Hospitalization with Infection and Incident Venous Thromboembolism: The ARIC Study

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Abstract

Background and Objectives—Acute triggers for VTE, which may include infection, are understudied, as is the timing and duration of VTE risk after infection. We hypothesized that there is an association between hospitalization with infection and short-term VTE risk that exceeds the known association between hospitalization and VTE.

Methods—VTE cases and infections were identified in the Atherosclerosis Risk in Communities (ARIC) cohort. A case-crossover design and conditional logistic regression were used to compare hospitalized infections among VTE cases (14, 30, 42, and 90 days before VTE) with corresponding control periods 1 year and 2 years prior. Since hospitalization is a known VTE trigger, study design and analytical techniques were used to isolate the impact of infection.

Results—There were 845 adjudicated incident VTE cases. Hospitalization with infection was more common in all case periods compared to equivalent control periods: 14 day OR (95% CI) = 1.7 (0.5, 5.8), 30 day OR (95% CI) = 2.7 (1.1, 6.4), 42 day OR (95% CI) = 2.2 (1.1, 4.7)), and 90 day OR (95% CI) = 1.2 (0.7, 2.0). The association was generally strongest in exposure periods closest to the VTE event and decreased as the time window before VTE increased.

Conclusions—These results support the hypothesis that hospitalized infection is a trigger of VTE. VTE preventive measures may prevent VTE events if used in the peri-infection period but clinical trials are needed.

Keywords

Infection; Pulmonary Embolism; Risk factors; Venous Thrombosis; Venous Thromboembolism

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Introduction

Venous thromboembolism (VTE) consisting of deep-vein thrombosis (DVT) and pulmonary embolism (PE) is a common, life-threatening disease with over 500,000 hospitalized VTE cases annually in the United States.[1] The Longitudinal Investigation of Thromboembolism Etiology (LITE) study, which is a community-based cohort of middle and older aged Americans, reported an incidence rate for VTE of 1.92 per 1000 person years.[2] Study participants experiencing a first incident VTE in the late 1980s through early 2000s had a 28-day case fatality rate of 11%.[2]

Previous epidemiologic research has worked to identify both chronic and acute (triggering) risk factors for VTE. Established VTE triggers include surgery, trauma, immobility, malignancy and chemotherapy, hormonal therapy, and pregnancy and puerperium.[3, 4] Infection has been investigated both as a chronic risk factor and acute precipitant or trigger of VTE. A 2012 systematic review by Tichelaar et al. summarized previous work on infection and risk of VTE and concluded that infections generally, and HIV, pneumonia, and urinary tract infections specifically, are associated with increased risk of VTE.[5] Recent work has identified an association between cytomegalovirus and VTE.[6, 7] A number of case reports have also identified a potential association between varicella and VTE.[8, 9] Further, Zhu et al.'s 2009 study showed influenza vaccination is associated with reduced risk of VTE.[10] Sepsis has also been shown to increase thrombosis and VTE risk.[11, 12]

Table 1 provides a summary of previous studies evaluating infection as a trigger of VTE. Rogers et al., for example, used a case-crossover design and found that infection occurred 2.9 times more often before a VTE hospitalization than in comparison periods.[4] It has been proposed that infection triggers VTE through activating inflammatory, coagulation, and fibrinolysis processes associated with thrombosis, although immobility could also contribute.[13]

Recognition of infection as a VTE trigger is growing but better understanding of infection as a VTE trigger is needed. In summarizing previous work related to pneumonia and VTE, Violi et al. concluded that data point to an association between pneumonia and VTE but "prospective studies are still lacking" and "it is unclear if pneumonia per se carries a risk of venous thrombosis or…some peculiar clinical characteristics are associated with an enhanced risk of venous thrombosis".[11] Previous studies often relied on case-control or retrospective designs and failed to properly account for potential confounding factors such as the seasonality of infection. Further, previous studies used different definitions for infection and evaluated risk over different time periods, making the timing and duration of VTE risk after infection unclear. Herein, we explore the relationship between hospitalization with infection and short-term VTE risk. An improved understanding of infection-triggered VTE risk could help patients with infections and their care providers take steps to reduce their elevated VTE risk.

We used data collected in the long-running, prospective Atherosclerosis Risk in Communities (ARIC) cohort to study this association further. We hypothesized that in the

ARIC study there is an association between hospitalization with infection and short-term VTE risk that exceeds the known general association between hospitalization and VTE.

Methods

Study Population

LITE is a prospective study of VTE occurrence in 2 pooled, multicenter, longitudinal population-based cohort studies: the Atherosclerosis Risk in Communities (ARIC) study and the Cardiovascular Health Study (CHS). The LITE study design, methods, and VTE incidence rates have been described in detail elsewhere.[24] For this analysis, only ARIC data were included as it had longer follow-up. The ARIC Study cohort comprises 15,792 adults aged 45–64 years at recruitment in 1987–1989. Subsequent exams took place 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4), and 2011–2013 (visit 5). Visit 6 (2016–2017) is currently underway. Cohort participants were selected from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. A detailed discussion of ARIC study design and objectives is provided elsewhere.[25]

Study Design

We conducted a case-crossover study in which each ARIC participant with PE or DVT during follow-up served as his/her own control. The case-crossover design affords the ability to isolate potential triggering exposures that vary over time within persons and better control for potential confounding that might occur between persons. Since hospitalization is a known VTE trigger, we attempted to isolate the impact of infection using two analytical approaches discussed below.

VTE case ascertainment

The outcome of interest was VTE as defined for ARIC between 1987 and 2011 (n = 845). VTE cases among ARIC participants were identified through participant report and surveillance of local hospital discharge lists for cohort members. For each hospitalization identified, ICD-9 codes were used to identify possible VTE cases. Information retrieved from the hospital records was assigned a VTE classification separately by 2 physicians; differences between the 2 physicians were adjudicated by discussion. Details on quality assurance for ascertainment and classification of VTE cases are found elsewhere.[24] The hospital admission date abstracted from the patient medical record was considered the VTE date. VTE was further classified as all PEs and all DVTs, and all PEs but restricting DVTs to those occurring in the leg because upper extremity DVTs were relatively few and almost always the result of venous catheters.

Main independent variable: hospitalization with infection

The exposure of interest was hospitalization with infection during case periods of 14, 30, 42, or 90 days prior to VTE diagnosis. Case periods were selected to address the timing and duration of VTE risk after infection similar to study methodology used by Cowan et al[26] and Elkind et al.[27] We employed two exposure classification schemes. First, exposure was dichotomized as hospitalization with infection or no hospitalization with infection (referent)

which includes participants not hospitalized and those with hospitalizations that did not include an infection. Second, exposure was classified as hospitalization with infection, hospitalization without infection (referent), or no hospitalization. For the control periods, we used equivalent length periods exactly 1 and 2 years before VTE diagnosis, to account for the seasonality of infection rates. Hospitalization with infection was assessed using hospital discharge ICD-9 codes. The following ICD-9 codes adapted from methodology used by Rogers et al.[4] for infections were included:

> 0xx.xx, 11x.xx, 245.0x, 254.1x, 320.xx, 321.xx, 322.xx, 323.xx, 324.xx, 357.0x, 360.0x, 370.55, 373.13, 376.01, 379.09, 380.1x, 382.0x, 382.1x, 382.2x, 382.3x, 382.4x, 383.0x, 386.33, 391.xx, 420.90, 420.99, 421.xx, 422.92, 429.89, 46x.xx, 475.xx, 478.22, 478.24, 478.29, 48x.xx, 491.1x, 510.xx, 511.1x, 513.xx, 519.01, 519.2x, 522.5x, 522.7x, 523.3x, 527.3x, 528.3x, 536.41, 540.xx, 566.xx, 567.0x, 567.1x, 567.2x, 567.30x, 569.5x, 569.61, 572.0x, 575.0x, 575.12, 577.0x, 590.xx, 595.0x, 597.0x, 599.0x, 601.2x, 604.0x, 607.1x, 607.2x, 608.0x, 608.4x, 616.10, 616.3x, 616.4x, 68x.xx, 711.xx, 727.89, 728.0x, 728.86, 730.xx, 785.4x, 785.52, 790.7x, 995.91, 995.92, 996.6x, 997.62, 998.5x, 999.3x, V09.xx

Codes in any position among the discharge diagnoses were counted. A washout period of 2 days was used to exclude infections diagnosed within two days of a VTE diagnosis that may have been diagnosed secondarily at the time of VTE hospitalization. The hospital discharge date for infection was considered the infection date and the infection date must have preceded the VTE diagnosis date. The study design is summarized in Figure 1.

Analysis

Two separate analyses were performed based on the two exposure classifications described above. First, the prevalence of hospitalization with infection 14, 30, 42, and 90-days prior to VTE was compared to the corresponding time periods exactly 1 and 2 years prior to the VTE event. Conditional logistic regression was used to estimate odds ratios (OR) of VTE and 95% confidence intervals (CIs) for each time period (14, 30, 42, and 90 days). We controlled for the number of hospitalizations in the 9 months preceding each case or control period to account for potential decline in overall health status due to age and immobility associated with hospitalization. We further controlled for the total number of hospitalizations in the 90-day exposure period to account for non-infection triggering due to hospitalization and isolate the impact of infection.

Second, we used conditional logistic regression to compare the trichotomized (3-level) exposure – occurrence of hospitalization with infection, no hospitalization, hospitalization without infection (referent) – at intervals of 14, 30, 42, and 90 days prior to the VTE with two preceding control periods (1 year and 2 years prior to the VTE). We controlled for the number of hospitalizations in the 9 months preceding each case or control period to account for potential decline in overall health status due to age and immobility associated with hospitalization.

Both analyses were designed to isolate the effect of infection and estimate the effect of infection independent of the known association between hospitalization and VTE. Both

analyses were conducted using all PEs and DVTs (All VTE cases) (n=845), and using all PEs but restricting DVTs to those occurring in the leg (n=755).

Results

Participant characteristics at the time of VTE diagnosis are provided in Table 2 for both all VTE cases and for PE and leg DVT cases. The majority of total VTE cases were female (56%) and white (62%), and the average age (±SD) was 70.5 (7.8) when the VTE events occurred.

Of the 845 total VTE cases, 75 had a hospitalization with an infection in the 90 days preceding the VTE event. Given that a hospitalization can contain more than 1 infection code, these hospitalizations contained 184 infection discharge diagnosis codes. Pneumonia (14.7%), urinary tract infections (13.6%), and septicemia/bacteremia (12.5%) were the most common infection types. Table 3 contains the frequency of infection types prior to VTE events. A total of 36 VTE cases had a hospitalization with infection during at least one of the 90-day control periods. For the 90-day exposure periods, the mean number of hospitalizations was 0.46, 0.11, and 0.09 for the case period, first control period, and second control period respectively. In the 9 months preceding each case or control period, the mean number of hospitalizations was 0.42, 0.28, and 0.22 for the case period, first control period, and second control period respectively.

The results from the primary analysis with exposure dichotomized as hospitalization with infection or no hospitalization with infection are shown in Table 4. Hospitalization with infection was more common in all case periods compared to equivalent control periods: 14 day OR (95% CI) = 1.7 (0.5, 5.8), 30 day OR (95% CI) = 2.7 (1.1, 6.4), 42 day OR (95% CI) = 2.2 (1.1, 4.7)), and 90 day OR (95% CI) = 1.2 (0.7, 2.0). Overall, the association appeared to be generally strongest in exposure periods closest to the VTE event and decreased as the time window before VTE increased.

The secondary analysis with exposure categorized as hospitalization with infection, hospitalization without infection, and no hospitalization (Table 5) yielded slightly smaller ORs as the dichotomized exposure analysis and with less precision. Hospitalization with infection was more common in all case periods compared to equivalent control periods: 14 day OR (95% CI) = 1.6 (0.5, 5.1), 30 day OR (95% CI) = 1.7 (0.7, 4.0), 42 day OR (95% CI) = 1.5 (0.8, 3.2), and 90 day OR (95% CI) = 1.3 (0.8, 2.2). Similar results were found when the analysis was restricted to PEs and leg DVTs (supplementary tables 1 and 2).

Discussion

This case-crossover study within a population-based cohort demonstrated that VTE risk is higher after hospitalization with infection independent of the known association between hospitalization and VTE. Patients with infection had higher odds of VTE in the 90 days after their hospitalization with infection compared to equivalent control periods 1 and 2 years previously. This supports our hypothesis that there is an association between hospitalization with infection and subsequent short-term VTE risk that exceeds the known association

between hospitalization and VTE. Thus hospitalized infection appears to trigger VTE events.

We employed two analytical approaches to control for potential confounding and isolate the association of hospitalization with infection on VTE risk. Both approaches produced similar effect estimates but the trichotomized analysis had less precision and no statistically significant results. VTE risk appears to be around 2 times higher in the 42 days following a hospitalization with infection compared to no infection. The association between hospitalization with infection and VTE was graded, such that VTE risk generally appeared highest in the exposure periods most proximal to the VTE event and decreased as the time window before VTE increased. These results corroborate previous work that found that infection may function as a VTE trigger.

Besides the possibility that infection leads to VTE through decreased mobility, Epaulard et al. summarized existing studies that showed that the inflammatory response to infection and the coagulation and fibrinolysis processes likely share common pathways, explaining why infection is associated with thrombosis.[13] That is, the risk of VTE due to infection arises through a link between inflammation and coagulation activation.[13]

Our study has a number of strengths, including a large sample size from a community cohort, a rigorous methodology to adjudicate VTE events, and a crossover design to control for potential confounding. It also has limitations. The vast majority of VTE events were symptomatic since events were captured via hospital records and were clinically diagnosed and verified by the investigators without specific screening for asymptotic VTE events. We were unable to look at VTE triggering by infection type due to insufficient numbers and corresponding low power. Like all case crossover studies, our study may suffer from survival bias as we did not consider infections in participants who did not have a VTE event. Our study only considered the relationship between infection and VTE among those who survived any infections and later had a VTE event. Confounding by age is possible, generally, because as participants age their risk of both VTE and hospitalization with infection increase. However, to reduce potential confounding by age, only control periods 1 and 2 years prior to VTE events were examined. We also adjusted for possible confounding by the number of hospitalizations. Other confounders such as medication use that may vary between the exposure and control periods were not ascertained. Relatively few infections prior to VTE events yielded OR estimates that were imprecise, with wide confidence intervals, particularly in the trichotomized analysis. We certainly under-ascertained infections, especially minor ones, by including only hospitalizations with infections. If minor infections similarly increase VTE risk, our missing them would most likely lead to non-differential misclassification of the exposure in both case and control periods, which would typically bias ORs towards the null for dichotomized hospitalization with infection.

Our study has a number of potential implications. Hospitalized patients with an infection should be considered potential candidates for VTE prophylaxis. Our results support the inclusion of infection information in the VTE risk assessment of hospitalized such as the Padua Prediction Score.[28] Identification of hospitalization with infection as a VTE trigger may prompt more aggressive treatment with standard preventive strategies, including such as

leg mobilization or compression or anticoagulants, during and immediately following hospitalization with infection to reduce the increased risk of acute VTE. This time period immediately following infection has been referred to in previous trigger research as a "treatable moment" that may be used to reduce otherwise elevated VTE risk.[27] Evidence-based infection control efforts such as influenza vaccination may be considered because of their ability to not only reduce infection but may also reduce VTE.[10]

Conclusion

VTE patients had higher odds of a hospitalization with infection within 90 days prior to their VTE event compared to equivalent control periods 1 and 2 years previous. There may be a role for infection in VTE prevention decision making, though clinical trials and a cost-benefit analysis should be considered.

Acknowledgments

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Highlights

- Hospitalized infection appears to trigger VTE events

- The triggering effect of infection on VTE decreases over time after an infection

- VTE preventive measures may prevent VTE events in the peri-infection period

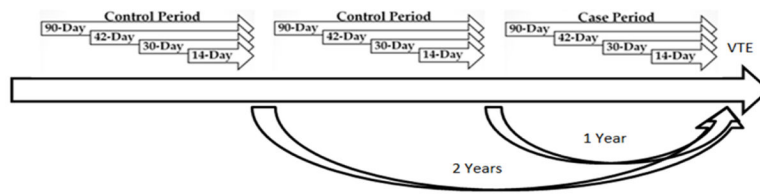- Hospitalized patients with an infection may be considered for VTE prophylaxis

Figure 1.
Case-crossover study design employed to study VTE in relation to triggering by hospitalized infection, ARIC. Presence of hospitalized infection was assessed for each of the 12 time periods, and case period was compared to control periods.

Table 1

Infection as a trigger of VTE in previous studies

Citation	Study Design	Infection Studied	Measure of Association, (95% CI)[*]
Masrouha et al, 2016[14]	Prospective Cohort	Preoperative Pneumonia	DVT – OR = 1.67 (1.32, 2.11) PE – OR = 2.18 (1.48, 3.22)
Chen et al, 2015[15]	Retrospective Cohort	Pneumonia	DVT – HR = 1.78 (1.39, 2.28) PE – HR = 1.97 (1.43, 2.72)
Dalager-Pedersen et al, 2014[16]	Prospective Cohort	Community Acquired Bacteremia	OR = 1.9 (1.4, 2.7)
Paran et al, 2013[6]	Prospective Cohort	Cytomegalovirus	OR = 2.49 (1.53, 4.06)
Rogers et al, 2012[4]	Case-Crossover	All infections	IRR = 2.9 (2.13, 3.94)
Schmidt et al, 2012[17]	Case-Control	Systemic respiratory tract infections, urinary tract infections, skin infections, intra-abdominal infections, and septicemia	IRR = 3.3 (2.9, 3.8)
Ribeiro et al, 2012[18]	Case-Control	Pneumonia	OR = 5.0 (3.9–6.3)
Clayton et al, 2011[19]	Case-Control	Respiratory Infections	DVT – OR = 2.64 (1.62, 4.29) PE – OR = 2.50 (1.33, 4.72)
Cimminiello et al, 2010[20]	Case-Control	All Infections	OR = 1.86 (1.16, 2.97)
Tichelaar et al, 2010[21]	Case-Control	All Infections	OR = 2.5 (1.4, 4.8)
Gangireddy et al, 2007[22]	Retrospective Cohort	Pneumonia	OR = 2.7 (2.10, 3.50)
		Urinary Tract Infections	OR = 1.8 (1.3, 2.50)
Smeeth et al, 2006[23]	Case-Crossover	Urinary Tract Infections	IR = 2.10 (1.56, 2.82)
		Systemic Respiratory Tract Infections	IR = 1.91 (1.49, 2.44)

[*] HR – Hazard Ratio, OR – Odds Ratio, IRR – Incidence Rate Ratio, IR – Cumulative Incidence Ratio

Table 2

At-Event Characteristics of ARIC Participants Who Developed VTE, 1987–2011

Characteristic	All VTE (n=845)	PE and Leg DVT (n= 755)
Age, years, mean ± SD	70.5 ± 7.9	70.5 ± v7.8
Sex, Count (%)		
Male	375 (44.4%)	332 (44.0%)
Female	470 (55.6%)	423 (56.0%)
Race, Count (%)		
White	526 (62.3%)	480 (63.6%)
Black	318 (37.6%)	274 (36.3%)
Asian	1 (0.1%)	1 (0.1%)

Table 3

Types of hospital discharge infections in the 90 days prior to developing VTE, ARIC, 1987–2011

Infection Type	Case Period - Count	Percent of Total
Pneumonia	27	14.7%
Other Respiratory Infections	9	4.9%
Urinary Tract Infection	25	13.6%
Other Genitourinary Infections	3	1.6%
Septicemia/Bacteremia	23	12.5%
Gastrointestinal Tract Infections	16	8.7%
Infections due to Surgical or Medical Care	14	7.6%
Other Drug-Resistant Infections	5	2.7%
Candidiasis	12	6.5%
Other Mycoses	1	0.5%
Staphylococcus infections	8	4.3%
Other Infections	41	22.3%
Total	**184**	**100%**

Table 4

Association of Dichotomized Recent Hospitalization with Infection and Risk of VTE, ARIC, 1987–2011

All VTEs	Case (n)	Control* (n)	Crude OR, 95% CI	Adjusted† OR, 95% CI
14 Days				
No Hospitalization	830	1684	Ref	Ref
Hospitalization with Infection	15	6	5.72 (2.07, 15.81)	1.74 (0.52, 5.83)
30 Days				
No Hospitalization	806	1680	Ref	Ref
Hospitalization with Infection	39	10	9.39 (4.38, 20.14)	2.65 (1.10, 6.39)
42 Days				
No Hospitalization	795	1676	Ref	Ref
Hospitalization with Infection	50	14	8.10 (4.31, 15.22)	2.23 (1.06, 4.69)
90 Days				
No Hospitalization	770	1654	Ref	Ref
Hospitalization with Infection	75	36	5.59 (3.52, 8.90)	1.15 (0.65, 2.03)

*Control periods were equivalent length periods exactly 1 and 2 years before VTE diagnosis

†Adjusted for 9 month and 90 day hospitalization totals

Table 5

Association of Trichotomized Recent Hospitalization Categories and Risk of VTE, ARIC, 1987–2011

All VTEs	Case (n)	Control* (n)	Unadjusted OR, 95% CI	Adjusted† OR, 95%CI
14 Days				
No Hospitalization	789	1659	0.29 (0.17, 0.47)	0.25 (0.15, 0.43)
Hospitalization without Infection	41	25	Ref	Ref
Hospitalization with Infection	15	6	1.80 (0.59, 5.52)	1.60 (0.51, 5.06)
30 Days				
No Hospitalization	698	1640	0.14 (0.09, 0.21)	0.13 (0.08, 0.19)
Hospitalization without Infection	108	40	Ref	Ref
Hospitalization with Infection	39	10	1.87 (0.80, 4.35)	1.69 (0.72, 3.99)
42 Days				
No Hospitalization	655	1621	0.14 (0.10, 0.20)	0.14 (0.10, 0.20)
Hospitalization without Infection	140	55	Ref	Ref
Hospitalization with Infection	50	14	1.57 (0.77, 3.20)	1.53 (0.75, 3.15)
90 Days				
No Hospitalization	563	1555	0.16 (0.12, 0.21)	0.16 (0.12, 0.22)
Hospitalization without Infection	207	99	Ref	Ref
Hospitalization with Infection	75	36	1.29 (0.76, 2.18)	1.27 (0.75, 2.16)

*Control periods were equivalent length periods exactly 1 and 2 years before VTE diagnosis

†Adjusted for 9 month hospitalization total