Empirical systemic anticoagulation is associated with decreased venous thromboembolism in critically ill influenza A H1N1 acute respiratory distress syndrome patients

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ABSTRACT

Background: An association between increased venous thromboembolism (VTE) events and influenza A H1N1 (H1N1) was noted in the first 10 patients with severe acute respiratory distress syndrome (ARDS). An empirical systemic anticoagulation protocol (heparin intravenous infusion) was initiated when autopsy of patients with severe hypoxemia confirmed multiple primary pulmonary thrombi and emboli. The purpose of this study was to examine the relationship between H1N1 and VTE events and to assess the efficacy of empirical systemic heparin anticoagulation in preventing VTE and death in H1N1 severe ARDS patients.

Methods: An observational cohort study of critically ill severe ARDS patients with possible H1N1 viral pneumonia was performed in a surgical intensive care unit in a single 990-bed academic tertiary care center. Early empirical systemic heparin anticoagulation for all severe ARDS patients with possible H1N1 viral pneumonia was initiated as a VTE preventive strategy.

Results: Univariate comparisons and multivariate logistic regression were used to identify risk factors for VTE. Independent risk factors for VTE included H1N1, culture-positive bacterial pneumonia, and vasopressor requirement. Independent risk factors for pulmonary embolism included H1N1, culture-positive bacterial pneumonia, and male sex. H1N1 ARDS patients had 23.3-fold higher risk for pulmonary embolism and 17.9-fold increased risk for VTE. Kaplan-Meier analysis and log-rank test confirmed that empirical systemic heparin anticoagulation provided significant protection from thrombotic events in the H1N1-positive but not in the H1N1-negative critically ill ARDs patients. In multivariate analysis, adjusting for H1N1 status, patients without empirical systemic anticoagulation were 33 times more likely to have any VTE compared with those treated with empirical systemic heparin anticoagulation ($P = .01$).

Conclusions: Critically ill patients with H1N1 ARDS have increased risk of venous thrombotic complications, particularly pulmonary thromboembolism. Empirical systemic heparin anticoagulation in this cohort of patients significantly reduced VTE incidence without increased hemorrhagic complications. (J Vasc Surg: Venous and Lym Dis 2019;7:317-24.)

Keywords: H1N1; Influenza A; Venous thromboembolism; Deep venous thrombosis; Pulmonary embolism; Anticoagulants

The emergence of pandemic influenza A H1N1 virus (H1N1) led to a significant increase in morbidity, mortality, and health care costs. The 2009 influenza season was associated with four times the number of cases, a doubling of emergency department influenza cases, and a surge in inpatient admissions.[1,2] The severity of illness associated with H1N1 was manifested by an increased incidence of extrapulmonary complications and a disproportionate number of deaths suffered by affected adults, despite overall younger age.[3-6]

Extrapulmonary vascular complications in affected patients with H1N1 as manifested by disseminated intravascular coagulation or extensive thrombosis have been described, although the true incidence remains unknown.[7-9] The relationship between pneumonia and predisposition to venous thromboembolism (VTE) is well described, although the mechanism remains unclear.[10-12] Most likely, this phenomenon is the result of interactions between activated leukocytes and cellular adhesion molecules on the vein wall.[13-19]

In the first 10 patients transferred to the University of Michigan surgical intensive care unit (ICU) for consideration for extracorporeal membrane oxygenation (ECMO), we noted a striking relationship between H1N1, VTE, and death. A clinically overt hypercoagulable state was noted in 7 patients, and 5 of 10 had pulmonary

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embolism (PE; 50%), with 3 deaths attributed to pulmonary thrombi and PE confirmed on autopsy (Fig 1). With the report of our findings, the Centers for Disease Control and Prevention issued a warning to clinicians of the possibility of "development of a hypercoagulable state and fatal thromboembolic events" in these patients.[20] The observation of this aggressive prothrombotic and highly lethal phenotype associated with H1N1 acute respiratory distress syndrome (ARDS) prompted initiation of an empirical systemic anticoagulation protocol with continuous heparin infusion for suspected cases of H1N1 pneumonia and ARDS in the critically ill.

This study was therefore undertaken to examine the relationship between H1N1 and VTE events and to assess the efficacy of empirical systemic heparin anticoagulation in preventing VTE and death in H1N1 severe ARDS patients.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study
- **Key Findings:** Of 75 patients with severe adult respiratory distress syndrome (ARDS), 31 had H1N1 viral pneumonia; this group had a 23.3-fold higher risk for pulmonary embolism and a 17.9-fold increased risk for venous thromboembolism (VTE). H1N1 ARDS patients without empirical systemic anticoagulation were 33 times more likely to have a VTE event compared with those treated with systemic anticoagulation ($P = .01$).
- **Take Home Message:** H1N1 ARDS patients have increased risk of VTE events, and empirical anticoagulation significantly reduced VTE events without increasing bleeding complications.

METHODS

Study design. This was a single-institution observational study in an adult surgical ICU with Institutional Review Board approval. Informed consent was not required as all data were deidentified.

Inclusion and exclusion criteria. Patients admitted to the surgical ICU with a diagnosis of ARDS from February 1, 2009, to December 30, 2010, were included. Pediatric patients (<18 years of age) and patients undergoing a major operation within the preceding 30 days were excluded. Patients were classified into two groups: H1N1 positive and H1N1 negative.

Data collection. Baseline demographic information, length of stay, and severity of illness parameters on admission were collected, including the ratio of the partial pressure of oxygen in arterial blood to the fraction of inspired oxygen (Pa_{O_2}/F_{IO_2}) and the Acute Physiology and Chronic Health Evaluation (APACHE) III score. Patients were considered H1N1 positive if bronchoalveolar lavage (BAL) fluid or nasopharyngeal swabs were positive by polymerase chain reaction analysis or viral culture, consistent with the Centers for Disease Control and Prevention criteria (https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm). Data from duplex ultrasound, computed tomography, outside hospital records, and autopsy reports were collected to determine diagnosis of VTE, which was classified as deep venous thrombosis (DVT), PE, or both. Nursing flow sheets, medication administration records, and computer order entry system confirmed whether anticoagulation was started before or after diagnosis of VTE. The type of anticoagulation, such as unfractionated heparin (UFH), argatroban, or low-molecular-weight heparin (LMWH), was documented. Additional parameters of ventilator days, requirement for renal replacement therapy, vasopressor requirement, high-frequency ventilation, and ECMO were collected. Mortality was defined as all-cause hospital mortality.

Statistics. Normally distributed continuous variables were analyzed using unpaired *t*-test with Welch correction and reported as mean ± standard deviation. Non-normally distributed continuous variables were analyzed with Mann-Whitney *U* test and reported as median ± interquartile range. Categorical variables were compared using χ^2 test or Fisher exact test. Univariate analysis was performed to compare differences between VTE and non-VTE patients or PE and non-PE patients. Potential risk factors for thromboembolic events identified through the univariate analysis were then entered in a multivariate logistic regression model to identify significant risk factors for overall thrombotic events as well as for DVT and PE. Goodness of fit for the logistic regression models was confirmed using the Hosmer-Lemeshow test. Kaplan-Meier analysis and log-rank test were used to analyze survival data. Stata version 9 software (StataCorp LP, College Station, Tex) and GraphPad Prism version 5.01 for Windows (GraphPad Software Inc, San Diego, Calif) were used for all statistical analysis. Statistical significance was identified for P value ≤.05.

RESULTS

H1N1 infection was confirmed by BAL fluid or nasopharyngeal swab (polymerase chain reaction analysis or viral culture) in 36 (51%) of 71 patients with severe ARDS (Table I). Severity of illness was similar between the two groups, as measured by physiologic parameters, APACHE score, ICU length of stay, and mortality. There was significantly overall higher body mass index in the H1N1 positive cohort ($P = .02$), and although there were more men in the H1N1 cohort, this did not reach statistical significance ($P = .054$).

Pandemic influenza cases occurred in a bimodal distribution (Fig 2). Patients in the early cohort were treated with UFH or LMWH thromboprophylaxis as recommended by the current American College of Chest Physicians

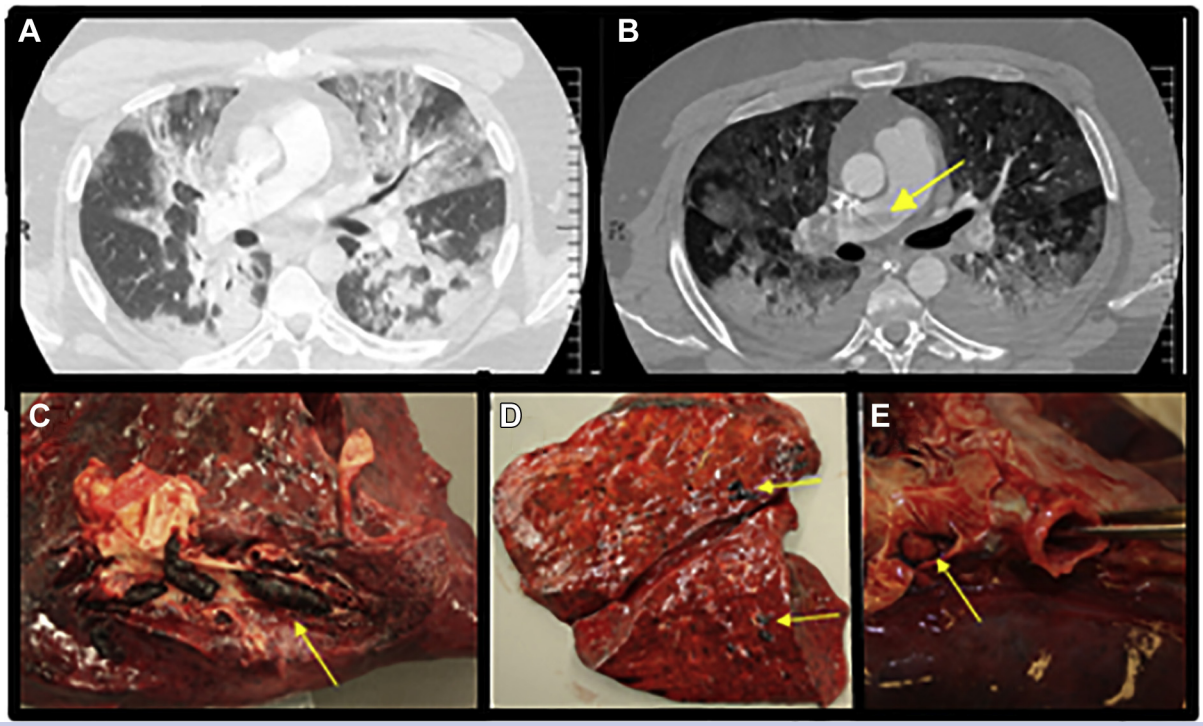

Fig 1. A and **B,** Serial computed tomography scan imaging of H1N1 bilateral viral pneumonitis and pulmonary emboli. **A,** Widespread bilateral, mainly peribronchial consolidation and scattered patchy ground-glass opacities are concerning for multifocal pneumonia and acute respiratory distress syndrome (ARDS) in a patient with influenza A H1N1 viral pneumonia. **B,** Five days later, there has been interval development of a saddle pulmonary embolus across the bifurcation of the pulmonary trunk. Additional thromboembolic material is noted within segmental and subsegmental pulmonary arteries. **C-E,** Autopsy photographs demonstrate multiple large, organized pulmonary thrombi distending the pulmonary artery **(C)** as well as fresh thrombi present in the main pulmonary artery **(E).** Multiple peripheral primary pulmonary thrombi are noted on the cut sections of the lung **(D).**

guidelines.[21] Patients admitted with ARDS and potential for H1N1 infection in the later cohort received empirical systemic heparin anticoagulation unless it was contraindicated. In addition, all patients undergoing ECMO were treated with full-dose anticoagulation regardless of H1N1 status. Importantly, baseline demographic characteristics (Table I) did not differ between patients included in the fall or spring cohort.

All ICU patients received either empirical systemic heparin anticoagulation or VTE pharmacologic thromboprophylaxis with low-dose UFH or LMWH (Fig 3). In total, 39 (55%) of the admitted patients received full-dose anticoagulation with heparin (n = 38) or argatroban (n = 1) within 24 hours of arrival. The standard protocol was to initiate heparin infusion with the goal of achieving a partial thromboplastin time of 50 to 70 seconds, which was lowered to 45 to 55 seconds if the patient was placed on ECMO. Monitoring goals were subject to change at the discretion of the intensivist because of thrombocytopenia and bleeding associated with ECMO. The remaining 45% of patients were prescribed VTE pharmacologic prophylaxis with low-dose UFH (dosing three times a day for 29 patients and twice a day for 1 patient) or LMWH (twice-daily dosing of enoxaparin for 2 patients) according to institutional VTE guidelines. Importantly, 99% of patients were prescribed either full-dose anticoagulant or thromboprophylaxis within 24 hours of admission. One patient experienced delay of 68 hours before receiving twice-daily low-dose UFH because of clinically significant hematuria and oropharyngeal bleeding.

The overall rate of thromboembolic events for all patients was 37%, much higher than 6.2% reported in our ICU with 4857 patient admissions during the last 5 years (L.M. Napolitano, unpublished data) and comparative international data from the multicenter Prophylaxis for Thromboembolism in Critical Care Randomized Trial (PROTECT; May 2006-June 2010) with lower extremity VTE rates of 5.1% (96/1873, dalteparin) to 5.8% (109/1873, UFH).[22] There was a nonsignificant increase in total VTE events, DVT, and combined DVT and PE in H1N1 patients compared with those without pandemic influenza (Fig 4). Overall VTE incidence (PE and DVT) was 44% in the H1N1 viral pneumonia ARDS cohort vs 29% in H1N1-negative ARDS patients. PE was identified in 29% of patients with H1N1 influenza compared with 8.5% of those without ($P = .06$). Whereas the rate of DVT did not differ significantly between those with (29%) and

Table I. Characteristics of patients admitted with acute respiratory distress syndrome (ARDS)

	Entire cohort	H1N1 negative	H1N1 positive	*P*
No.	71	35	36	
Age, years	40.5 (13.6)	41.5 (15.3)	39.5 (11.9)	.55
Male sex	61	49	72	.054
Body mass index, kg/m^2	34.7 (10.1)	31.8 (9.4)	37.4 (10.1)	.02[a]
APACHE III score	65.8 (19.9)	68.9 (20.0)	62.7 (19.3)	.19
Vasopressor requirement	80	80	81	1.00
Pao_2/Fio_2 ratio[b]	71 (62-109)	68 (62-109)	75 (63-110)	.63
Bacterial pneumonia	31	34	28	.61
Required ECMO	28	26	31	.79
Transfusion	59	54	64	.47
Renal replacement therapy	58	49	67	.15
ICU days	14 (9-25)	13 (6-24)	15 (10-25)	.19
Mortality	32	29	36	.61

APACHE, Acute Physiology and Chronic Health Evaluation; *ECMO,* extracorporeal membrane oxygenation; *Fio_2,* fraction of inspired oxygen; *ICU,* intensive care unit; *Pao_2,* partial pressure of oxygen, arterial.
Categorical variables are presented as number (%). Continuous variables are presented as mean (standard deviation) or median (interquartile range).
[a]Statistically significant ($P < .05$).
[b]Based on first arterial blood gas determination on admission to the ICU.

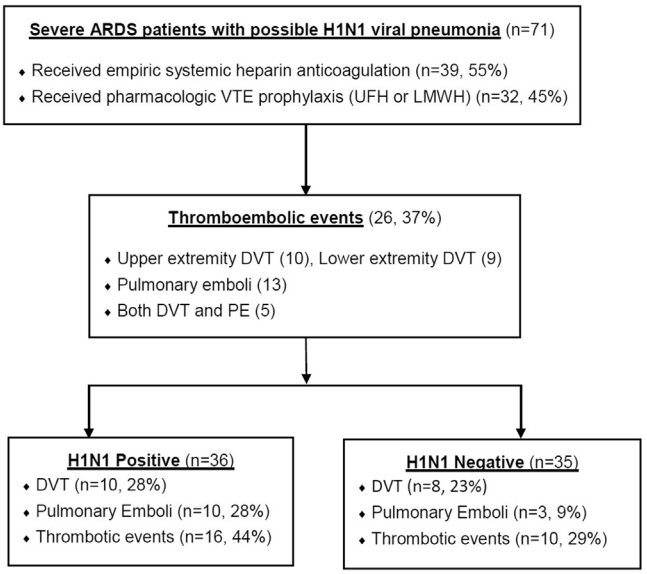

Fig 3. Consolidated Standards of Reporting Trials diagram. *ARDS,* Acute respiratory distress syndrome; *DVT,* deep venous thrombosis; *LMWH,* low-molecular-weight heparin; *PE,* pulmonary embolism; *UFH,* unfractionated heparin; *VTE,* venous thromboembolism.

those without (23%) the virus, the location of DVT was more commonly upper extremity DVT in the H1N1-negative patients (17% vs 11%).

On multivariate analysis, infection with H1N1 conferred the greatest risk for development of VTE or PE (Tables II and III; Hosmer-Lemeshow goodness of fit, 0.09). In addition, infection with bacterial pneumonia, defined as a positive quantitative respiratory culture from BAL fluid, also conferred increased thrombotic risk regardless of whether the infection occurred alone or in conjunction with H1N1. Bacterial pneumonia was confirmed in 23 of 71 patients (32.4%). Bacterial pneumonia was confirmed in 11 of 36 (30.6%) of the H1N1-positive patients and in 12 of 35 (34.3%) of the H1N1-negative patients.

In multivariate analysis, adjusting for H1N1 status, patients without empirical anticoagulation were 33 times more likely to have any VTE compared with those treated with empirical anticoagulation ($P = .01$). Importantly, there were no differences seen in bleeding complications (minor and major) between H1N1-positive and H1N1-negative patients (17% vs 20%; $P =$ NS) or patients empirically anticoagulated compared with those treated with standard subcutaneous UFH or LMWH thromboprophylaxis (18% vs 19%; $P =$ NS).

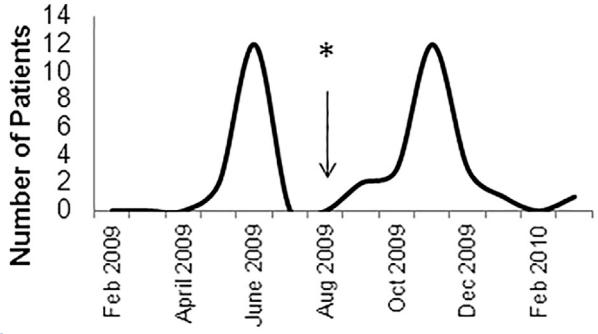

Fig 2. Bimodal distribution of H1N1-positive cases admitted to the surgical intensive care unit (ICU). The *arrow* marked with * denotes when the empirical systemic heparin anticoagulation protocol was initiated.

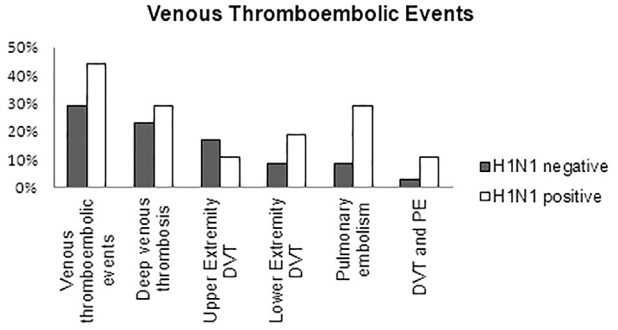

Fig 4. Distribution of venous thromboembolism (VTE) events between H1N1-negative and H1N1-positive patients. *DVT,* Deep venous thrombosis; *PE,* pulmonary embolism.

Table II. Predictors of venous thromboembolism (VTE): Multivariate logistic regression analysis

	Odds ratio	95% Confidence interval	*P*
H1N1 infection	17.9	2.4-130.6	.004
Bacterial pneumonia	6.0	1.6-22.9	.008
Vasopressor requirement	13.1	1.4-119.1	.022
Empirical anticoagulation	0.03	0.003-0.26	.001

Empirical anticoagulation in H1N1-infected patients conferred significant protection ($P < .0001$) from thrombotic events over time during the ICU stay (Fig 5). In patients with non-H1N1-associated ARDS or bacterial pneumonia, empirical anticoagulation was not associated with a significant decline in the rate of thrombotic events ($P =$ NS).

DISCUSSION

This study demonstrates a high incidence of VTE (44%) in severely ill adult patients (mean APACHE III score, 66) with ARDs due to infection with influenza A H1N1 viral pneumonia. Previous authors have documented a relationship between H1N1 and coagulopathy anecdotally[8,9,20] and in circumstances of staphylococcal coinfection.[7] To our knowledge, this is the first study to document VTE incidence in adult ICU patients with severe ARDS due to H1N1 viral pneumonia. Impressively, this high rate of VTE was encountered despite empirical anticoagulation in more than half of our cohort of patients and 99% compliance with American College of Chest Physicians guidelines for thromboprophylaxis as part of the Michigan Health and Hospital Association Keystone project.[22]

The type of VTE event was unequally distributed between the H1N1-positive and H1N1-negative cohorts. Whereas the rate of DVT was not different between the two groups, the incidence of PE was 3.4-fold greater in the H1N1-positive cohort (29% vs 8.5%; $P = .06$), and on multivariate analysis, infection with H1N1 conferred the greatest risk for development of PE. One possible explanation for these findings includes a higher (2.2-fold) preponderance of lower extremity DVTs in the H1N1 patients, which represents a higher risk for PE (15%-32%) compared with upper extremity DVTs (5%-10%).[23,24]

A second explanation could be that infection with this virus results in a local procoagulant environment and in situ thrombosis of larger pulmonary vessels. Pulmonary coagulopathy and microscopic fibrin deposits are a common pathologic feature of diffuse alveolar damage caused by seasonal influenza.[25] An autopsy series of eight H1N1 adult patients admitted to our ICU demonstrated a high rate of peripheral primary pulmonary thrombi, raising the possibility of de novo thrombosis rather than PE.[26]

In this study of critically ill patients infected with H1N1, we found that empirical systemic heparin anticoagulation using a specific treatment algorithm (Fig 6) was protective from all VTE and specifically PE compared with standard maximum VTE prophylaxis. Although there was no reduction in overall mortality with empirical systemic heparin anticoagulation, other benefits to VTE prevention exist, such as elimination of potential post-thrombotic syndrome and pulmonary hypertension.[27,28] The small sample size and otherwise nonstandardized management of the patients may have contributed to lack of mortality benefit.

Neither VTE nor mortality decreased in H1N1-negative patients, suggesting that standard prophylaxis per guidelines is effective in this group. A potential explanation for these findings was the strong relationship for VTE in H1N1-positive patients (odds ratio, 17.9; $P = .004$), who were thus more likely to benefit from anticoagulation as observed in multivariate analysis. Interestingly, whereas H1N1 infection status conferred the greatest risk of VTE, bacterial pneumonia also conferred an increased risk of VTE. These findings confirm those of other studies documenting a link between respiratory infection and VTE.[10-12] The propensity toward thrombosis may be related to the ability of the infecting organism to activate innate immune responses (such as Toll-like receptors, complement, extracellular neutrophil traps, and P selectin), with H1N1 representing an extreme along the continuum.[13]

Whereas a relationship between H1N1 influenza and propensity toward thrombotic events has been suggested by clinical reports and animal studies, a relationship between seasonal influenza and thromboembolic complications has previously not been proved.[9,20,26,29-33] Our data are the first to confirm such a relationship. Interestingly, observational studies in medical and surgical patients have demonstrated a relationship between pneumonia and VTE, which was confirmed in our multivariate analysis.[10-12] One possible proposed mechanism linking pulmonary infection to thrombosis is activated protein C deficiency. In mice infected with murine-adapted H1N1 influenza, treatment with an anti-activated protein C antibody aggravated pulmonary coagulopathy[31]; however, these findings were not

Table III. Predictors of pulmonary embolism (PE): Multivariate logistic regression analysis

	Odds ratio	95% Confidence interval	*P*
H1N1 infection	23.3	2.1-260.9	.011
Bacterial pneumonia	10.4	1.7-62.2	.010
Male sex	8.8	1.1-76.2	.048
Empirical anticoagulation	0.09	0.01-0.67	.019

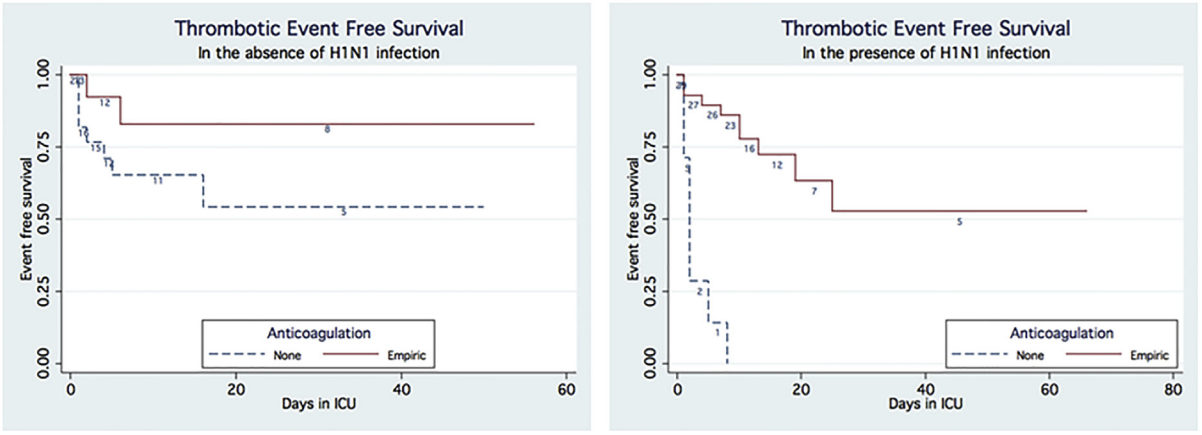

Fig 5. Kaplan-Meier analysis of freedom from thrombotic events in each cohort. There was no difference seen in freedom from thrombotic events in patients without H1N1 influenza (*left*). Difference between H1N1 patients with and without empirical systemic heparin anticoagulation (*right*) was significant with $P < .0001$ by stratified log-rank test. *ICU,* Intensive care unit.

confirmed in mice with factor V Leiden mutation, which represents a state of anti-activated protein C resistance.[30] Another possible mechanism is inflammation-induced elevation of tissue factor, demonstrated in a non-H1N1 murine model of acute lung injury[34] and in a cohort of cancer patients experiencing DVT.[35]

The risk of preventing potentially fatal PE and sequelae of VTE should be weighed against the risks of hemorrhagic complications. Three patients in our cohort suffered fatal intracranial hemorrhage related to the use of anticoagulants. All three were treated with veno-venous ECMO, which requires the use of anticoagulation to maintain line patency and to prevent thrombi from forming in tubing segments.[36] Additional contributing factors to fatal bleeding events include thrombocytopenia and consumptive coagulopathy related to the ECMO circuit.[37,38] Fatal intracranial hemorrhage has been described to occur in 18% of adults undergoing ECMO therapy in one series, similar to our rate of 15%.[39]An additional eight patients suffered nonfatal bleeding events, seven of whom were treated with ECMO or diagnosed with VTE, mandating the use of anticoagulants. One patient treated with empirical anticoagulation suffered from a rectus sheath hematoma that was minor and did not require transfusion. There was no difference between H1N1-positive and H1N1-negative patients treated with ECMO with regard to bleeding complications or mortality. Overall, our data suggest that the benefits of full-dose systemic anticoagulation outweigh the risks of fatal PE or hemorrhagic complications. We have continued this early systemic heparin anticoagulation protocol for all influenza A H1N1 ARDS patients at our institution and to date have had no more deaths related to VTE in this cohort.

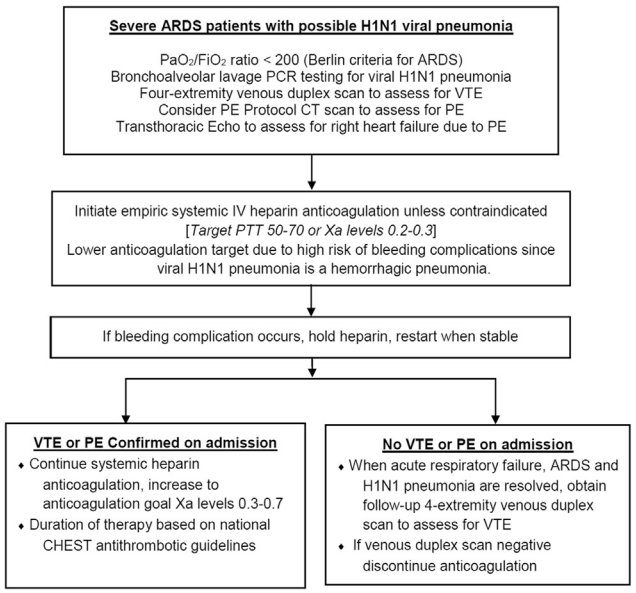

Fig 6. Treatment algorithm for empirical systemic heparin anticoagulation in patients with acute respiratory distress syndrome (*ARDS*) due to influenza A H1N1. *CT,* Computed tomography; *IV,* intravenous; *PCR,* polymerase chain reaction; *PE,* pulmonary embolism; *PTT,* partial thromboplastin time; *VTE,* venous thromboembolism.

The limitations of this study include lack of randomization and evenly matched cohorts, with a significantly higher body mass index in the H1N1-positive cohort compared with the H1N1-negative comparison cohort. Both variables were adjusted for in our multivariate regression models, which still achieved highly significant findings in favor of therapeutic anticoagulation. The mean APACHE III score of 66 in our series was high, and thus caution should be taken in extrapolating these data to lower risk populations. Similar to lack of benefit with protein C in patients with an APACHE II score of <25, these findings are likely applicable only to the

severely critically ill.[40] In less severely ill patients, a relationship between VTE and influenza was not found,[8] suggesting that these results may be applicable only to a cohort of patients with similar characteristics to ours. A final limitation of this study was our small sample size, restricted to 71 patients and only 36 with H1N1; given this limitation, further research is needed to validate our findings.

CONCLUSIONS

This study confirms that H1N1 ARDS patients had 23.3-fold higher risk for PE and 17.9-fold increased risk for VTE. Kaplan-Meier analysis and log-rank test confirmed that empirical anticoagulation provided significant protection from thrombotic events in the H1N1-positive but not in the H1N1-negative critically ill ARDs patients. In multivariate analysis, adjusting for H1N1 status, patients without empirical systemic heparin anticoagulation were 33 times more likely to have any VTE compared with those treated with empirical anticoagulation ($P = .01$). We recommend consideration of systemic anticoagulation in critically ill patients with influenza A H1N1 viral pneumonia and severe ARDS.

AUTHOR CONTRIBUTIONS

Conception and design: AO, CT, BJ, SA, PP, TW, PH, LN
Analysis and interpretation: AO, CT, BJ, SA, PP, TW, PH, LN
Data collection: AO, CT, BJ, SA, PP, TW, PH, LN
Writing the article: AO, CT, BJ, SA, PP, TW, PH, LN
Critical revision of the article: AO, CT, BJ, SA, PP, TW, PH, LN
Final approval of the article: AO, CT, BJ, SA, PP, TW, PH, LN
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Overall responsibility: LN

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