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A surge of flu-associated adult respiratory distress syndrome in an Austrian tertiary care hospital during the 2009/2010 Influenza A H1N1v pandemic

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Schweres Influenza-assoziiertes Lungenversagen in einem österreichischen Tertiärkrankenhaus während der 2009/2010 Influenza A H1N1v Pandemie

Zusammenfassung. Wir berichten über 17 Patienten mit Influenza A H1N1v assoziiertem schweren Lungenversagen (ARDS), welche zwischen 11. Juni 2009 und 10. August 2010 an einer Intensivstation (ICU) aufgenommen wurden (w/m: 8/9; Alter: median 39 (IQR 29–54) Jahre; SAPS II: 35 (29–48)). Der Body Mass Index war 26 (24–35); 24 % waren übergewichtig und 29% fettleibig. Der Charlson Comorbidity Index war 1 (0–2) und nur ein Patient hatte keinerlei Vorerkrankungen. Die mediane Zeit zwischen Symptombeginn und ICU Aufnahme betrug 5 Tage (Range 0–14). Keiner der Patienten hatte eine H1N1v Vakzine erhalten. Neun Patienten erhielten Oseltamivir, jedoch lediglich zwei innerhalb der ersten 48 Stunden nach Symptombeginn. Alle Patienten entwickelten ein schweres ARDS (PaO_2/FiO_2-Ratio: 60 (55–92); lung injury score: 3.8 (3,3–4,0)), waren maschinell beatmet und benötigten Vasopressoren. Vierzehn Patienten erhielten Corticosteroide, 7 wurden hämofiltriert, und 10 Patienten benötigten extrakoporale Membranoxygenation (ECMO; 8 Patienten veno-venös, 2 Patienten veno-arteriell). Drei Patienten erhielten eine ILA (Intenventional Lung Assist), und 2 Patienten eine pumpengetriebene extrakorporale low-flow CO_2-Elimination.

Sieben von 17 Patienten (41 %) verstarben auf der Intensivstation (4 aufgrund von Blutungen, 3 aufgrund von Multiorganversagen), alle anderen überlebten das Krankenhaus (59 %). Die ECMO-Mortalität betrug 50 %. Die mediane ICU Liegedauer betrug 26 (19–44) *vs.* 21 (17–25) (Überlebende *vs.* Nichtüberlebende), die Beatmungsdauer 18 (14–35) *vs.* 20 (17–24), und die ECMO Dauer 10 (8–25) *vs.* 13 (11–16) Tage (p = n.s.).

Verglichen mit einer Kontrollgruppe von 241 erwachsenen ICU Patienten ohne H1N1v war die Liegedauer, Beatmungsrate, Beatmungsdauer, und der TISS 28 Score bei Patienten mit H1N1v signifikant höher. Die Kontrollgruppe bot ein tendeziell höheres ICU-Überleben (79 *vs.* 59 %; $p = 0{,}06$).

Patienten mit H1N1v an unseren ICUs waren jung, überproportional übergewichtig, und hatten fast alle Vorerkrankungen. Alle Patienten entwickelten ein schweres ARDS, welches unerwartet häufig mit extrakoroporalem Gasaustausch behandelt werden musste. Patienten mit H1N1v hatten kompliziertere Verläufe verglichen mit Kontrollpatienten.

Summary. We report on 17 patients with influenza A H1N1v-associated Adult Respiratory Distress Syndrome who were admitted to the intensive care unit (ICU) between June 11th 2009 and August 10th 2010 (f/m: 8/9; age: median 39 (IQR 29–54) years; SAPS II: 35 (29–48)). Body mass index was 26 (24–35), 24% were overweight and 29% obese. The Charlson Comorbidity Index was 1 (0–2) and all but one patient had comorbid conditions. The median time between onset of the first symptom and admission to the ICU was 5 days (range 0–14). None of the patients had received vaccination against H1N1v. Nine patients received oseltamivir, only two of them within 48 hours of symptom onset. All patients developed severe ARDS (PaO_2/FiO_2-Ratio 60 (55–92); lung injury score 3.8 (3.3–4.0)), were mechanically ventilated and on vasopressor support. Fourteen

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patients received corticosteroids, 7 patients underwent hemofiltration, and 10 patients needed extracorporeal membrane-oxygenation (ECMO; 8 patients veno-venous, 2 patients veno-arterial), three patients Interventional Lung Assist (ILA) and two patients pump driven extracorporeal low-flow CO_2-elimination ($ECCO_2$-R).

Seven of 17 patients (41%) died in the ICU (4 patients due to bleeding, 3 patients due to multi-organ failure), while all other patients survived the hospital (59%). ECMO mortality was 50%. The median ICU length-of-stay was 26 (19–44) *vs.* 21 (17–25) days (survivors *vs.* nonsurvivors), days on the ventilator were 18 (14–35) *vs.* 20 (17–24), and ECMO duration was 10 (8–25) *vs.* 13 (11–16) days, respectively (all p = n.s.).

Compared to a control group of 241 adult intensive care unit patients without H1N1v, length of stay in the ICU, rate of mechanical ventilation, days on the ventilator, and TISS 28 scores were significantly higher in patients with H1N1v. The ICU survival tended to be higher in control patients (79 *vs.* 59%; $p = 0.06$).

Patients with H1N1v admitted to either of our ICUs were young, overproportionally obese and almost all with existing comorbidities. All patients developed severe ARDS, which could only be treated with extracorporeal gas exchange in an unexpectedly high proportion. Patients with H1N1v had more complicated courses compared to control patients.

Key words: H1N1, respiratory failure, ARDS, ECMO, TISS 28, SAPS II.

Introduction

In November 2009 first reports on critically ill patients with influenza A, H1N1v, emerged from Australia and New Zealand [1], Mexico [2] and North America [3, 4]. Several authors reported on a high rate of acute respiratory distress syndrome (ARDS) [3–5]. While some centres did not have to use extracorporeal membrane oxygenation (ECMO) [2, 6], others employed ECMO in up to 34% of patients with ARDS [7, 8]. Young age and comorbidities, such as obesity, diabetes, chronic heart failure, pregnancy, as well as the late administration of oseltamivir (>48 h after onset of first flu symptoms) have been described to be associated with the risk of becoming critically ill [1–4]. Furthermore, virus-related factors, like the 222G/N polymorphism of haemagglutinin may contribute to complicated courses of the disease [9].

Based on these reports, intensive care services in Europe had to expect a surge of patients associated with the H1N1v pandemic to a certain extent. Herein, we report on a cohort of ICU patients with H1N1v-associated ARDS admitted to the General Hospital of Vienna, Austria.

Patients and methods

We retrospectively studied all patients with confirmed influenza A H1N1v admitted to any intensive care unit of the Medical University of Vienna, General Hospital during phase 6 of the influenza pandemic alert as declared by the World Health Organization (June 11th 2009 until August 10th 2010). The study protocol was approved by the local ethics committee. Written informed consent was waived. The investigation was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

The following parameters were recorded: Demographics, the presence of any co-existing condition, the Charlson Comorbidity Index [10], time from onset of flu-like symptoms to ICU admission, use, timing and duration of oseltamivir, SAPS II [11], and the use and duration of the following therapy modalities: Invasive mechanical ventilation, extracorporeal gas exchange, catecholamine support, and renal replacement therapy. Furthermore, the lowest PaO_2/FiO_2-ratio within the first 24 hours after intubation, or the last PaO_2/FiO_2-ratio prior to the start of extracorporeal gas exchange, if applicable, the highest lung injury score [12], ICU length of stay, as well as ICU- and hospital-mortality were recorded. These parameters were compared between survivors and non-survivors and between patients with and without extracorporeal membrane oxygenation (ECMO) therapy, respectively. Patients undergoing extracorporeal CO_2-removal (ILA, or $ECCO_2$-R) for supporting conventional mechanical ventilation were categorized as not undergoing ECMO.

In the second step, ICU length of stay, proportion of ventilated patients, total TISS 28 scores [13, 14], median daily TISS 28 scores, as well as survival were compared between patients with H1N1v and an unselected group of critically ill adult patients (i.e. at least 18 years of age) without H1N1v who were consecutively admitted to our ICUs between September 2009 and April 2010 (control patients).

Continuous data are presented as median and interquartile ranges (25–75%) unless otherwise indicated. Dichotomous data are presented as number and percentage. For univariate hypothesis testing we employed the Fisher's Exact test for dichotomous variables, and the Mann–Whitney *U*-Test for continuous variables. Differences were considered to be statistically significant when p was <0.05.

Results

Seventeen patients with H1N1v infection were admitted to our ICUs during the observation period (female/male: 8/9; age: 39 (29–54); SAPS II: 35 (29–48)). Body Mass Index (BMI) was 26 (24–35), 24% of patients were overweight (BMI: 25–29.9) and 29% were obese (BMI ≥ 30). Charlson comorbidity Index (CCI) was 1 (0–2), and only one patient had been without any co-existing condition so far (see Tables 1 and 2 for further details). Eleven patients (65%) were referred from ICUs from all over eastern Austria and Slovenia, respectively. The remaining six patients were primarily admitted to our hospital as were 24 adult patients treated as inpatients for influenza A H1N1v according to ICD-10 diagnoses coding not in need for intensive care. Patients were admitted between November 18th 2009 and January 18th 2010. Admissions cumulated within the last week of 2009 (see Fig. 1 for details). By that time two 8-bed ICUs of our facility were nearly exclusively devoted to the treatment of patients with H1N1v-associated ARDS.

Median time from onset of first flu symptoms to ICU admission was 5 days (range 0–14). Five patients were admitted to the ICU within 48 hours after onset of flu-like symptoms. None of the patients had received vaccination against H1N1v virus. Antigen-testing was performed in 10 patients and showed false-negative results in 3 patients.

Table 1. Patient characteristics and outcome parameters

	All patients	Survivors	Non-survivors	*p*-value	ECMO	No ECMO	*p*-value
Demographics							
Number of patients	17	10	7	n.s.	10	7	n.s.
Male/female	9/8	5/5	4/3	n.s.	4/6	5/2	n.s.
Age (years)	39 (29–54)	39 (31–50)	46 (28–57)	n.s.	45 (28–54)	38 (30–63)	n.s.
Body Mass Index	26 (24–35)	28 (24–35)	25 (24–38)	n.s.	26 (25–38)	26 (21–32)	n.s.
SAPS II (points)	35 (29–48)	41 (28–49)	33 (29–48)	n.s.	41 (30–49)	31 (29–42)	n.s.
CCI	1 (0–2)	1 (0–2)	1 (0–3)	n.s.	1 (0–3)	1 (0–2)	n.s.
Lung							
Lung Injury Score	3.8 (3.3–4.0)	3.7 (3.3–3.9)	4.0 (3.8–4.0)	< 0.05	4.0 (3.5–4.0)	3.5 (2.8–3.7)	<0.05
PaO_2/FiO_2	60 (55–92)	84 (57–134)	57 (48–71)	n.s.	56 (43–59)	86 (71–141)	<0.01
$PaCO_2$ (mmHg)	63 (51–68)	63 (53–68)	55 (50–88)	n.s.	65 (51–68)	62 (51–76)	n.s.
PEEP (cm H_20)	19 (16–20)	16 (14–20)	20 (16–20)	n.s.	20 (16–20)	16 (12–20)	n.s.
PIP (cm H_20)	32 (30–35)	30 (28–32)	35 (32–36)	< 0.01	32 (31–38)	31 (27–35)	n.s.
Therapy							
CVVH, *n* (%)	7 (41)	1 (10)	6 (86)	< 0.01	5 (50)	2 (29)	n.s.
Steroids, *n* (%)	14 (82)	8 (80)	6 (86)	n.s.	8 (80)	6 (86)	n.s.
Oseltamivir, *n* (%)	9 (53)	5 (50)	4 (57)	n.s.	7 (70)	2 (29)	n.s.
Outcome							
Ventilator days	19 (16–26)	18 (14–35)	20 (17–24)	n.s.	17 (16–24)	22 (12–59)	n.s.
ECMO days	9 (0–13)	10 (8–25)	13 (11–16)	n.s.	13 (8–25)	n.a.	n.s.
ICU days	23 (18–38)	26 (19–44)	21 (17–25)	n.s.	21 (17–30)	25 (20–44)	n.s.
ICU survival, *n* (%)	10 (59)	n.a.	n.a.	n.a.	5 (50)	5 (71)	n.s.

ECMO extracorporeal membrane oxygenation; *CCI* Charlson Comorbidity Index; *PEEP* positive end expiratory pressure; *PIP* peak inspiratory pressure; *CVVH* continuous veno-venous hemofiltration; *n.a.* not applicable; *n.s.* not significant.

Table 2. Comorbidities of intensive care unit patients with H1N1v

Comorbidity	Number of patients (%)
Obesity	5 (29)
Overweight	4 (24)
Chronic liver disease	3 (18)
Psychiatric disorders	3 (18)
Smoker	2 (12)
Substance abuse	2 (12)
Arterial hypertension	2 (12)
Chronic heart disease	2 (12)
Congenital pulmonary disease	2 (12)
Other*	10 (59)

*Diabetes type 1, multiple myeloma, hypothyreosis, sigma diverticulosis, history of pulmonary embolism, cerebellar atrophy, massive kyphoscoliosis, celiac disease, trisomy 21, gastric ulcer.

H1N1v-PCR was positive in respiratory secretions (mostly broncho-alveolar lavage) in all patients. Nine patients received oseltamivir, but only two of them within 48 hours of symptom onset. Eight patients received oseltamivir 150 mg per day and one patient received 150 mg from day one to three followed by 200 mg on day four and five. The duration of anti-viral therapy was 5 days (range 2–9), whereas only one patient received the therapy shorter then 5 days.

All patients presented with ARDS according to the consensus definition [5]. The lowest PaO_2/FiO_2-ratio as defined in the method section was 60 (55–92). All patients received mechanical ventilation and vasopressor therapy. Continuous veno-venous hemofiltration was performed in 7 (41%) patients for acute renal failure. Extracorporeal gas exchange was applied to 13 (77%) patients. Ten patients underwent ECMO (8 patients veno-venous, 2 patients veno-arterial), three patients Interventional Lung Assist (iLA®, Novalung, Germany), and two patients $ECCO_2$-R [15]. One patient was switched from ECMO to iLA and one patient from $ECCO_2$-R to ECMO. The median time from ICU admission to endotracheal intubation was 0 days (range 0–1) and 2 days (range 0–6) from ICU admission to start of extracorporeal gas exchange.

Steroids were administered to 14 (82%) patients. Thirteen patients received a bolus (100 or 200 mg) hydrocortisone i.v. followed by a continuous infusion of 200 mg hydrocortisone per day. The median time between the onset of ARDS and start of hydrocortisone was 1 day (range 0 – 6 days). Tapering started when ARDS was resolved and / or catecholamine therapy could be terminated and did not follow a specific protocol. One patient received prednisolone 40 mg bid starting on day 12 after the onset of ARDS and one patient who had been treated with hydrocortisone received dexamethasone later in the course due to cerebral oedema.

At ICU admission, only one patient showed signs of infection other than H1N1v (staphylococcus epidermidis-positive blood cultures), while three other patients developed secondary infections during their ICU stay: One patient with staphylococcus epidermidis-positive blood cultures on day 12 of the ICU stay, one patient with urinary tract infection caused by candida albicans on day 9, and one patient with serial growth of acinetobacter baumannii in blood cultures, bronchoalveolar lavage, and various smears, respectively.

Seven patients (41%) did not survive the ICU, four due to bleeding (cerebral twice, gastro-intestinal, and pulmo-

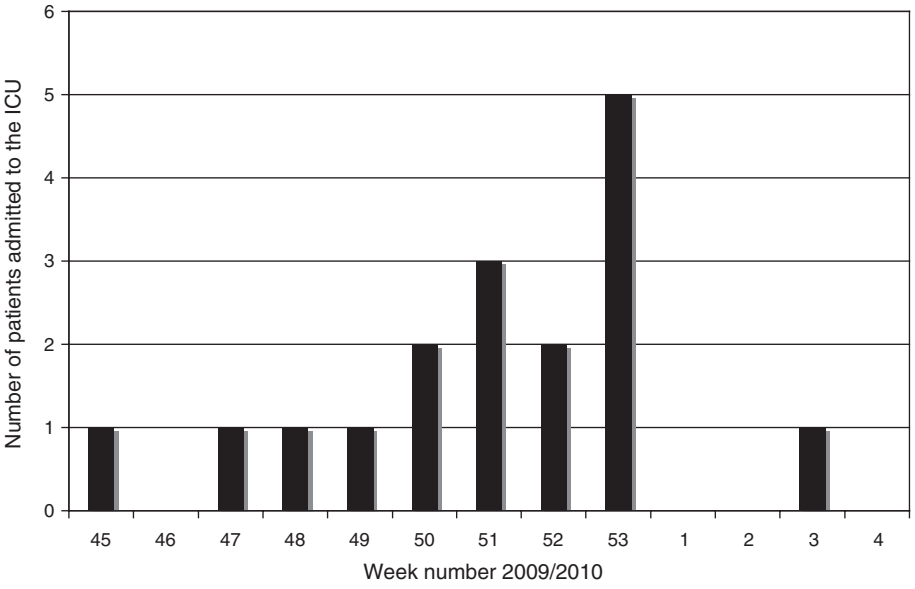

Fig. 1. Number of patients with H1N1v admitted to an intensive care unit per week

nary once), and three due to multi-organ failure. Three of the four cases with fatal bleeding occurred in patients receiving ECMO therapy. Mortality of patients undergoing ECMO was 50%. In survivors and non-survivors, respectively, ICU length-of-stay, days on ventilator and duration of ECMO therapy were not statistically different. Survivors presented with significantly lower lung injury scores, lower peak inspiratory pressures, and received hemofiltration in a much lower percentage. Patients receiving ECMO therapy had higher lung injury scores and lower PaO_2/FiO_2-ratios (see Table 1). All patients surviving the ICU were discharged from the hospital and were alive after a median follow-up of 122 days (range 91–165 days).

Laboratory parameters at ICU admission were not predictive with respect to survival: no statistically significant differences were found between ICU-survivors and ICU-non-survivors regarding red blood cell count, white blood cell count, haemoglobin, thrombocytes, lactate dehydrogenase, creatinine, creatine kinase, ASAT, ALAT, C-reactive protein, prothrombin time, and fibrinogen, respectively (see Table 4).

Table 3. Comparison between critically ill patients with and without H1N1v (controls)

	H1N1v patients ($n = 17$)	Controls ($n = 241$)	p-value
Male/female	9/8	129/112	n.s.
Age (years)	39 (29–54)	63 (51–73)	<0.0001
ICU length of stay (days)	21 (14–25)	4 (3–12)	<0.001
Ventilated (%)	100	69	<0.05
SAPS II (points)	35 (29–48)	41 (28–54)	n.s.
Cumulative TISS 28/ patient	909 (653–1172)	177 (90–432)	<0.0001
TISS 28/patient/day	47 (41–52)	38 (33–42)	<0.0001
ICU survival (%)	59	79	0.06

Table 4. Laboratory parameters of ICU-survivors and ICU-non-survivors at ICU admission

	ICU-survivors	ICU-non-survivors
Red blood cell count (T/l)	3.7 (3.3–4.1)	4.3 (3.7–5.0)
White blood cell count (G/l)	7.0 (4.3–9.8)	13.0 (10.0–14.0)
Haemoglobin (g/dl)	11.5 (9.0–12.0)	13.0 (10.0–14.0)
Platelets (G/l)	143 (68–192)	161 (106–246)
Lactate dehydrogenase (U/l)	651 (434–1513)	753 (296–876)
Creatinine (mg/dl)	1.15 (0.77–1.46)	1.22 (1.04–1.65)
Creatine kinase (U/l)	1059 (163–2667)	319 (221–418)
ASAT (U/l)	44 (22–55)	76 (30–103)
ALAT (U/l)	97 (62–162)	153 (90–262)
C-reactive protein (mg/dl)	20.0 (15.9–31.0)	15.0 (9.3–23.0)
Prothrombin time (seconds)	90 (83–99)	84 (65–106)
Fibrinogen (mg/dl)	479 (430–557)	481 (360–646)

ASAT alanine aspartate aminotransferase; *ALAT* alanine aspartate aminotransferase. There were no statistically significant differences in any laboratory parameter between ICU-survivors and ICU-nonsurvivors.

H1N1v patients vs. control patients

H1N1v patients were compared to 241 critically ill patients without H1N1v infection. SAPS II at ICU admission was not different between H1N1v patients and controls. H1N1v patients had longer ICU length of stay (21 (14–25) *vs.* 4 (3–12) days, $p < 0.001$) and were ventilated significantly more often (100% *vs.* 69%, $p < 0.05$). Cumulative TISS 28 scores per patient and TISS 28 per patient per day was significantly higher in H1N1v patients. ICU survival was higher in control patients (79 *vs.* 59%). However, this dif-

ference did not reach statistical significance ($p = 0.06$, see Table 3 for details).

Discussion

We report on a cohort of 17 critically ill patients with severe ARDS due to Influenza A H1N1v. All but one patient had at least one underlying disease and patients with overweight and obesity were overrepresented. All patients developed severe ARDS requiring endotracheal intubation. The proportion of multi-organ failure was high, and all patients were dependent on vasopressors. An unexpectedly high 77% of patients needed extracorporeal gas exchange. Mortality was 41% in all patients and 50% in patients who had received ECMO therapy.

We chose to not categorize extracorporeal CO_2-elimination (iLA, $ECCO_2$-R) as ECMO due to the following reasons: The goal of CO_2-elimination was to achieve conventional mechanical ventilation according to the guidelines for lung protective of the ARDS-Network [16]. By means of these extracorporeal procedures ventilation settings comparable to the patients without iLA or $ECCO_2$-R could be achieved. In contrast, patients undergoing ECMO suffered from severe hypoxemia despite maximally invasive mechanical ventilation and, thus, required total lung support.

Several outcome parameters are matching with reports of other authors. The mortality rate in our patients is comparable to a large cohort of mechanically ventilated patients with H1N1v [2]. Mortality in patients receiving ECMO therapy is in the same range as in a recently published series of patients [17], yet is somewhat higher than the one reported by the ANZ ECMO Influenza Investigators [8]. However, the observation period in this particular study was short and by the time of the report not all patients had been discharged from the ICU or the hospital. Thus, true hospital mortality remains unknown.

In our investigation, need for hemofiltration correlated with adverse outcome. The association between acute kidney injury, renal replacement therapy and excess mortality in critically ill patients with H1N1v has been described before [18, 19]. Furthermore, we observed higher peak inspiratory pressures and higher lung injury scores in patients who did not survive the ICU.

Some of our observations are unique. To our knowledge, the rate of applied extracorporeal gas exchange (77%) is the highest reported in any cohort of H1N1v patients with ARDS so far. The ANZ ECMO Influenza Investigators reported on the use of ECMO in 68 of 201 intubated patients with H1N1v, resembling a proportion of 34% [8]. In all other case series the need for ECMO was even lower [2, 6, 7]. The high rate of extracorporeal gas exchange in our patient cohort has to be attributed to the fact that most patients were referred from an ICU of another hospital to our tertiary care facility for possible ECMO therapy.

It has been reported that scoring systems like APACHE II [20] and SOFA [21] correlate with ICU survival in critically ill patients with H1N1v [2, 4]. Interestingly, we found that SAPS II was not helpful in discriminating survivors from non-survivors in the cohort of patients with H1N1v. This finding has to be interpreted with restraint due to the small number of patients reported. Furthermore, SAPS II was even somewhat higher in control group patients than in patients with H1N1v, while ICU courses of H1N1v patients were more severe in terms of duration of ICU stay, higher rate of mechanical ventilation, higher TISS 28 scores, and mortality, respectively.

We compared ICU-patients with H1N1v to a non-selected group of ICU-patients without H1N1v with special regard to the severity of illness, workload in terms of diagnostic and therapeutic measures, and outcome. A matching process was not performed as we aimed at comparing an average patient population representative for the respective intensive care units to the very particular cohort of patients with H1N1v. Thus, we chose all adult patients who were consecutively admitted to our ICUs within a period of 6 months around the peak of H1N1v-associated ICU admissions as control group. Cumulative TISS 28 scores, as well as median TISS 28 scores per patient per day were higher in patients with H1N1v compared to control group patients. This particular score can be used to objectify the amount of work load per patient in terms of diagnostic and therapeutic measures, and, furthermore, correlates with patient-specific costs [22]. One has to keep in mind that the TISS 28 score does not account for extracorporeal gas exchange therapies, so that effort and costs were, in fact, even underestimated in patients with H1N1v.

To estimate the burden on intensive care units, it would have been of major interest to know how many patients were admitted with proven or highly suspected influenza A H1N1v infection to our hospital during the observation period. However, only cases admitted to intensive care units were registered centrally in our hospital, whereas all other admitted cases were reported directly to the respective health authority. In Austria, 1569 patients with proven influenza A H1N1v infection were admitted to a hospital during phase 6 of pandemic. More than half of them were younger than 19 years [23]. Recording of outpatients was not required from November 2009 on. Unfortunately, it is not possible to extract data on specific hospitals from this registry. Since the majority of our patients (11 out of 17; 65%) were referred from other hospitals, the number of ICU patients does not reflect a proportion of patients with H1N1v treated in our hospital. However, the intent of this report was to study the clinical courses of critically ill patients with influenza A H1N1v and to describe the associated burden for the effected intensive care units as part of an ECMO referral center.

Conclusively, in our cohort of critically ill patients with H1N1v the rate of applied extracorporeal gas exchange was unexpectedly high. The example of our facility illustrates that flu pandemics may put tremendous pressure on supra-regional referral centres for extracorporeal therapy in terms of beds, medical equipment, personal resources, and costs, respectively. Our experience underlines the demand for institutional response plans and superordinate coordination of ICU capacities in case of disaster [24].

Conflict of interest
The authors declare that there is no conflict of interest.

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