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Venous Thromboembolism: A Case-Control Study of Patients in the Neuroscience Intensive Care Unit

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VENOUS THROMBOEMBOLISM: A CASE-CONTROL STUDY OF PATIENTS IN THE NEUROSCIENCE INTENSIVE CARE UNIT

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ABSTRACT

VENOUS THROMBOEMBOLISM: A CASE-CONTROL STUDY OF PATIENTS IN THE NEUROSCIENCE INTENSIVE CARE UNIT

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Venous Thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant source of morbidity and mortality in hospitalized patients. However, despite ample research into VTE in hospitalized subpopulations, critically ill patients with primary neurological disorders have been insufficiently studied. We hypothesized that there is a high incidence of VTE in the NICU despite a high thromboprophylaxis rate and that this population would carry a unique set of risk factors. Our goal was to identify those patients at higher risk for VTE who may then be served by more aggressive screening and thromboprophylaxis.

We performed a retrospective chart review and case-control study of patients admitted to the NICU of a major urban hospital for three or more days, between 2001 and 2005. The two groups were matched, 2:1 (two controls per case), based on year of hospital discharge and presence of surgical intervention.

The incidence of VTE in the NICU was 9.5% (125 of 1,318 patients), despite an overall thromboprophylaxis rate of 97.6%. 55% of DVTs were in the upper and 45% in the lower extremity. 48 PE patients had PE. Univariate analysis utilizing $p<0.05$ as a statistical threshold revealed 12 factors associated with VTE. These factors were entered into a multivariable analysis logistic regression, which yielded 5 factors that remained independently with VTE: higher rates were associated with use of a central-venous catheter (OR:2.5, CI: 1.4 – 4.6, p=0.003), arteriovenous malformation (OR:4.9, CI: 1.2 – 20.1, p=0.026), prior VTE (OR:5.6, 1.4 – 22.4, p=0.014), and mechanical ventilation (OR:2.1, CI: 1.1 – 4.2, p=0.036). VTE prophylaxis was protective (OR:0.8, CI: 0.0 – 0.9, p=0.043). In conclusion, VTE remains common among NICU patients despite a high rate of prophylaxis. Several factors appear to be associated with VTE in this population. Future studies are needed to validate the association between these factors and VTE and to determine if more aggressive surveillance and prophylaxis can decrease the frequency and complications associated with VTE.

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INTRODUCTION

History

Venous thromboembolism (VTE) is a spectrum of disease encompassing deep venous thrombosis (DVT) and pulmonary embolism (PE). Peripheral vascular disease has been a long-known condition, first referenced in 1550 BC on the Ebers medical papyrus of Egypt. In 1644, Schenk first observed venous thrombosis when he described an occlusion in the inferior vena cava (1). The concept that PEs most commonly originate from clots in lower extremity veins, was originally proposed by Rudolf Virchow and Armand Trousseau in 1846 (2). Virchow's Triad, first described in 1860, includes: venous stasis, vessel wall injury and hypercoagulable state, and is still considered the primary mechanism by which venous thrombosis occurs (3).

Incidence

The precise incidence of DVT is unknown because the condition is often misdiagnosed or is asymptomatic and may spontaneously resolve prior to reaching medical attention. However, current estimates place the incidence of VTE in the general population around 117 per 100,000 people per year (48 DVT per 100,000, 69 PE per 100,000) (4). Similarly, another study places the incidence at 100 VTE per 100,000 people, per year (5). A study of the Olmstead County, Minnesota population showed an incidence of VTE of 1 per 1000 per year, consistent with prior studies (4). However, estimates of the number of people developing DVTs annually in the United States range from 250,000 (6, 7) to two million (8, 9).

Among hospitalized patients, the incidence of DVT is considerably higher and varies widely, from 13 to 80%, depending on the specific population studied (10 - 12).

Without prophylaxis, the incidence of DVT has been shown to be 10 to 20% among general medicine and 10 to 40% among general surgical patients, who were not receiving thromboprophylaxis (13), and 40 to 60% among patients specifically undergoing orthopedic surgery who did receive thromboprophylaxis (14).

Among the ICU populations, the rates of DVT vary widely. A study of the incidence of DVT in Medical Intensive Care Unit (MICU) patients demonstrated DVT in 33%, despite an overall prophylaxis rate of 61% (15). A study of Surgical Intensive Care Unit (SICU) patients demonstrated a DVT rate of 13% (10). Finally, a study of critically ill patients undergoing mechanical ventilation for >7 days showed a DVT rate of 23.6%, despite a 100% of patients receiving prophylaxis consisting of either SCDs or subcutaneous heparin twice daily (11).

Multiple neurological and neurosurgical populations have been studied thus far. One prospective trial of patients suffering acute spinal cord injury demonstrated a DVT rate of 26% without prophylaxis in the first two weeks (16). The overall rate of DVT on a general neurosurgical service was 4% (17). Among patients in neurorehabilitation, 11% had DVT and the rate was higher among patients with brain tumor and intracerebral hemorrhage than with Traumatic Brain Injury (18).

Morbidity and Mortality

Estimates of hospitalizations related to DVTs place the rate at 270,000 hospitalizations per year in the United States (9, 19). Similarly, the Olmstead Co. study extrapolated the number of hospitalizations related to VTE in the U.S. at more than 250,000, making it a topic of economic importance as well (4,6). In fact, the 6-month

cost for inpatient treatment of DVT ranges from $3,906 - $17,168 per patient (20). An estimated 60,000 to 100,000 Americans die each year from PE (9, 21) and approximately 10% of hospital deaths are attributable to PE (13).

Most DVTs are clinically silent. A study of major trauma patients found that only 1.5% of patients with DVT had any symptoms suggestive of DVT, such as, pain, swelling, erythema, or palpable cord, despite a proximal DVT (a clot affecting the common or superficial femoral veins, or internal or external iliac veins) rate of over 57% (12). One study of recent stroke patients showed death was the presenting manifestation in 50% of patients with PE, verifying that VTE may be clinically silent before culminating in death (22). Although benefit has not been proven, these observations suggest that routine screening for DVT in asymptomatic patients may be valuable, particularly in high-risk populations, because waiting for symptoms to develop may cause clinicians to miss the majority of DVTs and place patients at risk for potentially life-threatening PE.

While most DVTs are clinically inapparent, they may become clinically important. While the morbidity associated with clinically silent DVT is unknown, the morbidity associated with apparent DVT is considerable, and includes swelling, erythema and pain. Post-thrombotic syndrome may ultimately result and is characterized by persistent swelling, pain, chronic ulcers and dermatitis. Among patients in the general population with a history of DVT, the rate of post-thrombotic syndrome ranges from 22% to 55% at 2 years, and over 29% at 8 years (23, 24). In stroke patients who did not progress to PE, those whose DVTs were untreated had a rate of post-thrombotic syndrome approaching 90% (25).

In addition to the morbidity associated with DVTs, the thromboses may propagate and eventually embolize to the pulmonary circulation, resulting in PE. Approximately 30 to 40% of calf thromboses do propagate proximally (13, 26). Furthermore, even those clinically silent DVTs in critical care patients pose a potential threat of embolization, as there is a significantly higher rate of PE in these patients than in those patients without DVT (19). An article in the journal, *Stroke*, estimates that PE accounts for between 13 and 25% of deaths within four weeks following acute stroke (27). The International Cooperative Pulmonary Embolism Registry (ICOPER) was a registry of 2,454 patients with PE at 52 hospitals in 7 countries. The study reported the overall mortality at 3 months following PE was 17.4%. 45.1% of these deaths were attributable to PE (28). More effective prevention and treatment could decrease the number of patients with VTE and the morbidity and mortality associated with this condition.

Risk Factors

Multiple risk factors for VTE have been identified, most of which relate back to Virchow's Triad of immobility, hypercoagulable state, and endothelial injury (29 - 32). (See Table 1 for previously identified risk factors of VTE). General risk factors for VTE include: major surgery within the previous four weeks, pregnancy or the postpartum period, and immobilization (13, 30). Age is another known risk factor for VTE: the Olmstead study demonstrated that for each 10-year increase in age, the incidence of VTE doubled (4, 6).

Risk factors relating to medical history include malignancy, history of DVT, stroke leading to paresis or plegia, acute myocardial infarction (MI), congestive heart failure (CHF), nephrotic syndrome, ulcerative colitis (UC), and sepsis (13, 32). Trauma

is another well-known risk factor for VTE due to associated endothelial injury (29). Specifically, multiple trauma, central nervous system (CNS)/spinal cord injury, burns, and lower extremity/long bone fractures have all been shown to be VTE risk factors (12).

A number of vasculitides and hematologic disorders, many hereditary, result in a hypercoagulable state. Examples include systemic lupus erythematosus (SLE) and the lupus anticoagulant, Behçet syndrome, homocystinuria, thrombocytosis and polycythemia rubra vera. Inherited disorders of fibrinolysis and coagulopathies which predispose to VTE include Antithrombin III deficiency, Protein C and Protein S deficiency, Prothrombin 20210A mutation, Factor V Leiden, and dysfibrinogenemias and disorders of plasminogen activation (32).

Certain drugs may contribute to or predispose to VTE. Proven agents include oral contraceptives and estrogens. In predisposed individuals, heparin may cause heparin-induced thrombocytopenia, which can increase the risk of VTE (33). Intravenous drug abuse predisposes to VTE as well (13, 26).

Certain diagnoses among neurological/neurosurgical populations have been shown to be risk factors for DVT and are useful for identifying at-risk patients. Hemorrhagic stroke has been demonstrated to be an independent risk factor for DVT compared to patients with thrombotic stroke, though this study did not control for varying prophylaxis techniques (34). Among neurorehabilitation patients, the rate of DVT was higher among patients with intracerebral hemorrhage (18). Patients undergoing surgery for brain tumor removal were studied and the rate of DVT was found to be significantly higher among those undergoing craniotomy as opposed to other surgical approaches (9.5% vs. 3.7%) (17). Furthermore, specific risk factors for VTE among neurology

patients include gastrostomy tube, tracheostomy, and urethral catheter (35). Finally, a study of neurology patients found a 51-fold higher risk of DVT among patients with hemiparesis (36).

Thromboprophylaxis

Fortunately, there are effective options for prophylaxis against VTE. Current practices rely primarily upon the use of low-dose anticoagulation and mechanical compression devices applied to the lower extremities (13). When the risk of VTE is very high, prophylactic inferior vena cava (IVC) filter placement may be used to prevent clots from reaching the pulmonary circulation when they embolize (13).

Mechanical methods of thromboprophylaxis are based upon the concept of reducing venous stasis and inducing anti-thrombotic, pro-fibrinolytic, vasodilatory biochemical alterations. The minor endothelial shear stress induced by the Sequential Compression Devices causes the release of nitric oxide, tissue plasminogen activator and prostacyclin, and decreases levels of plasminogen activator inhibitor, decreasing the risk of clot formation (37). A meta-analysis appearing in *Chest*, the journal of the American College of Chest Physicians, found that while no mechanical method of thromboprophylaxis has been shown to reduce the rate of PE or death, they are effective in reducing rates of DVT and may be a good alternative in patients for whom anticoagulation is contraindicated (13). Another meta-analysis of original studies between 1966 and 1996 demonstrated a 62% reduction in the rate of DVT with SCD use compared with placebo (38). A study of serial compression devices (SCDs) in 1998

demonstrated a more than 40-fold risk reduction when SCDs were added to anticoagulation with 5000 units of heparin twice daily in thrombotic stroke patients (36).

Anticoagulation has been a known method of preventing and treating VTE since the 1960s. Current anticoagulation practices vary, but most commonly involve the use of unfractionated heparin (UFH), usually 5000 units subcutaneously twice or three times daily, or low molecular weight heparin (LMWH). The first evidence that heparin reduces mortality in patients with PE was presented in *Lancet* in 1960 (39). Both LMWH and UFH have been proven effective in prophylaxis against VTE (40). (See Tables 2 - 4 for a summary of thromboprophylaxis available and the studies investigating the efficacy of various methods of thromboprophylaxis.) Both LMWH and UFH have been endorsed by the American Stroke Association, the American Academy of Neurology, and the American Heart Association as effective and safe when used subcutaneously for VTE prophylaxis, with a low rate of hemorrhage after ischemic stroke (41). The American College of Chest Physicians recommends the use of LMWH or low-dose UFH, as well as SCDs, for use as thromboprophylaxis in most medical and surgical populations (13, 42).

A 2004 study demonstrated the efficacy of therapeutic anticoagulation and heparin prophylaxis during stroke rehabilitation in prevention of VTE, as well as the inferior efficacy of antiplatelet agents in this population (35). A meta-analysis of VTE prophylaxis of surgical patients demonstrated that LMWH was at least as effective as UFH in reducing the incidence of VTE (40). However, a very recent study demonstrated the superiority of LMWH over unfractionated heparin for DVT prophylaxis after ischemic stroke, based on its once daily administration schedule, and its increased effectiveness at preventing VTE (43).

The Cochrane review demonstrated a three-fold increase in bleeding risk when stroke patients receive full anticoagulation after stroke (44). In contrast, a 2002 study demonstrated no increased bleeding in patients with severe head injury receiving early unfractionated heparin as thromboprophylaxis (45). More generally, most studies have shown minimal risk of hemorrhage in the average hospital patient receiving thromboprophylaxis with low dose heparin along with a favorable risk:benefit ratio to its use (13). While individual methods of prophylaxis are effective, a 1998 study demonstrated the improved efficacy, in a neurosurgery population, of using Lovenox and SCDs combined, when compared to SCDs alone (5% DVT rate vs. 13% DVT rate, respectively). The study also showed no increased bleeding risk in this population (46). The finding of improved efficacy with two forms of thromboprophylaxis was verified for SCDs and UFH as well (36).

Despite the evidence demonstrating the efficacy of thromboprophylaxis, and current guidelines recommending its use, a study in the 1990s estimated that only one-third of hospitalized patients with multiple risk factors for VTE received prophylaxis (47). More recently, the 2008 multinational cross-sectional ENDORSE study investigated the percentage of hospitalized patients who would qualify for VTE prophylaxis based on current guidelines. The study found that nearly half of all hospitalized patients meet criteria for thromboprophylaxis, yet only half of those patients received prophylaxis (48). This lack of consistent thromboprophylaxis is apparently resulting in a large number of preventable VTE. A 2001 study showed that over 17% of VTE in inpatients was potentially preventable if proper prophylaxis had been implemented. (49). Therefore, despite clear evidence for the safety and efficacy of

thromboprophylaxis, and the detrimental effects of withholding prophylaxis, the intervention remains underutilized.

Upper Extremity DVT

Current studies indicate that 1 to 4% of DVTs involve the upper extremities (UEDVT), primarily the subclavian, axillary, brachial or internal jugular veins. UEDVTs can be divided into primary (unprovoked) and secondary (e.g., in the setting of central venous catheter, cancer or pacemaker), the latter making up 75 to 80% of cases (42, 31). Primary UEDVT is quite rare and is usually either idiopathic, or due to effort or exertion leading to microtrauma, called Paget-Schroetter Syndrome (50). UEDVTs have unique risk factors and include use of pacemakers and central venous catheters. Furthermore, patients with UEDVT are less often Caucasian and more likely to be younger, leaner, and smokers compared with those with LEDVT (51).

The American College of Chest Physicians (ACCP), in *Chest* 2008, determined that there have been no randomized-controlled trials investigating the efficacy of unfractionated heparin or low-molecular weight heparin for the treatment of UEDVT. However, there have been sufficient smaller studies to support the use of both as prophylaxis against UEDVT (42). Moreover, like previous DVT prophylaxis studies, a 2004 study showed that only 20% of patients with UEDVTs, without any contraindication, actually received prophylaxis (51).

Chest also provided a meta-analysis of UEDVT studies investigating the outcome and side effects of interventions. Fewer patients with UEDVT present with overt PE, compared to those with lower-extremity DVT. However, their three-month outcome in

terms of recurrent DVT or PE, major or fatal bleeding, or fatal PE, is similar (52). While rare, UEDVTs do embolize, leading to potentially fatal PEs (52). However, the estimates of PE among patients with UEDVT have varied widely. One study found that up to one-third of patients with UEDVT may suffer from PE (53), while another study found a vastly lower incidence of PE in the range of 0.5% to 4% (54). This discrepancy highlights the great variation in findings related to UEDVT. One likely explanation may be variations in screening practices. As with any condition, when it is screened for, UEDVT is more likely to be discovered. In either case, the presence of proximal UEDVTs is clinically significant and treatment is recommended (42).

It should be noted that location of proximal UEDVT does not appear to influence risk of embolism. One study found no significant difference in risk of embolism between internal jugular vs. subclavian and/or axillary vein DVTs (54). However, there should be a suspicion of lower extremity DVT in patients with UEDVT, because the two are often comorbid (55).

Finally, while superficial vein thrombosis (SVT), also known as superficial thrombophlebitis, is generally considered benign, studies have shown rates of thromboembolic complications ranging from 5-15% (56). Most studies, however, have focused on lower extremity SVT; upper extremity SVT remains understudied. However, the ACCP recommends treatment of SVT with prophylactic doses of LMWH after ultrasound verification of the absence of concurrent DVT (42).

In summary, while there is an apparent lower incidence of clinically overt PE in patients with UEDVT, they do embolize and, as such, should be considered clinically significant.

Previously Studied Populations

Previous studies of VTE have examined a variety of inpatient populations, including neurosurgical, spinal cord injury, and Medical Intensive Care Unit (MICU) populations (10 - 12, 15 - 18, 34, 35, 57,). Detailed recommendations have been made regarding subpopulations of both medical and surgical patients (e.g., laparoscopic surgery, knee and hip arthroplasty, gynecologic surgery, urologic surgery, trauma, burns, and cancer patients). (See Table 5 for data on DVT prevalence in previously studied populations).

However, despite the extensive research in this area, to date Neurological/Neurosurgical ICU (NICU) patients have never been studied specifically. There are several reasons to suspect that NICU patients are at high risk for VTE. First, ICU patients in general tend to have numerous risk factors for VTE: they are often immobile, mechanically ventilated, sedated, septic, with central venous catheters, or suffering from respiratory or cardiovascular failure. Second, certain patient-types common in the NICU, such as neurosurgical patients and acute spinal cord injury patients have been studied individually and shown to be subject to high rates of VTE (13, 16 - 18, 29, 57).

Further, this population includes patients suffering from unique medical conditions, including brain tumor, epilepsy, intracerebral, subarachnoid and subdural

hemorrhage, spinal cord injury, hydrocephalus and cerebral aneurysms. This population also presents distinctive challenges with regard to anticoagulation. For example, patients in the NICU due to intracranial hemorrhages (intracerebral, subdural, epidural or subarachnoid) pose a particular problem in determining appropriate prophylaxis. Clinicians are often concerned about providing any anticoagulation in this subpopulation, even though only full anticoagulation increases the risk of worsening hemorrhage or rebleed after the initial insult (44). A meta-analysis performed in *Stroke*, showed a significantly increased risk of hemorrhage after ischemic stroke when higher, therapeutic doses of either UFH or LMWH were used, highlighting the unique VTE treatment challenges faced by this population (41). Oftentimes these patients may only be mechanically prophylaxed, which may be less effective than anticoagulants for thromboprophylaxis. Therefore, these patients, though theoretically at significant risk for VTE, may, as a result of their neurological condition, not receive effective prophylaxis.

Moreover, the development of DVT in the NICU creates problematic treatment choices because, for many patients, full anticoagulation could increase the risk of central nervous system hemorrhage. Therefore, the ability to identify NICU patients at highest risk for VTE could allow them to be targeted for closer screening and potentially more aggressive thromboprophylaxis. This could decrease risk for VTE as well as the potential consequences of treatment, extended hospital stay, and consumption of additional hospital resources.

HYPOTHESIS

VTE in the NICU is common, despite near-universal use of prophylaxis, and specific factors can be identified to help identify those patients at higher risk for VTE.

STATEMENT OF PURPOSE

The goal of this study was to examine the NICU population and answer the following questions:

1. What is the incidence of VTE in NICU patients?
2. What risk factors predispose NICU patients to develop VTE?
3. What is the clinical outcome of NICU patients with VTE? That is, what are their rates of mortality, pulmonary embolism, associated complications and lengths of NICU and total hospital stay?

In investigating the incidence of VTE within the NICU population, it may be determined whether this population is generally well-served by continuing thromboprophylaxis, despite risk of hemorrhage. Further, if a particular subgroup of the NICU population could be identified as at increased risk of developing VTE, then this subpopulation could be targeted for more aggressive surveillance and prophylaxis, for example, with higher dose anticoagulation or prophylactic insertion of an IVC filter.

METHODS

With approval from the Human Investigation Committee of Yale University, an Excel file was obtained from Janis Bozzo, MSN, RN, Clinical Coordinator, Decision Support, Yale-New Haven Health System, and an Assistant Clinical Professor, Yale School of Nursing, New Haven, CT. The file contained a list of all patients who were coded as having stayed in the NICU for three days or longer, discharged between January 1, 2001, and December 31, 2005, under the care of the Neurology or Neurosurgical services. The Excel file also included name, age, gender, race, principal operation

performed (if any), principal diagnosis, dates of hospital admission and discharge, and whether the patient was coded as having a DVT. The total number of patients on the Excel file provided by Ms. Bozzo was 1,318. This approach was the most complete way to capture the entire population of NICU patients between 2001 and 2005. All subsequent data collection was performed by Rachel Wolfson, medical student.

For each patient listed in the Excel file, an independent review was conducted to verify acute DVT diagnosis and investigate those patients with documented PE as well. This review was conducted using Sunrise Clinical Manager, the Yale-New Haven Hospital electronic medical record, and all diagnostic imaging related to DVT/PE. The imaging modalities included Doppler ultrasounds (DUS) of upper and lower extremities, computerized tomographic angiography (CTA) - P.E. Protocol, ventilation/perfusion (V/Q) scans, and angiography/venography. If a DUS showed a nonocclusive or occlusive thrombus in any of the deep veins of the lower extremities or of the brachial, basilic, axillary, internal jugular or subclavian veins of the upper extremities, this was documented as a positive result. Additionally, a positive CTA, or a high probability/intermediate probability V/Q scan, were documented as a positive result. Intermediate V/Q scans were considered positive for VTE because these patients were treated clinically as though they had a PE. According to the Excel file, 77 patients had documented DVT, whereas after review, 104 patients had documented DVT.

Because this is a case-control study, those patients with positive results (acute VTE) during NICU stay or within 3 days after NICU discharge were considered our cases. Patients with VTE during their hospital stay but prior to NICU admission were not considered cases. There were 125 cases (104 patients with DVT and 21 with isolated PE)

matched 2 controls per case. The groups were matched on year of discharge from the hospital to control for any temporal changes regarding DVT prophylaxis and screening. The groups were also matched on whether a surgery of any kind was performed during the hospitalization*.

The matching was conducted by the following process: for each case group (e.g., 2004, surgery, VTE), the eligible controls (2004, surgery, no VTE) were assigned a number. Then, using a number randomizer from the website: http://www.randomizer.org/form.htm, the requisite number of random numbers was generated. That is, if ten controls were needed, ten random numbers were generated and the eligible controls corresponding to those random numbers were then chosen as controls. This was done in order to prevent selection bias.

Data for all cases and controls were gathered from two sources: Sunrise Clinical Manager/CCSS from hospital computers, and paper charts pulled with the assistance of the YNHH medical records department. Data was collected first on a Microsoft Word form (see Figure 1). All information was saved on both a thumb-drive and hard drive of a personal computer, both of which were password protected and designated to be destroyed following completion of the study. Dr. Mark D. Siegel (MDS) and Rachel H. Wolfson (RHW) were the only two investigators with access to the files. Throughout the data collection process, the data was periodically entered, and rechecked, into a Microsoft Access Database, created by RHW. The database was then used to analyze our results.[1]

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[1] Appendix 1 contains detailed descriptions of how each data-point was defined and the specific chart locations where that data-point was gathered.

*During data collection, 13 cases were discovered with surgery after VTE diagnosis. However the results of the study are largely the same with and without inclusion of this population.

ANALYSIS

Analysis was performed by RHW with assistance from MDS and James Dziura, PhD., biostatistician. Data from the Microsoft Access database were imported into Excel files and into Statistical Package for the Social Sciences (SPSS) version 17.0 for analysis.

First, for the cases, an analysis of VTEs was undertaken, including number, location, and outcome, specifically, length of stay, mortality, and complications. Furthermore, the NICU population as a whole (cases and controls) was described using the following variables:

1. General descriptive data, including: incidence of underlying pre-existing medical problems, age, height, weight, BMI, days admitted to the hospital and NICU, and Glascow Coma Score (GCS). Using kurtosis as a measure of normality of distribution, those variables with kurtosis < +/- 1.00 were described with mean +/- SD and those variables with kurtosis > +/- 1.00 were described using median with quartiles. Chi-squared was used to describe race, smoking status and alcohol consumption.
2. Primary diagnosis- number and percentage of each diagnosis was calculated.
3. Use of central venous catheters or PICC lines– number and percentage of each type of central venous catheter was calculated,
4. Use of ultrasounds and Computerized Tomography Pulmonary Angiograms.

To evaluate the relationship between number of scans and yield over time Spearman Correlation tests were used. Using Epi Info Version 3.5.1 (CDC), chi square for trend was calculated to measure case rate according to year.

5. Administration of prophylaxis, and type – number and percentage of thromboprophylaxis techniques were described
6. Outcomes – to compare lengths of NICU and hospital stays, Mann-Whitney U tests were performed. Number of deaths, and complications were also given.

Second, to measure differences between cases and controls, and identify potential risk factors for VTE, binary logistic regression was used. Initially, univariate screening with binary logistic regression, including calculation of p-values and odds ratios with 95% confidence intervals, was performed on 50 potential risk factors. A multivariable logistic regression model was created in order to identify variable(s) showing an independent association with VTE. To be eligible for entry into the multivariable analysis, factors had to meet the following criteria: 1) $p<0.05$ and clinically useful on univariate analysis, To be considered "clinically useful," a variable found to be significant on univariate analysis had to be present upon admission to the NICU or represent an intervention occurring during the NICU stay but before detection of VTE. Goodness-of-fit was assessed using the Hosmer – Lemeshow test. All statistical analyses were performed using two-tailed testing with a p-value <0.05 taken as a threshold to indicate statistical significance.

RESULTS

General Descriptive Results

1,318 patients were admitted to the NICU for three or more days on the neurology or neurosurgical services at Yale New-Haven Hospital between January 1, 2001 and December 31, 2005. Of the 1,318, 125 cases (9.5%) had DVT, PE, or both.

Characteristics of the Study Population

Characteristics of the study population are summarized in Table 6, below.

Table 6: Characteristics of the Study Population

Characteristic	Number of Cases (N=125)	Number of Controls (N=250)
Race		
Caucasian, %	97, (77.6%)	197, (78.8%)
African-American, %	14, (11.2%)	31, (12.4%)
Hispanic, %	13, (10.4%)	17, (6.8%)
Asian, %	1, (0.8%)	3, (1.2%)
Other Race, %	0	2, (0.8%)
GCS (median, IQR)	11 (6-14)	13 (6-15)
General Characteristics		
Height (mean +/- SD), cm	171.6 (+/- 10.9) cm	168.3 (+/-10.8) cm
Weight (mean +/- SD), kg	85.0 (+/-24.4) kg	77.1 (+/-19.6) kg
BMI (mean +/- SD), kg/(m^2)	28.7 (+/-7.6) kg/(m^2)	27.2 (+/-6.4) kg/(m^2)
Age (mean +/- SD) years	55.2 (+/-16.9) years	54.2 (+/-18.5) years
Gender (N female), %	56 (44.8%)	141 (56.4%)
Never Smoker, %	47 (37.6%)	129 (51.6%)
Former Smoker, %	18 (14.4%)	33 (13.2%)
Current Smoker, %	31 (24.8%)	72 (28.8%)
No EtOH, %	49 (39.2%)	130 (52.0%)

Social/Occasional EtOH, %	34 (27.2%)	62 (24.8%)
Abusing/Excessive EtOH, %	14 (11.2%)	40 (16.0%)
Diagnoses		
Subarachnoid hemorrhage	48 (38.4%)	77 (30.8%)
Plegia/Paresis	43 (34.4%)	48 (19.2%)
Cerebral aneurysm	31 (24.8%)	65 (26.0%)
Intracerebral hemorrhage	30 (24.0%)	31 (12.4%)
Brain Tumor	17 (13.6)	40 (16.0%)
Other*	13 (10.4%)	39 (15.6%)
Subdural hemorrhage	13 (10.4%)	28 (11.2%)
Thrombotic stroke	8 (6.4%)	13 (5.2%)
Spinal Cord Injury	3 (2.4%)	15 (6.0%)
Ateriovenous Malformation (AVM)	9 (7.2%)	7 (2.8%)
C-spine fracture	4 (3.2%)	9 (3.6%)
Traumatic Brain Injury	5 (4.0%)	4 (1.6%)
Hydrocephalus	3 (2.4%)	9 (3.6%)
Skull Fracture	4 (3.2%)	6 (2.4%)
Epilepsy	4 (3.2%)	6 (2.4%)
Medical History		
Atrial Fibrillation, %	12 (9.6%)	21 (8.4%)
Prosthetic Valves, %	1 (0.8%)	4 (1.6%)

Cardiomyopathy, %	4 (3.2%)	1 (0.4%)
History of MI, %	6 (4.8%)	2 (0.8%)
Hypertension, %	38 (30.4%)	97 (38.8%)
Leg Fracture, %	1 (0.8%)	8 (3.2%)
Prior VTE, %	9 (7.2%)	4 (1.6%)
Malignancy, %	15 (12.0%)	39 (15.6%)
Metastases, %	5 (4.0%)	14 (5.6%)
Home Medications		
Aspirin, %	10 (8.0%)	32 (12.8%)
Coumadin, %	10 (8.0%)	11 (4.4%)
Plavix, %	4 (3.2%)	4 (1.6%)
NICU Interventions		
Mechanical Ventilation, %	102 (81.6%)	144 (57.6%)
Sedation, %	56 (44.8%)	74 (29.6%)
Paralytics, %	8 (6.4%)	12 (4.8%)
Bed Rest, %	120 (96.0%)	236 (94.4%)
Tracheotomy, %	16 (12.8%)	123 (9.2%)
Central Venous Catheter, %	91 (77.6%)	124 (49.6%)

Surgery

469 total surgeries were performed on 320 total cases and controls (84.7%), of which 46.5% involved craniotomies and 4.7% involved burr holes. 71.0% used intraoperative VTE prophylaxis, usually in the form of SCDs. Failure to use

intraoperative prophylaxis was not significantly associated with VTE (OR: 0.8, CI: 0.5 – 1.1, p=0.169). Table 7 summarizes the surgeries performed on the population (cases and controls).

Table 7: Frequency of Surgery Types

Type of Surgery	Frequency	Percent of Surgeries
Other*	180	38.4%
Vascular Surgery	110	23.5%
Evacuation of blood	70	14.9%
Tumor removal	52	11.1%
Shunt insertion	35	7.5%
Spinal surgery	19	4.1%
Total	469	100%

*Other surgery includes tracheotomy, cranial reconstruction, wound debridement, ventriculostomy, pacemaker insertion, open reduction internal fixation of long bones, abscess drainage, and grid strip placement and removal

Incidence

Of the 125 VTE cases discovered, 104 were DVTs: 67 upper (64.4%), 54 lower (51.9%), 17 both (16.3%). Of the 104 DVT cases, 77 were DVT only (74.0%), and 27 were both DVT and PE (26.0%). There were 48 PEs (38.4% of cases) of which 21 were PE only (16.8% of cases). Table 8 contains a summary of VTE prevalence.

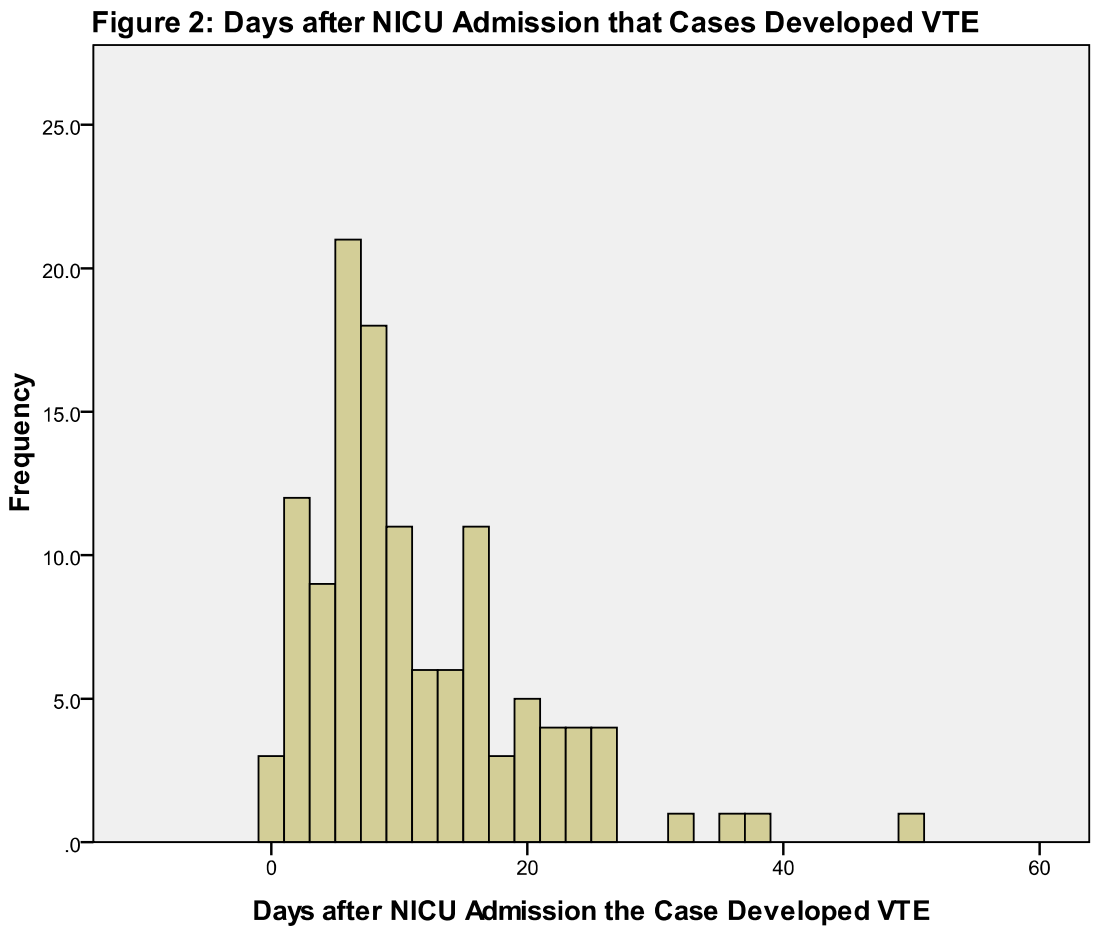
Of the cases of PE, 11 of the 48 (22.9%) had demonstrated lower extremity DVTs either prior to, or at the time of PE discovery.[2] Further, 9 of the PEs (18.8%) had UEDVTs, 8 (16.7%) had both upper and lower extremity DVTs, and 20 (41.7%) had no identified DVT, despite a verified PE.

Table 8: Summary of VTE Occurrence

Type of VTE	Number of Cases
VTE	125
DVT Total	104
DVT only	77
PE only	21
DVT and PE	27
UEDVT only	50
LEDVT only	37
UEDVT and LEDVT	17

Figure 2 describes how soon after NICU admission, patients were diagnosed with VTE. The median length was 8 days (IQR: 4 – 15 days).

[2] Occasionally DVT was discovered several days after initial PE and this was counted as a potential source of the PE if no other DVT was discovered at the time of PE diagnosis.



Cephalic Thromboses

42 patients had cephalic clots. Cephalic clots qualify as superficial thrombophlebitis, also known as superficial vein thrombosis, and therefore those patients with cephalic clots only, were not considered cases or included for further analysis. 19 patients with cephalic clots never developed VTE. However, 16 patients who were positive for cephalic clot only, initially, were subsequently shown to have true UEDVT. 7 patients with cephalic clot initially, were subsequently shown to have PE. This suggests that cephalic thromboses may, in fact, propagate and embolize to become VTE.

Use of Imaging

44 of the 48 PEs were diagnosed by CTA, and four by V/Q scan. There were 27 imaging episodes for PE that were negative, resulting in a 63.2% yield (48 positive scans/76 total scans). There were 625 total lower extremity Doppler ultrasounds (DUS) with 122 positive results, a yield of 19.5% (122/625).[3] There were 207 total upper extremity DUS, with 169 positive results, a yield of 81.6%.

To evaluate screening practices, the number of ultrasounds was further investigated. The median number of ultrasounds per patient was 1 scan (IQR: 0-2). Cases received a median of 2 (IQR: 1-3) scans per patient and controls received 1 (IQR: 0-2) scan per patient. The median number of ultrasounds per patient per week for the entire population was 0.44 scans (IQR 0.00 – 0.78). Cases received a median of 0.45 (IQR: 0.22 – 0.71) scans/patient/week while controls received 0.41 (IQR: 0.00 – 0.78) scans/pt/week (p=0.063). That is, cases received more ultrasounds per patient and per patient per week, compared to controls. 142 of the 250 controls (56.3%) received at least one scan during their NICU stay, which means nearly 40% of controls were not evaluated for VTE.

Hospital Year

In the entire NICU patient population (N=1,318), the percentage of patients diagnosed with VTE was highest in 2004 (14.1%) and lowest in 2001 (5.7%). The percent of NICU patients diagnosed with VTE increased over the years of the study (Chi-Square for trend, p=0.009) (Table 9).

[3] This includes repeat ultrasounds after the initial DVT was discovered.

In the study population (restricted to those entered into the case-control study, N=375), the number of ultrasounds increased annually from 2001 to 2005 **(Spearman's rho= 0.900, p=0.037)**. From 2001 to 2005, there was a trend towards a lower rate of DVT diagnosed on ultrasounds performed **(Chi-Square for trend, p=0.06)** (Table 10). The rate of ultrasounds positive for DVT was negatively correlated with the number performed each year **(Spearman's rho=-0.900, p=0.037)**, suggesting the possibility that more ultrasounds were being done for routine screening, rather than due to the presence of clinical symptoms. At the same time, in any given year, the number of ultrasounds correlated with the number of DVTs discovered **(Spearman's rho=1.000, p=0.01)**, suggesting that the apparent prevalence in any given year might be related, at least partially, to the number of scans performed.

Table 9: Incidence of VTE Cases per Year

Year	Total Number of Patients Per Year (N=1,318)	Number of VTE Cases (N=125)	Percentage of Admissions
2001	229	13	5.7%
2002	272	19	7.0%
2003	245	25	10.2%
2004	271	38	14.1%
2005	301	30	10.0%

Table 10: Ultrasounds and Yield per Year

Year	Number of Cases per Year	Number of Ultrasounds on the Study Population (N=375)	Yield (Number of Cases per year/Number of Ultrasounds per Year)
2001	13	66	19.7%
2002	19	97	19.6%
2003	25	158	15.8%
2004	38	280	13.6%
2005	30	229	13.1%

Thromboprophylaxis

97.6% of patients received some kind of VTE prophylaxis. Only two controls and seven cases did not receive prophylaxis. That is, 99.2% of controls and 94.4% of cases received some kind of VTE prophylaxis. Cases were less likely to receive thromboprophylaxis compared to controls. Thromboprophylaxis was significantly protective against VTE development (**OR: 0.2, CI: 0.0 – 0.8. p=0.025**). Use of an increasing number of thromboprophylaxis modalities (heparin bid, heparin tid, SCDs, or Lovenox) employed during NICU stay, was protective against VTE (**OR: 0.6, CI: 0.4 – 0.9, p=0.025**). 67.1% of patients received two forms of thromboprophylaxis, while

30.2% received one. Table 11 summarizes the percentage of patients receiving prophylaxis.

Table 11: Thromboprophylaxis Received

Type of Thromboprophylaxis Received	Number of Cases (N=125)	Number of Controls (N=250)	P-value
Heparin bid, %	77 (61.6%)	173 (69.2%)	0.395
Heparin tid, %	3 (2.4%)	13 (5.2%)	0.216
Lovenox, %	3 (2.4%)	3 (1.2%)	0.386
Mechanical Compression Devices, %	111 (88.8%)	235 (94.0%)	0.621

Treatment of VTE

Treatment for DVT was generally insertion of an IVC filter, or IV unfractionated heparin, or both. Of the 125 cases, 67 received an IVC filter (53.6%). Further, 38 cases received IV unfractionated heparin (30.4%) for VTE treatment, 16 (12.8%) received both IV UFH and IVC filter.

Morbidity and Mortality

There was a trend towards increased mortality among patients with VTE. Only one death was related to PE, perhaps due to the paucity of autopsies and the difficulty determining cause of death from the charts. Patients with VTE spent more time in both the hospital and NICU.

There were two cases of heparin-induced thrombocytopenia (HIT), both in patients VTE receiving unfractionated IV heparin for VTE treatment. Neither of the

patients who experienced HIT died as a result. None of the patients given anticoagulation for VTE had a significant bleed as a result. The median NICU stay of cases after VTE diagnosis was 8 (IQR: 2-16) days. The length of NICU stay after VTE diagnosis in cases compared to total length of NICU stay of controls, was not significantly different (OR: 0.997, CI: 0.987 – 1.007, p=0.568). The median hospital stay of cases after VTE diagnosis was 17 (IQR: 9-28.75) days. The length of hospital stay after VTE diagnosis in cases compared to total length of hospital stay of controls, was not significantly different (OR: 1.008, CI: 0.999 – 1.017, p=0.087). This indicates that the increased length of stay may not be due to the presence of VTE. Table 12 summarizes the morbidity and mortality associated with VTE.

Table 12: Morbidity and Mortality Associated with VTE

Outcome	Cases (N=125)	Controls (N=250)	OR (95% CI)	P-value
Length of NICU Stay (median, IQR), days	18.5 (10-30) days	6 (4-11) days	1.024 (1.01 – 1.04)	0.005
Length of Hospital Stay (median, IQR), days	31 (16.5 – 46) days	13 (8-19) days	1.02 (1.01 – 1.03)	<0.001
Death, %	19 (15.1%)	22 (8.7%)	OR: 1.9 (1.0 – 3.6)	0.060

NICU Population and Potential Risk Factors: Univariate Analysis

Tables 13 – 18 describe the demographic and clinical features of the study population (125 cases, 250 controls) and their association with VTE.

Table 13: Race of the NICU Population and Association with VTE

Race	OR (95% CI)	P-value
Caucasian, %	0.9 (0.6 – 1.6)	0.790
African-American, %	0.9 (0.5 – 1.7)	0.736
Hispanic, %	1.6 (0.7 – 3.4)	0.229
Asian, %	0.66 (0.07 – 6.45)	0.724
Other Race, %	0.000 (0.000 - *)	0.999

General Characteristics

Table 14 summarizes the general characteristics of the study population. Cases were less likely to be female (**OR: 0.6, CI: 0.4 – 1.0, p=0.034**). Cases were also taller and heavier than controls. Specifically, height (**OR: 1.03 per cm, CI: 1.01 – 1.05, p=0.010**) and weight (**OR: 1.0 per kg, CI: 1.01 – 1.03, p=0.002**) were both significantly associated with VTE, although BMI was not. Of note, BMI could not be calculated for all patients because height, weight, or both were unknown, so the missing data may have contributed to lower statistical power. Plegia on admission to the NICU was significantly associated with VTE (**OR: 2.2, CI: 1.4 – 3.6, p=0.001**), but GCS and age were not.

Table 14: NICU characteristics

Characteristic/Variable	Odds Ratio (95% CI)	P-value
GCS	0.96 (0.92– 1.01)	0.119
Height	**1.03 per cm(1.01 – 1.05)**	**0.010**

Characteristic/Variable	Odds Ratio (95% CI)	P-value
Weight	**1.0 per kg (1.01– 1.03)**	**0.002**
BMI	1.033 per kg/(m^2) (0.999 – 1.067)	0.055
Age	1.0 per year (0.99 – 1.02)	0.613
Gender (female)	**0.6 (0.4 – 1.0)**	**0.034**
Never Smoker	0.8 (0.5 – 1.3)	0.308
Former Smoker	1.4 (0.7 – 2.6)	0.290
Current Smoker	1.1 (0.6 – 1.8)	0.786
No EtOH	0.8 (0.5 – 1.3)	0.360
Social/Occasional EtOH	1.5 (0.9 – 2.5)	0.131
Abusing/Excessive EtOH	0.8 (0.4 – 1.6)	0.531

Diagnoses

The most common diagnosis in the NICU study population was subarachnoid hemorrhage (33.3%). See Table 15 for a summary of the most common NICU diagnoses and their prevalence.

A diagnosis of intracerebral hemorrhage or arteriovenous malformation (AVM) was associated with VTE on univariate analysis. No other neurological or neurosurgical diagnosis was associated with VTE, as shown in Table 15.

Table 15: Neurological Diagnoses and Association with VTE

Diagnosis	Odds Ratio (95% CI)	P-value
Subarachnoid hemorrhage	0.1 (0.9 – 2.2)	0.142

Diagnosis	Odds Ratio (95% CI)	P-value
Plegia/Paresis	**2.2 (1.4 – 3.6)**	**0.001**
Cerebral aneurysm	0.9 (0.6 – 1.6)	0.835
Intracerebral hemorrhage	**2.3 (1.3 – 3.9)**	**0.004**
Brain Tumor	0.8 (0.5 - 1.5)	0.562
Other*	0.6 (0.3 – 1.2)	0.181
Subdural hemorrhage	0.9 (0.5 – 1.9)	0.835
Thrombotic stroke	1.3 (0.5 – 3.1)	0.621
Spinal Cord Injury	0.4 (0.1 - 1.4)	0.141
Ateriovenous Malformation (AVM)	**4.8 (1.5 – 16.0)**	**0.010**
C-spine fracture	0.9 (0.3 – 3.0)	0.853
Traumatic Brain Injury	1.5 (0.5 – 4.7)	0.527
Hydrocephalus	0.7 (0.2 – 2.5)	0.545
Skull Fracture	1.4 (0.4 – 4.9)	0.642
Epilepsy	1.4 (0.4 – 4.9)	0.642

* “Other” diagnoses included epidural hematoma, carotid artery occlusion, CNS vasculitis, hypoxic brain injury, carotid blowout, brain abscess, headache, meningitis, pancerebellar dysfunction, myasthenia gravis, venous sinus thrombosis, transverse myelitis, shunt malfunction, to encephalitis, gunshot wound to the head and Guillan-Barre Syndrome.

Medical History

A variety of medical conditions were included in the univariate analysis and the results are summarized in Table 16.

Table 16: Medical History and Association with VTE

Characteristic	OR (95% CI)	P-value
Atrial Fibrillation	1.2 (0.6 – 2.5)	0.682
Prosthetic Valves	0.5 (0.1 – 4.5)	0.537
Cardiomyopathy	8.3 (0.9 – 75.1)	0.060
History of MI	**6.3 (1.3 – 31.7)**	**0.025**
Hypertension	0.7 (0.4 – 1.1)	0.123
Leg Fracture	0.2 (0.0 – 2.0)	0.188
Prior VTE	**4.8 (1.5 – 16.0)**	**0.010**
Malignancy	0.7 (0.4 – 1.4)	0.365
Metastases	0.7 (0.2 – 2.0)	0.518
Chronic Renal Insufficiency	1.4 (0.4 – 4.9)	0.642

History of myocardial infarction (MI) and prior VTE were significantly associated with VTE.

Several home medications were evaluated as potential risk factors and the results are summarized in Table 17. None of the medications had were associated with VTE

Table 17: Home Medications and VTE Association

Medication	OR (95% CI)	P-value
Aspirin	0.6 (0.3 – 1.3)	0.176
Coumadin	1.9 (0.8 – 4.6)	0.153

Medication	OR (95% CI)	P-value
Plavix	2.0 (0.5 – 8.4)	0.316
Heparin	0.5 (0.1 – 4.5)	0.537

Potential Risk Factors – In Hospital

A number of in-hospital potential risk factors were investigated for association with VTE and the results are summarized in Table 18.

Table 18: In-Hospital Interventions and Association with VTE

Intervention	OR (95% CI)	P-value
Central Venous Catheter	**3.5 (2.2 – 5.7)**	**<0.001**
Mechanical Ventilation	**3.4 (2.0 – 5.8)**	**<0.001**
Sedation	**2.0 (1.3 – 3.1)**	**0.003**
Bed Rest	1.8 (0.5 – 5.5)	0.319
Tracheotomy	1.5 (0.7 – 2.9)	0.272
Paralytics	1.4 (0.5 – 3.4)	0.505

Both mechanical ventilation and sedation were significantly associated with VTE. However, use of paralytics, tracheotomy and bed rest were not associated with VTE.

Central-Venous Catheters

415 central-venous catheters, including PICC lines, were inserted. Cases were more likely to have a catheter than controls**.** Catheter placement appeared to be associated with both upper, (**OR: 2.4 CI: 1.3 – 4.3, p=0.004**) and lower (**OR: 4.8 CI: 2.2 – 10.5, p=0.000**) DVTs. See Table 19 for a summary of catheter site frequencies and association with VTE. 30 patients with VTE had a central-venous catheter on the same side as the clot prior to VTE diagnosis.

Table 19: Frequencies of Catheter Sites – Population as a Whole, and Association with VTE

Catheter site	Frequency	Percentage of Total Catheters	OR (95% CI)	P-value
Any Catheter	**417**	**100.0%**	**3.5 (2.2 – 5.7)**	**<0.001**
Femoral	**29**	**7.0%**	**9.557 (2.7 – 34.2)**	**0.001**
Internal Jugular	26	6.3%	2.3 (1.0 – 5.6)	0.063
PICC	**102**	**24.6%**	**1.9 (1.1 – 3.2)**	**0.023**
Subclavian	**257**	**61.9%**	**1.7 (1.1 – 2.6)**	**0.019**

Subclavian catheters (OR: 1.2, CI: 0.7 – 2.0, p=0.525) and PICC lines (OR: 1.5, CI: 0.8 – 2.8, p=0.258) were not significantly associated with UEDVT. However IJ catheters (**OR: 3.1, CI: 1.2 – 7.8, p=0.017**) were significantly associated with UEDVT. Femoral central-venous catheters were strongly associated with LEDVT (**OR: 11.9, CI: 4.1 – 34.4, p=0.000**).

Univariate Analysis: Summary of Positive Results:

We identified 12 variables associated with VTE. They are summarized in Table 20, below.

Table 20: Factors associated with VTE on Univariate Analysis

Variable	Odds Ratio (95% Confidence Interval)	P-value
History of MI	6.3 (1.3 – 31.7)	0.025
Prior VTE	4.8 (1.5 – 16.0)	0.010
AVM	4.8 (1.5 – 16.0)	0.010

Central Venous Catheter	3.5 (2.2 – 5.7)	<0.001
Mechanical ventilation	3.4 (2.0 – 5.8)	<0.001
Intracerebral hemorrhage	2.3 (1.3 – 3.9)	0.004
Plegia/paresis	2.2 (1.4 – 3.6)	0.001
Sedation	2.0 (1.3 – 3.1)	0.003
Height (cm)	1.03 per cm (1.01 – 1.05)	0.010
Weight (kg)	1.02 per kg (1.01 – 1.03)	0.002
Sex (Female)	0.6 (0.4 – 1.0)	0.034
VTE prophylaxis	0.16 (0.03 – 0.80)	0.025

Multivariable Analysis

The univariate variables from Table 20 were entered into a multivariable logistic regression analysis are shown in Table 21. Of note, individual catheter types were not included in multivariable analysis because they each significantly correlated with catheter use overall and we wished to investigate catheter placement itself as a risk factor. Similarly, number of prophylaxis techniques was not included in multivariable analysis because it significantly correlated with overall prophylaxis use and we chose to use the dichotomous variable because we were trying to control for presence of prophylaxis. After multivariable analysis, significant variables included: presence of a central-venous catheter (OR: 2.5, CI: 1.4 – 4.6, p=0.003), AVM (OR: 4.9, CI: 1.2 – 20.0, p=0.026), mechanical ventilation (OR: 2.1, CI: 1.1 – 4.2, p=0.036), and documented prior VTE (OR: 5.6, CI: 1.4 – 22.4 p=0.014). VTE prophylaxis was significantly protective (OR: 0.1, CI: 0.0 – 0.9, p=0.043).

Table 21: Factors Associated with VTE: Multivariable Analysis

Factor	OR (95% CI)	P-value
Documented Prior VTE	**5.6 (1.4 – 22.4)**	**0.014**
MI	5.5 (1.0 – 31.6)	0.056
AVM	**4.9 (1.2 – 20.1)**	**0.026**
Central-venous Catheter	**2.5 (1.4 – 4.6)**	**0.003**
Mechanical Ventilation	**2.1 (1.1 – 4.2)**	**0.036**
Plegia/Paresis	1.6 (0.9 – 2.8)	0.147
Intracerebral Hemorrhage	1.6 (0.8 – 3.0)	0.190
Sedation	1.2 (0.7 – 2.2)	0.474
Female Gender	1.02 (0.50 – 2.08)	0.952
Weight (kg)	1.01 per kg (1.00 – 1.02)	0.078
Height (cm)	1.01 per cm (0.98 – 1.05)	0.438
DVT Prophylaxis	**0.8 (0.0 – 0.9)**	**0.043**

To address the closely-related variables, a correlation matrix was developed, which showed significant correlation between mechanical ventilation, sedation, and ICH. Height and weight were also correlated, as were height and plegia. However, all factors were included in the multivariable analysis because we had a reasonable belief that each could be independently associated with VTE. P=0.639 on Hosmer Lemeshow indicating the model was a good fit.

DISCUSSION

Incidence

Venous thromboembolism is a common cause of in-hospital morbidity and mortality. Numerous patient subpopulations have been studied to date to investigate the incidence of, and risk factors for, VTE, in an attempt to tailor prophylaxis of VTE. However, despite the studies performed thus far, no study exists that specifically focuses on critically ill neurology and neurosurgery patients. This population's unique diagnoses and high rates of surgery and immobility theoretically put it at higher risk for VTE. However, because VTE prophylaxis is not without cost and morbidity, it was important to investigate risk factors in this unique population, so that clinicians could identify those patients at highest risk for VTE and work to prevent this potentially fatal condition.

Our findings demonstrated a NICU VTE rate of 9.5%, despite an overall thromboprophylaxis rate of 97.6%, a rate of prophylaxis higher than those of most previous studies investigating MICU and SICU populations. The VTE rate of 9.5% is lower than that of the previously-studied MICU population (33%), and consistent with previously-studied neurorehabilitation (11%) and SICU populations (13%) (10, 15, 18). The lower rate of VTE may be due to the high thromboprophylaxis rate in our population. Interestingly, the rate of VTE was significantly higher than the 4% found in a previously-studied neurosurgical population, suggesting patients requiring the ICU are, indeed, at higher risk of VTE compared to those with comparable diagnoses and surgeries on the neurosurgical floor (34). Furthermore, of patients with VTE, over 38.4% had clinically apparent PE, a rate much higher than anticipated, although consistent with estimated rates of DVT propagation between 30% – 40% (13, 26). Of course, we cannot account for

clinically silent PEs, as they are not screened for, so the true rate of PE may, in fact, be higher. Furthermore, we cannot account for clinically silent DVTs which went undiagnosed, so the true percentage of VTE resulting in PE may, in fact be higher.

In addition to a higher thromboprophylaxis rate, the rate of VTE may also be affected by possible ascertainment bias. That is, only VTE for which a diagnostic test is performed have the potential to be discovered. To explore this, we investigated the relationship between the number of scans performed per year and the number of VTE diagnosed, assuming that the true prevalence rate should not change year to year if the population characteristics and approach to prophylaxis did not change. The number of scans per year and number of VTE diagnosed both varied over the years. The number of ultrasounds was highest in 2004, the same year the number of VTE was highest. This indicates that there may be ascertainment bias – the more scans performed, the more VTE diagnosed. The yield was highest in 2001, the year with the fewest number of scans and VTE. This may indicate that more scans were performed for clinical suspicion in 2001, rather than for screening purposes, which would result in more VTE diagnosed and a lower yield.

While the number of scans per year was significantly different, the number of scans was negatively correlated with VTE diagnosis. That is, the number of VTE discovered did increase overall but the percent of positive scans decreased, indicating that ascertainment bias is less likely to be a major contributor. Also, 110 controls received no ultrasounds at all, so it is certainly possible that there were VTEs in the control group that remained undiagnosed. Furthermore, the number of scans per patient per week, did not differ significantly between cases and controls ($p=0.061$), though cases did tend to

receive more scans, on average. Of course, cases, by definition, received at least one scan, so this may bias towards more scans among cases. Finally, without a study in which screening ultrasounds are performed at regular intervals, the true rate of VTE will likely be underestimated.

Upper-Extremity DVT

One finding of particular interest was the rate of upper extremity DVT. There were 169 positive DUS for upper extremity clot out of 207 DUS performed on upper extremities – an 81.6% yield. This is likely due to the fact that upper extremity ultrasounds were primarily performed when there was clinical suspicion for DVT as opposed to routine screening. In comparison, there were 625 lower extremity DUS performed, and the yield was 19.4%. This suggests that upper extremity DVT occurs slightly more frequently (4.3% of the total population) than the previously demonstrated 1%-4% (42), and it may be prudent to include upper extremities in routine screening for DVT in NICU patients.

One statistic further supporting the importance of UEDVT diagnosis was the high rate of PE among patients with UEDVTs. There was nearly an equal number of PEs associated with UEDVTs as LEDVTs (34.7% of PEs were potentially due to UEDVT or both UEDVT and LEDVT). At least 11 out of 54 (20.4%) LEDVTs were associated with PE, and at least 9 out of 67 (13.4%) UEDVTs were associated with PE. Thus, although the rate of clinically apparent PE was higher with LEDVT, the rate with UEDVT was not insignificant

Superficial Vein Thrombosis

One other finding of particular interest was the high rate (3.2% of the total population) of cephalic vein thromboses - superficial vein thrombosis. While these thromboses are not considered DVTs, a high proportion did, in fact, extend into the deep venous system. We found that 38.1% of cephalic thromboses ultrasounds were also positive for UEDVT, suggesting that cephalic clots are of clinical significance, if only because they are strongly associated with DVT. In fact, 7 patients with "cephalic only" ultrasounds later proceeded to later develop PE. However, it is possible that some of the ultrasounds positive for both UEDVT and cephalic clots began as an UEDVT which extended into the superficial system, rather than the reverse. Therefore, further studies should be done to verify the rate of cephalic clots and their propagation into the deep venous system. Given these findings, and the fact that SVT carries a 4.32-fold increased risk for VTE, additional studies may also be needed to investigate the efficacy of treating cephalic thromboses as DVTs (29). Furthermore, additional studies investigating the rates of post-thrombotic syndrome in those patients with superficial vein thrombosis would be helpful to determine the extent of morbidity associated with cephalic thromboses.

Thromboprophylaxis

Another impressive finding was the high rate of thromboprophylaxis received by this patient population (over 97.6%). The 9.5% rate of VTE, despite the high prevalence of thromboprophylaxis, may indicate the need for more effective thromboprophylaxis techniques, and for VTE screening even while patients are receiving thromboprophylaxis. Conversely, the fact that the rate of VTE is lower than that of MICU patients, as reported

in the literature, of which only 61% received prophylaxis, may be an example of effective prophylaxis at work (15).

Also of interest is the use of multiple thromboprophylaxis techniques. The majority (66.7%) of patients received two forms of thromboprophylaxis, most commonly a combination of SCDs and subcutaneous heparin bid. Increasing number of thromboprophylaxis techniques was protective against VTE (OR: 0.6, CI: 0.4 – 0.9, p=0.013). This may be an additional reason why the rate of VTE in the NICU was lower compared to other ICU populations. Further studies may be needed to determine the efficacy and cost-effectiveness of using multiple prophylaxis techniques.

Despite a 40-fold risk reduction with use of SCDs and heparin bid demonstrated in an earlier study (36), thromboprophylaxis did not appear to be as strongly associated with VTE reduction in the NICU. However, due to the near universal use of prophylaxis, our study may not be able to accurately assess the association between SCDs, heparin bid and VTE.

Finally, after multivariable analysis, VTE prophylaxis was shown to be significantly protective against VTE. This verifies the value of VTE thromboprophylaxis in the NICU population.

Risk Factors

Four potential risk factors for VTE in NICU patients were discovered after multivariable analysis: central venous catheter, AVM, mechanical ventilation and history of prior VTE. In addition, history of MI and weight, while not statistically significant, were trended toward association with VTE. These factors may be mechanistically related to VTE, that is, the direct cause, or may simply be markers for the true cause of VTE.

Central-venous catheter use (previously demonstrated OR: 5.55, CI: 1.57 – 19.58) (29), mechanical ventilation, documented prior VTE, weight and acute MI have all been shown to be VTE risk factors in other populations (12, 13, 29, 32, 58). However, AVM has not been previously shown to be a risk factor for VTE, nor has a history of MI. Given our findings, those patients undergoing mechanical ventilation, central-venous catheter insertion, suffering from AVM, or with a history of DVT, may have an identified risk for VTE compared to other NICU patients, though these risk factors need to be individually verified. Studies investigating the efficacy of more aggressive thromboprophylaxis or screening for these patient populations are needed.

AVM was found to increase the risk for VTE in the NICU population by 4.9-fold and may be useful as an admission screening tool. To our knowledge, AVM is a previously undiscovered risk factor for VTE. The etiology of AVM as a risk factor is unknown as well. However, one might speculate that the abnormal vasculature comprising the AVM may either predispose to a localized vasculitis or release of clotting factors. Of note, there were 13 cases of AVM (3.5% of the NICU population), 3 of which had concurrent ICH. Despite the relatively uncommon nature of AVMs, the large odds ratio for AVM as a VTE risk factor argues for the clinical importance of this risk factor. Based on these findings, patients admitted to the NICU with AVM may be at higher risk for VTE. Future studies are needed to investigate whether more aggressive screening and prophylaxis would be of clinical benefit for these patients.

Central venous catheter placement has also been shown to be a risk factor for VTE in the NICU population and is a previously-demonstrated VTE risk factor in other populations. In fact, among the general population, placement of a central venous

catheter has been shown to increase the odds of VTE by 5.55 (29). Our study found that central venous catheter placement carries an odds ratio of 2.5, lower than that of previous studies. The risk is likely lower because, in a population with a higher background risk of VTE, the relative additional increase in risk from central-venous catheter, while high, is lower compared to populations without any existing risk factors for VTE. The finding that catheter placement is a risk factor for VTE in the NICU, is of great relevance because 41.1% of the NICU population received a central venous catheter, placing a large portion of this population at nearly three-times the risk of VTE.

Mechanical ventilation is a known risk factor for VTE (11). Our study demonstrates a 2.1-fold increase in VTE risk. This is of particular interest in the NICU population due to the high rate of mechanical ventilation (65.8%). Mechanical ventilation may be used as a "red flag" for VTE in the NICU and future studies are needed to investigate whether more aggressive screening and thromboprophylaxis would decrease the risk of VTE in patients undergoing mechanical ventilation.

Prior VTE is a known risk factor for VTE. While patients with known history of VTE would theoretically be well screened and appropriately prophylaxed, it was important to verify this as a risk factor for VTE in the NICU population. There were only 13 patients (3.5% of the population) with known history of VTE. Therefore, while the frequency of patients with this condition is low, the utility as a screening factor is not, due to the high associated OR (5.6). In fact, patients with prior VTE had the greatest increased risk of VTE after multivariable analysis.

Acute myocardial infarction is a known risk factor for VTE and, in fact, 33% of patients not receiving thromboprophylaxis after acute MI developed VTE (59).

Interestingly, debate exists over whether common risk factors for cardiovascular disease, including hypertension and dyslipidemia, are also risk factors for VTE. A 2002 study showed no association of cardiac risk factors with VTE, while a recent, 2008 study, did (60, 61). However, history of myocardial infarction has not previously been demonstrated to be a risk factor for VTE. History of MI was shown to be trending toward association with VTE, in the NICU population, though not statistically significant ($p=0.056$). History of MI, though rare (2.1%) is a useful screening tool, since this past medical history should be known upon admission to the NICU.

Weight, another previously-known VTE risk factor, was also shown to be trending towards association with VTE, though not statistically significant ($p=0.078$). The OR of 1.01 per kg indicates that the increased risk of VTE is incrementally small per kg. Further studies are needed to more specifically determine if there is a weight at which the risk of VTE rises to the level of requiring more aggressive screening and prophylaxis.

Morbidity/Mortality

VTE was significantly associated with longer median NICU stays (18.5 days [IQR: 10 – 30] vs. 6 days [IQR: 4 – 11], $p=0.004$) and hospital stays (31 days [IQR: 16.5 – 46] vs. 13 days [IQR: 8 – 19], $p<0.001$.) Interestingly, while there was a higher rate of overall mortality associated with VTE (15.1% of cases vs. 8.7% of controls, $p=0.060$), and VTE was correlated with a 1.9-fold increase in death, there was only one death attributable to PE. This low rate of death attributable to PE may have been due to difficulty determining cause of death from the charts and the low rate of autopsies performed. However, patients with VTE may have been sicker than controls, and

therefore, VTE may be a marker for patients at increased risk for death. The fact that VTE was not significantly associated with death on multivariable analysis indicates that VTE may simply be a marker for increased risk of death, rather than an actual risk factor.

The rates of heparin-induced thrombocytopenia (HIT) and bleeding were both very low, and, while there were two cases of HIT among the cases, there were no episodes of serious bleeding among cases. Presumably the rates of bleeding were so low because patients at risk for hemorrhage had IVC filters placed rather than being anticoagulated. However, this hypothesis would require further investigation. None of the patients with either HIT or serious bleeding died during their hospitalization.

STRENGTHS OF THE STUDY

This study has several important strengths. First, it is relatively large – investigating a NICU population of 1,318 patients over 5 years. A total of 375 patients were investigated in detail. The remarkably detailed data collected allowed for a more complete analysis of the NICU population as a whole and of potential risk factors. Data collection was obtained directly from the chart and did not rely on ICD-9 codes, increasing the reliability of data collection and, in particular, case identification. Furthermore, the fact that each VTE diagnosis was confirmed and all 1,318 potential patients had the veracity of their VTE status verified, improves the validity of our incidence calculations. Finally, this is the first study of the NICU population, which has a high rate of thromboprophylaxis, and several useful risk factors were identified. These risk factors, once validated, may be of great clinical utility.

LIMITATIONS

There are several limitations to our study. First, the population studied was limited to NICU patients admitted for longer than three days. Therefore, conclusions drawn from this study are limited to this specific patient population and we cannot draw any conclusions about NICU patients admitted for less than 3 days. Additionally, there were only 125 cases of VTE in this population, thus leading to wide confidence intervals and limiting our statistical power to fully investigate potential risk factors. However, our total number of cases was much greater than that of one similar previous study (15) and similar to others (31, 18).

Another potential limitation of this study is that cases and controls were matched based on whether they received surgery of any kind during their hospitalization. However, they were not matched based on length or type of surgery. In fact, upon review, there are 13 cases that received surgery after the diagnosis of VTE and therefore may not be true matches. However, upon further analysis of the dataset with those 13 cases and their respective controls removed, the statistically significant factors on univariate analysis were unchanged other than the exclusion of sex. After multivariable analysis, the significant factors remained unchanged, though history of MI was also significant and the OR for each variable was affected. This indicates that those 13 mismatched cases did not affect the ultimate conclusions regarding our above stated potential risk factors. However, further studies are needed to verify the rates of surgery and the conclusions of this study with surgery correctly controlled for, particularly the ORs.

One potential limitation to the finding of only one death attributable to PE is that official cause of death was difficult to determine in many cases. Patients generally suffered from multiple serious medical conditions, so an exact cause of death could not be determined in many cases. In such cases, those deaths were coded as not attributable to PE. Therefore, the true number of deaths attributable to PE may be higher, particularly given the higher rate of overall mortality among cases vs. controls.

Another limitation is the inability to be completely certain that all VTE were diagnosed. There is always a possibility that clinically silent VTEs occurred, which was not detected on screening. However, a large number of scans were performed, making the possibility that VTEs were missed due to a paucity of scans, less likely. However, only a study which screens for VTE at regular intervals could determine the precise incidence of VTE in this population. Additionally, it is possible that documented "prior VTE" in certain patients was still present upon NICU admission and not a new clot developed while in the NICU. Also, due to inconsistencies with recording hemorrhagic strokes, we were unable to study this known risk-factor, as a potential risk factor in the NICU population (34). Nasogastric tube and urethral catheter were nearly universal in their use in the NICU and therefore unable to be studied as potential risk factors in the NICU (35).

Limitations intrinsic to all retrospective studies must be acknowledged as well. Many of the risk factors studied were not hypothesized beforehand. Rather, we used univariate logistic regression to identify potential associations. Therefore, the risk factors determined by this study require validation. Furthermore, we did not perform a statistical adjustment for multiple comparisons, again, indicating the need for future validation.

Also, we cannot account for the potential for residual confounding by factors not included in our multivariable analysis. Finally, intrinsic to all case-control studies, we cannot test for the factors which were controlled for, mainly year and presence of surgery. While preliminary analysis shows different rates of VTE across the 5 years, future studies are needed to further investigate this trend, as well as surgical trends.

An additional limitation is that ICH, mechanical ventilation and sedation were all correlated. Each of those factors was included in the multivariable analysis despite this correlation because they still had potential to be independently associated with VTE. Therefore, future studies are needed to validate our findings after controlling for potential interactions among variables.

Finally, limitations due to the population size must be addressed. Due the relatively small patient number, many of the confidence intervals were quite wide and ORs are unstable. That is, with the addition or loss of even a few patients, the ORs may change dramatically. However, those factors with more narrow confidence intervals are more likely to be truly significant and not subject to instability based on population size. Therefore, while we can be confident in our conclusions regarding association with VTE, a larger study repeating this investigation is needed to give more precise estimates of OR. Also, due to the size of the study, we were unable to include previously-demonstrated risk factors that had $p>0.05$ into our multivariable analysis. Only those factors with $p<0.05$ on univariate analysis were included in multivariable analysis. This study does not disprove the role of those known variables as risk factors in the NICU population. Rather, they require further investigation as potential risk factors in the NICU.

IMPLICATIONS AND FUTURE DIRECTIONS

This study of VTE in the NICU population contributes to our understanding of which patients are at particular risk for VTE, which may prove helpful to clinicians caring for this population. Future investigation is needed to confirm the findings in this study. Additional studies into whether more aggressive surveillance and prophylaxis, in fact, decrease rates of VTE, are needed. Finally, further investigation into the morbidity and mortality associated with cephalic clots, is needed.

CONCLUSION

In conclusion, we found a VTE rate of 9.5% in the NICU population, despite a high rate of thromboprophylaxis. There was a trend towards increased mortality in patients with VTE and a significant increase in length of hospital and NICU stay. The study also uncovered a high rate of upper-extremity DVTs and SVTs, many of which appeared to propagate into the deep venous system. There was also a large number of PEs that was potentially due to upper-extremity DVTs. These findings, taken as a whole, argue for further investigation of more aggressive upper-extremity DVT screening and thromboprophylaxis. Further studies are also needed to investigate the potential morbidity, cost and benefits associated with treating cephalic thromboses as DVTs.

Risk factors for VTE in this patient population include central-venous catheter use, mechanical ventilation, history of VTE and diagnosis with AVM. History of MI and increasing weight were trending toward association with VTE. Future studies will need to be done to determine if patients with these factors would benefit from more intensive surveillance and prophylaxis.

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TABLES and FIGURES

Table 1 – Previously Determined Risk Factors for VTE (13, 29, 32)

Surgery
Trauma (Major or lower extremity)
Immobility
Paresis
Malignancy
Cancer therapy (chemotherapy, hormonal, radiotherapy)
Previous VTE
Increasing Age
Pregnancy and the postpartum period
Heart or Respiratory Failure
Inflammatory Bowel Disease
Smoking
Estrogen and selective estrogen receptor modulators
Nephrotic Syndrome
Obesity
Myeloproliferative Disorders
Central Venous Catheterization
Inherited or acquired thrombophilia – Factor V Leiden, Protein C or S deficiency, Antithrombin deficiency, prothrombin gene mutation

Acute medical illness
Spinal cord injury
Varicose veins

Table 2: Summary of Prior Studies Demonstrating Thromboprophylaxis Efficacy

Regimen	No. of Trials	No. of Patients	No. of Patients With DVT	Incidence, %	95% CI	Risk Reduction, %
Untreated controls[90–143]	54	4,310	1,084	25	24–27	—
Aspirin[110, 122–124, 146]	5	372	76	20	16–25	20
ES[120, 138, 141]	3	196	28	14	10–20	44
Low-dose heparin[90–92, 94, 95, 98–102, 104–111, 113, 114, 116, 117, 147–171]	47	10,339	784	8	7–8	68
LMWH[147–160, 170, 172–177]	21	9,364	595	6	6–7	76
IPC[129, 140]	2	132	4	3	1–8	88

*Pooled data from randomized trials using fibrinogen leg scanning as the primary outcome; superscript numbers are references.

Table from Reference 13, p. 137S

Table 3: Summary of Rationale for Thromboprophylaxis in Hospitalized Patients

Table 2—*Rationale for Thromboprophylaxis in Hospitalized Patients*

Rationale	Description
High prevalence of VTE	Most hospitalized patients have risk factors for VTE
	DVT is common in many hospitalized patient groups
	Hospital-acquired DVT and PE are usually clinically silent
	Difficult to predict which at-risk patients will develop symptomatic thromboembolic complications
	Screening at-risk patients using physical examination or noninvasive testing is neither effective nor cost-effective
Adverse consequences of unprevented VTE	Symptomatic DVT and PE
	Fatal PE
	Costs of investigating symptomatic patients
	Risks and costs of treating unprevented VTE, especially bleeding
	Increased future risk of recurrent VTE
	Chronic post-thrombotic syndrome
Efficacy and effectiveness of thromboprophylaxis	Thromboprophylaxis is highly efficacious at preventing DVT and proximal DVT
	Thromboprophylaxis is highly effective at preventing symptomatic VTE and fatal PE
	The prevention of DVT also prevents PE
	Cost-effectiveness of prophylaxis has repeatedly been demonstrated

Table from Reference 13 p.339S

Table 4: Meta-analysis of DVT Prevalence in Critical Care Populations Previously Studied, Not Receiving Thromboprophylaxis

Table 16—*Prospective Studies of DVT Rates in Critical Care Patients Not Receiving Prophylaxis*

Study/Year	Type of ICU patient	Method of Diagnosis	No.	DVT Prevalence, %
Moser et al[755]/1981	Respiratory ICU	FUT	33	13
Cade[688]/1982	General ICU	FUT	Approximately 60	29
Goldberg et al[752]/1996	Respiratory failure	Proximal DUS	16	19
Kapoor et al[756]/1999	Medical ICU	Serial DUS	390	31
Fraisse et al[754]/2000	Ventilated COPD	Venography	85	28

Table from Reference 13 p.373S

Table 5: DVT Prevalence Among Previously Studied Populations

Table 4—*Absolute Risk of DVT in Hospitalized Patients

Patient Group	DVT Prevalence, %
Medical patients	10–20
General surgery	15–40
Major gynecologic surgery	15–40
Major urologic surgery	15–40
Neurosurgery	15–40
Stroke	20–50
Hip or knee arthroplasty, hip fracture surgery	40–60
Major trauma	40–80
Spinal cord injury	60–80
Critical care patients	10–80

*Rates based on objective diagnostic testing for DVT in patients not receiving thromboprophylaxis.

Table from Reference 13 p.340S

FIGURE 1

Data Collection Form: NICU study of DVT/PE[4]

Demographics:

- MRN: _____
- Date of hospital admission: _____
- Date of hospital discharge: _____
- Date of NICU admission: _____
- Date of NICU discharge: _____
- Date of birth: _____
- Sex (circle): M / F
- Race (circle): White Black Hispanic Asian Other
- Height (cm): _____

[4] See Appendix 1 for sources used for data collection, as well as, definitions and rules for each data piece.

- Weight (kg): _____

Status Upon NICU Admission

- Primary Diagnosis upon admission to NICU: (circle)
  - Stroke: Thrombotic Hemorrhagic
  - Brain Tumor
  - Spinal Cord Injury
  - Hemorrhage: Subdural Subarachnoid Intracranial
  - Hydrocephalus
  - Cerebral aneurysm
  - Pharmacologically resistant epilepsy
  - Other (specify): _____
- Neuro exam results upon admission to NICU:
  - GCS:
  - Plegia/paresis (circle): Paraplegic Quadraplegic
  - Limb side (circle): Left Right

Medical History:

(As documented upon NICU admission. Circle any applicable conditions)

- Cardiac: Atrial fib. Prosthetic valve(s) Myocardial infarct. Cardiomyopathy
- Nephrotic Syndrome
- Leg fracture (in a cast/on crutches/ immobilized)
- Smoking status: Current Former Never
- Alcohol intake:
  - No EtOH Non-abusing level
  - EtOH (social or one drink per day)
  - Abusing/excessive level EtOH (larger quantity recorded or “alcoholic”)
- Documented prior DVT or PE:

DVT Date of DVT diagnosis: _____

PE Date of PE diagnosis: _____

Actively being treated at time of NICU admission? YES NO

Filter: YES NO

- Malignancy (w/in 12 mos, other than non-melanoma skin cancer: YES NO

  Metastatic: YES NO

- Hypercoagulability state: YES NO

  (Includes: Factor V Leiden, Antiphospholipid Antibody Syndrome, Factor S deficiency, Factor C deficiency, Heparin-induced thrombocytopenia syndrome, Mutation in methyltetrahydrofolate gene, Prothrombin mutation, Hyperhomocystenemia, Antithrombin III deficiency)

- Pregnant (currently): YES NO

Current Medications/Drugs upon NICU admission (circle):

Estrogen (HRT) Birth Control

Coumadin Heparin Plavix Aspirin

Other related drugs (specify): _____

Procedures/Conditions During Nicu Stay (including 3 days prior)

Post-NICU admission meds (circle):

- Estrogen (HRT) Birth control
- SQ heparin 5000 bid SQ heparin 5000 tid
- Lovenox 30 mg/d (LMWH) Clopidogrel/Plavix
- Aspirin 324 mg/d
- Mechanical device
- Other related anticoagulants_____

- **Bed Rest –** assumed unless documented as ambulatory**:** YES NO
- **Mechanical Ventilation** (within 3 days prior to NICU admission or any time during NICU stay):

  - YES NO
  - date of first ventilation day in NICU:_____

    defined as a day where the patient is ventilated for more than 3 hours for reasons other than surgery

(only the first time if there were periods without ventilation)

- date of last ventilation day in NICU:_____

(the very last time if there were periods without ventilation)

- **Intubation** (if length of time between multiple intubations is <48 hours, count as one intubation episode)
  - date of insertion _____
  - date of removal _____
- **Sedation – continuous infusions only** (record dates of start/finish)
  - Fentanyl: start:_____ finish:_____
  - Morphine: start:_____ finish:_____
  - lorazepam (Ativan): start:_____ finish:_____
  - midazolam (Versed) start:_____ finish:_____
  - propofol (Diprivan) start:_____ finish:_____
  - Other:_____ start:_____ finish:_____
- **Paralytics:** (record dates of start/finish):
  - YES NO
  - Start date:_____
  - Finish date :_____
- **Catheters:**
  - groin catheter #: _____ LEFT RIGHT
    - dates: insertion _____ removal _____
  - subclavian #: _____ LEFT RIGHT
    - dates: insertion _____ removal _____
  - IJ line #: _____ LEFT RIGHT
    - Dates: insertion _____ removal _____
- **Tracheostomy:** YES NO
  - **Date:**_____
- **Blood transfusion during stay:** YES NO

- **Urethral catheter:** YES NO
    - Dates: insertion _____ removal_____
- **Feeding tube:** YES NO
    - Dates: insertion_____removal _____

Surgery

- **Surgery:** *Y / N*
    - Date: _____
    - Length to the minute:_____
    - Type (circle):

      Tumor removal Evacuation of blood Shunt insertion

      Vascular surgery (aneurysm/AVMs etc) Other:_____
    - Craniotomy: YES NO
- **Prophylaxis: type/dosage used intraoperatively** (circle):
    - SQ heparin 5000 bid
    - SQ heparin 5000 tid
    - Lovenox 30 mg/d (LMWH)
    - Clopidogrel/Plavix
    - Aspirin 324 mg/d
    - Mechanical Device
    - Other

DVT Diagnosis

- **Date of DVT diagnosis:_____**
- **Date of PE diagnosis (if applicable):_____**

  (including within two days of discharge from NICU)
- **Test(s) used to diagnose:** (circle and fill in date of every test):
    - DUS POS NEG
        - Date_____
    - V/Q POS NEG

- Date_____

- Pulmonary angiography POS NEG
  - Date_____

- Venography POS NEG
  - Date_____

- CT angiography POS NEG
  - Date_____

- Other Date_____

- **Why the test was done** (circle):
  - routine (e.g., biweekly, standing order test)
  - clinical suspicion (e.g., special doctor's order due to presence of S/S

- **Ambulatory status upon diagnosis** (assumed immobile unless documented as ambulatory) (circle):

  Ambulatory NOT ambulatory

- **Prophylaxis in use prior to diagnosis** (type, dose, frequency, route):
  - SQ heparin 5000 bid
  - SQ heparin 5000 tid
  - Lovenox 30 mg/d (LMWH)
  - Clopidogrel/Plavix
  - Aspirin 324 mg/d
  - Mechanical

- **Mechanical prophylaxis prior to diagnosis** (include dates initiated/discontinued if more than 3 hours per day):
  - Intermittent external pneumatic calf compression (IPC)/Venodyne boots dates: start

    _____ finish _____
  - Graduated compression stockings/TED stockings

    dates: start _____ finish _____
  - Electrical stimulation of calf muscles

    dates: start _____ finish _____
  - Rotating tables

dates: start _____ finish _____

- **Location of DVT if documented** (circle):
  - LEFT RIGHT

    proximal lower limb distal lower limb

    proximal upper limb distal upper limb

- **Presence of PE at time of DVT diagnosis:** YES NO

(based on concurrent diagnosis)

- **Presence of and type of associated symptoms at time of diagnosis (circle if applicable):**
  - palpable cords: Left Right
  - swelling Left Right
  - redness Left Right
  - warmth Left Right
  - pain Left Right

DVT TREATMENT UPON DIAGNOSIS (CIRCLE ALL APPLICABLE):

- **IVC filter:** Date of insertion: **_____**

- **Pharmacological:** circle dose/freq/route
  - Date initiated: _____
  - IV unfractionated heparin
  - SQ LMWH
  - Coumadin
  - Other

- **Radiological intervention**
  - Date_____
  - Type_____

COMPLICATIONS/NEGATIVE OUTCOMES: circle any applicable

- **Pulmonary embolism:**
  - date of diagnosis_____
  - test used to diagnose_____

- treatment_____

- **Bleeding** (defined as hemorrhage requiring a blood transfusion or intracranial hemorrhage as demonstrated by change in neuro exam and supported by CT scan)
  - date diagnosed:_____
  - transfusion required: *YES* *NO*
- **Venous ulceration**
  - Date diagnosed:_____
  - Limb: L R
- **Death**
  - Date of death (must be within 3 days of d/c):_____
  - Related to the PE?: YES NO

  (Record all deaths in the time frame so can report percentage of deaths attributed to DVT/PE)

APPENDIX 1

Specific information gathered and rules for each data piece (source of information, definition of positive result) are contained below:

Demographics:

- MRN: Excel file.
- DOB: SCM Patient info section or from paper chart.
- Hospital admission/discharge dates: Excel file.
- NICU dates: Dates of first and last acute care flow sheets, provided stay was three days or longer. (If there was a break between 3+ day stays, entered the very first day and the very last day.) If there was any indication in progress notes or discharge summary that part of hospital stay was in a non-neuro ICU, the progress notes were thoroughly reviewed so that the accurate NICU-specific flow sheets were reviewed.
- Race and Gender: SCM
- Height (inches) /Weight (kilograms): Obtained from nursing admission assessments, paper chart or CCSS, anesthesia pre-op or intra-operative flow sheets, or from nutrition initial assessment. Occasionally the weight was obtained from the daily flow sheets.

Status Upon NICU Admission:

- Diagnosis: Primarily obtained from discharge summary. If a secondary diagnosis was listed, (e.g., subarachnoid hemorrhage due to cerebral aneurysm), both were recorded. Occasionally, diagnosis was obtained from the patient info section on SCM or CCSS.
- GCS: First GCS listed on first acute care flow sheet. If the patient was intubated or had a C for eyes closed, only the number was recorded. For example, if the GCS was 7I on the flow sheet, a GCS of 7 was entered. However, if the GCS was recorded as less than 3, it was recorded as 3.
- Plegia/Paresis: Obtained from discharge summary and was the status upon admission to the NICU. If the patient was recorded as moving all fours, or 5/5 strength, or good strength on the progress notes or discharge summary, then it was assumed no paresis/plegia was present. Also, if it was recorded in the discharge summary that the patient did, in fact, have a hemiparesis, even if not initially recognized, that was recorded as a hemiparesis.

Medical History:

- Medical History: Obtained from Discharge summary, progress notes, occasionally CCSS. Specific medical history data recorded included:
    - Cardiac: recorded hypertension, presence of prosthetic valves, congestive heart failure (CHF), cardiomyopathy, hypercholesterolemia/lipidemia, Diabetes Mellitus (DM), myocardial infarction (MI), and coronary artery disease (CAD). There was also a place for "cardiac other."
    - Renal: nephrotic syndrome or chronic renal insufficiency (CRI).
    - Fracture: leg fracture, or arm fracture.
    - Smoking/Alcohol status: Obtained from admission nursing assessment in CCSS or chart, from anesthesia notes, or progress notes. Smoking status was recorded as current, former, or never. Alcohol status was recorded as either none, non-abusing (1-2 drinks/day), or abusing/excessive (>2 drinks/day). Abusing/excessive was also recorded for those patients listed in the chart as a known EtOH user, alcoholic, abuser or drinker.
    - Prior DVT/PE, including date and treatment prior to admission: Obtained from progress notes, discharge summary, and occasionally, from the diagnostic imaging on SCM.
    - Malignancy: Non-melanoma skin cancer was not included. Only malignancies within the past 12 months were considered positive. Whether malignancy was metastatic was also included. Primary brain tumors generally not considered metastatic, e.g., GBM or oligodendroglioma.
    - Hypercoagulable state (hereditary): If documented, or discovered during hospital stay, the disorders were listed on the form.
    - Pregnant – If documented anywhere in chart.
- Admission Medications: Documented home medications were obtained from progress notes, and included anything relating to sedation or anticoagulation initiated in the emergency department. In addition to those listed, heparin, Lovenox and Vioxx/Celebrex were also recorded.

Procedures/Conditions During NICU Stay:

- Post-NICU Medications (including mechanical prophylaxis): Any relevant medications were recorded. Information obtained from 7MED medication administration documents, order sheets or patient records for drugs. Recorded relevant drugs administered at any time during NICU stay. Mechanical device information was obtained from acute care flow sheets.
- Bed Rest: Assumed, unless documented as out of bed (OOB) within the first 3 days of stay.
- Mechanical Ventilation: Patient was considered to receive mechanical ventilation if on a ventilator, CPAP, or BiPAP. For the specific dates of mechanical ventilation, a day was defined as a day where the patient is ventilated for more than 3 hours for reasons other than surgery. If there were multiple ventilation periods, the first date is the first date recorded as having mechanical ventilation, and the last date is the last date recorded from acute care flow sheets, despite periods without ventilation.
- Intubation: The first date and last date were obtained from flow sheets. Again, intubation defined as being intubated longer than three hours, consecutively, for reasons other than surgery. Again, if there were periods in between without intubation, only the first and last dates were recorded.
- Sedation: We had originally intended to record first date and last dates of sedation, but later determined the presence or absence of sedation for longer than six hours was a more relevant finding. Continuous infusions were only as listed on acute care flow sheets, and were the only form of sedation considered positive. That is, intermittent injections or intermittent oral doses of benzodiazepines were not considered positive.
- Paralytics: For paralytics, start and end dates were recorded for any period of paralysis longer than six hours. If multiple times, then the very first and last were recorded. This data was obtained from acute care flow sheets (continuous infusions only).
- Catheters: Use of internal jugular (IJ), subclavian, PICC, and femoral lines were considered positive. Dates inserted and removed based on acute care flow sheets were recorded, as was body side. Occasionally, if ultrasound record of a catheter was present on SCM, that was used as well.
- Tracheostomy during hospitalization: This was obtained from the operative note on SCM, or in chart, from discharge summary, or from anesthesia assessments.

- Blood Transfusion: Based on transfusion record in chart.
- Urethral Catheter and Feeding Tubes: Initially recorded for cases, but not recorded for controls, as we did not deem them as potential risk factors to investigate at this time, and results would be confounded by the increased immobility of patients with these devices.

Surgery:

- Surgery: Details were based on operative report. Start and stop time from circulator nurse record, secondarily from the anesthesia intraoperative record. The type of surgery performed was categorized as evacuation of blood, tumor removal/biopsy, spinal surgery (e.g., fusions),. or vascular (e.g., aneurysm clipping/coiling). We also recorded craniotomy or burr hole technique if recorded on operative report or intraoperative records.
- Intraoperative Prophylaxis: Recording was based on circulator nurse flow sheet. If heparin 2000 units or more was documented as being administered, then this information was recorded.

DVT Information:

- DVT Information: Date of PE or DVT diagnosis based on first positive diagnostic imaging result.
- DVT Imaging : Information gathered from SCM. As described above, all DUS, V/Q, CTA, and relevant venography/angiography results were documented for the entire hospital stay, both positive and negative, including date, limbs imaged if relevant, as well as V/Q results as low, intermediate, or high probability.
- Signs and Symptoms: Any signs or symptoms leading to the imaging were obtained from the imaging report or from the discharge summary or progress notes. If there were any signs/symptoms present at the time of the imaging modality, the imaging was considered to have been conducted based on clinical suspicion. If only “prolonged ICU stay” or “bed rest” or “immobility” were listed on the imaging report, the screening test was considered routine.
- If there was a PE at the time of DVT diagnosis, or vice versa, then that information was gathered from the SCM diagnostic imaging. Positive results were defined as above, and were recorded in detail – occlusive vs. nonocclusive, limb side, and all veins involved. Ambulatory status on diagnosis was based on the acute care flow sheet and occasionally progress notes. Patients were considered not ambulatory unless documented as being “ad lib” or “OOB”.

- Prophylaxis used prior to diagnosis was based on flow sheets (for mechanical devices) and 7MED summaries.
- Mechanical prophylaxis start and end dates were recorded for cases only, in an attempt to document use prior to DVT. However, only the use or non-use of mechanical prophylaxis during the NICU stay was documented for controls.

DVT Treatment Upon Diagnosis:

- Treatment information for PE/DVT was based on several sources. IVC filter placement date was primarily from SCM, although occasionally from the discharge summary. Pharmacologic information was obtained from flow sheets for heparin drips and from 7MED summaries for all other pharmacologic interventions.

Complications/Negative Outcomes:

- Pulmonary embolism details were obtained from the sources above, primarily SCM for date, and method used to diagnose. Treatment was from SCM (IVC filter), discharge summary, and 7MED summary.
- Bleeding: Defined as hemorrhage requiring a blood transfusion, or intracranial hemorrhage as demonstrated by change in neuro exam and supported by CT scan. Based on mention in the discharge summary and supported by progress notes or radiographic confirmation.
- Venous Ulceration: Based on mention in discharge summary, and corroborated by progress notes noting date and limb side.
- Heparin-Induced Thrombocytopenia (HIT): Recorded if developed or not, based on discharge summary.
- Date of Death: Based on SCM patient info section and corroborated by acute care flow sheets. All deaths were recorded, but were only documented as due to PE if autopsy report indicates, or if death appears to be due to hypoxic event in/around time known PE was diagnosed, and no other obvious cause of death is apparent (e.g., patient not known to be rebleeding or herniating).