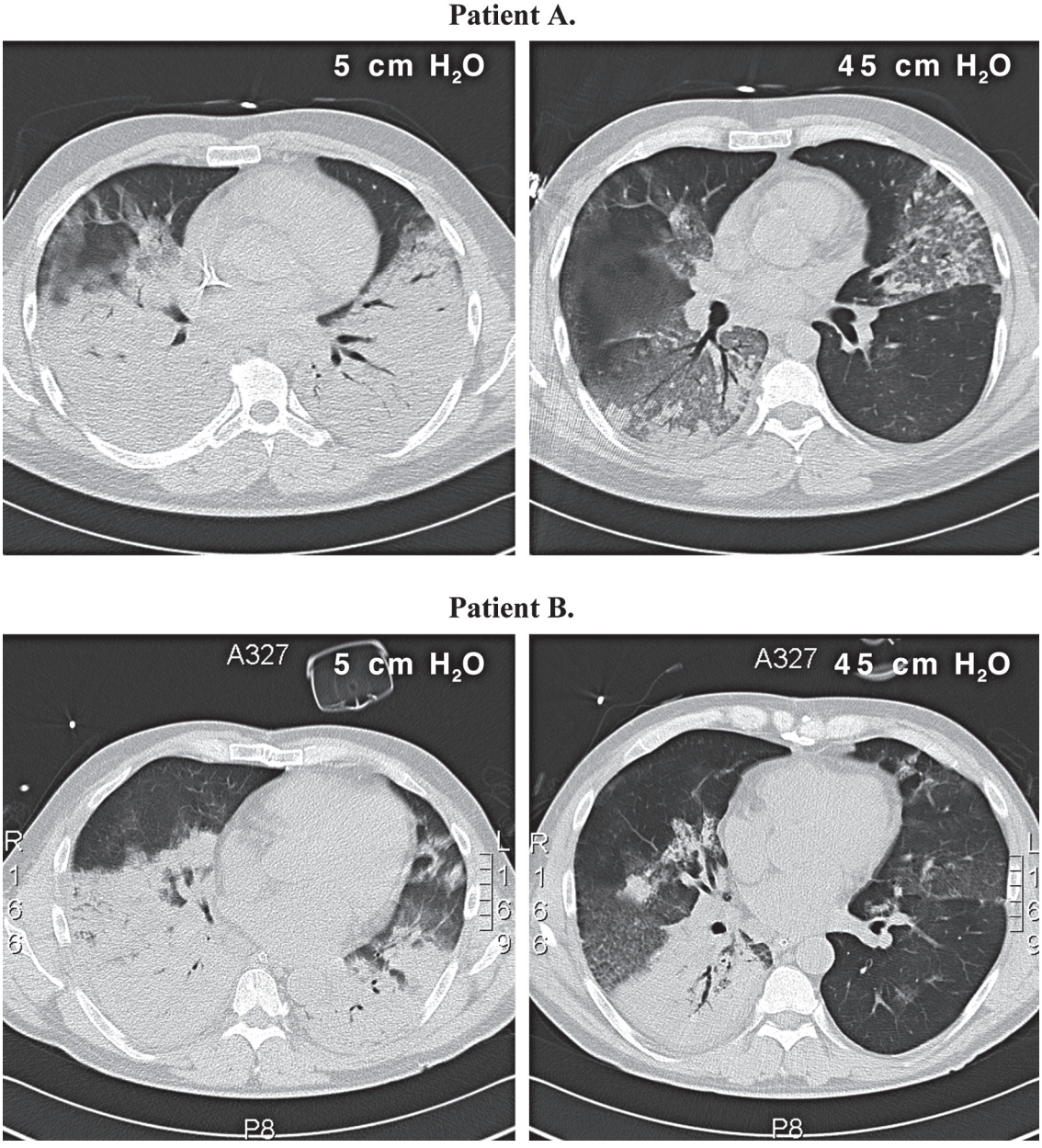

Figure 3.—Potentially recruitable lung: chest CT images obtained during breath-holding sessions at consecutive airway pressures of 5 and 45 cmH_2O, with the patient in the supine position. The percentage of potentially recruitable lung was defined as the proportion of lung tissue in which aeration is restored when increasing airway pressures from 5 to 45 cmH_20.[13] CT slices of the lung obtained 2 cm above the diaphragm dome at airway pressures of 5 cmH_20 (left) and 45 cmH_20 (right) from two patients with ARDS due to the novel influenza virus. The percentage of potentially recruitable lung was 35% in patient A (case 4), and 30% in patient B (case 16).

to refractory hypoxemia. Nevertheless, observed mortality was lower than predicted according to ARDS severity and comparable with the lowest mortality rates obtained in developed countries.[6-8] These results may be related to management by an intensive care team with experience in severe ARDS and systematic use of ventilatory and non-ventilatory strategies. Although the

Table III.—*Comparison of clinical variables between survivors and non-survivors.*

Variables	NS, n=4	S, n=15	p
Age (years)	37±20	42±11	0,480
Gender (Male: Female)	2:2	7:8	0,910
BMI (kg/m^2)	22.2±5.4	28.8 ± 6.4	0,076
Comorbidities	4/4	7/15	0,103
Severe comorbidities	3/4	1 /15	0,016
Time to treatment (days)	3±2	5.6±2	0,063
Time to MV (days)	4.3±1.5	6.7±2.7	0,104
APACHE II	21±6	15±7	0,155
SOFA	12±5	8±3	0,05
WBC x (10 x ^{3}/mm^3)	15±5	10.9±9	0,407
Platelets x (10 x ^{3}/mm^3)	170±96	188±147	0,821
LDH (U/l)	881±315	1218 ±596	0,297
CRP (mg/l)	85±31	211±149	0,115
$^1PaO_2/FiO_2$ (mmHg)	82±20	114±33	0,101
$^2PaO_2/FiO_2$ (mmHg)	87±29	101±42	0,527
OI	26.6±16.6	20.5±12.6	0,434
Rescue therapies	3/4	4/15	0,603

BMI: body mass index; Severe comorbidities were defined according Acute Physiology and Chronic Health Evaluation II score (APACHE II) criteria.[17] Time to treatment:Time between onset illness and Oseltamivir treatment; Time to MV: Time between onset illness and mechanical ventilation;SOFA:Sequential Organ Failure Assessment score.[9] WBC: white blood cells;LDH:lactate dehydrogenase; CRP:C-reactive protein; $^1PaO_2$:FiO_2 before connection to mechanical ventilation and initiation of of the systematic approach; $^2PaO_2/FiO_2$:partial pressure of oxygen in arterial blood/inspired oxygen fraction ratio worst values between the first 12 to 24 h after initiating the systematic approach. OI: oxygenation index measured at the same time than $^2PaO_2/FiO_2$

limited number of patients does not allow major conclusions to be drawn, we believe that a similar strategy could be used to treat severe cases of A(H1N1) influenza in other countries.

As in recent publications, patients were young adults and previously healthy or obese, without any risk factor for complications of seasonal influenza.[1, 3-11] Notably, all of our deceased patients had comorbidities. Most patients received vasopressor drugs, but only a minority required high-dose norepinephrine. Patients had prolonged ICU stay and time of MV, as well as a high rate of respiratory infections, delirium, and CINMAs. This was probably due to severe and prolonged respiratory failure.

We systematically applied a lung-protective strategy in an attempt to achieve 6 ml/kg of TV and plateau pressures ≤30 cmH_2O. However, in some patients, despite our best efforts, we were unable to maintain these parameters within the recommended limits[23] before the use of rescue therapies (Table II). RM was performed before setting PEEP to optimize oxygen exchange and as part of a physiologic approach to set PEEP. Although the use of higher PEEP levels in ARDS has been associated with lower incidence of refractory hypoxemia and less need of rescue therapies, it may be useless if not applied on an individual basis.[35] Apparently, higher PEEP levels should be reserved for ARDS patients with abundant pulmonary edema, collapse, and lung recruitability.[33, 36] Indeed, in this series, those patients with high potentially recruitable lung, as assessed by CT scan, required high levels of PEEP (14-18 cmH_2O).

Given that mortality risk of the most severe influenza patients seems to be higher when not treated with rescue therapies[1, 5, 10] and that different advanced therapies are difficult to compare in a pandemic context, the implementation of feasible, reproducible and safe strategies as determined by the local resources available is mandatory. A few years ago, we implemented an algorithm for the management of patients with severe ARDS, with prolonged prone ventilation as the cornerstone of treatment.[22] Prone ventilation is a feasible, relatively safe and inexpensive therapy, which results in better oxygenation,

more homogeneous distribution of aeration, and probably reduces lung stress and strain in early ARDS.[37, 38] Although the impact of prolonged prone ventilation on the most relevant clinical outcomes remains to be demonstrated, some meta-analyses suggest that only patients with severe ARDS,[39, 40] such as the patients that received prone ventilation in our series, could benefit from this therapy.

From the time of admission to the ICU, all patients received antiviral drugs, antibiotics and corticosteroids and were treated with several evidence-based strategies included in the non-ventilatory approach to patient management. The role of corticosteroids in this setting is unclear and controversial. Two patients who developed organizing pneumonia responded to high-dose corticosteroids.[34] In addition, all patients received hydrocortisone 300 mg/day from the time of admission. These doses do not seem to increase the risks and might be helpful in ALI/ARDS.[41] The real contribution of corticosteroids to the outcome of influenza patients should be further evaluated in a larger series.

The implementation of a protocol with ventilatory and non-ventilatory strategies was based on the observation that the most effective interventions in ICU seem to be multifaceted. There is evidence demonstrating the benefit of bundles in different contexts, such as ventilator-associated pneumonia,[12, 13] catheter-related bloodstream infections,[14] sedation, [15] and 6-hour and 24-hour sepsis care bundles.[16] However, bundles are not universally successful. Lack of resources, low compliance rate and low adherence are some of the reasons for this lack of success. Additionally, skeptics of what they call "protocol-based medicine" are concerned that these may supplant clinical judgment, creating complacency and making learning more difficult. However, far from impeding the development of clinical expertise, bundles are therapeutic tools to facilitate decision making using the best available evidence, allowing valuable time for assessing clinical details and reasoning on a case-by-case basis.

Our study has the limitations of a single-center case series focused only on the most severe subgroup of patients with influenza A(H1N1) requiring MV. However, the study has several strengths: application of a uniform and systematic approach to ventilatory and non-ventilatory therapies, avoidance of a delay in initiating potential life-saving maneuvers; prolonged prone position, an inexpensive and highly available therapy, as the cornerstone of advanced therapy; and one-year follow-up.

For a brief period of time, our 12 ICU beds harbored only severe influenza patients, with two of them in ECMO and six in the prone ventilation at the same time. It is difficult to infer benefits directly related to this systematic approach and even more difficult to compare our results with those obtained by other groups that used mainly ECMO as rescue therapy[6] due to baseline differences in usual care, the potential for selection bias and differences between groups. However, we believe that our strict multifaceted management protocol was safe, useful, and helpful in overcoming the difficulties inherent to the treatment of severely ill patients in the context of a pandemic.

Conclusions

Severe hypoxemia with a high requirement for rescue therapies was observed in our critically ill influenza patients. Nevertheless, mortality was lower than previously reported in comparable populations, which may be related to the management by a critical care team and systematic use of ventilatory and non-ventilatory strategies. These results should be viewed with caution due to the limited number of patients and lack of a control group.

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Conflicts of interest.—The authors declare that they have no competing interests.

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