THE ROLE OF INHERITED THROMBOPHILIA IN PERIPHERAL VEIN INFUSION THROMBOPHLEBITIS: A PILOT STUDY

Vasiliki (Vicky) Tagalakis, MD
Department of Epidemiology and Biostatistics
McGill University, Montreal

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Table of Contents

Appendix

List of figures, tables, and graphs

Chapter 2

Chapter 3

Chapter 4

Abstract

The Role of Inherited Thrombophilia in Peripheral Vein Infusion Thrombophlebitis: A Pilot Study

Background. Peripheral vein infusion thrombophlebitis (PVIT) is a complication of intravenous therapy. We hypothesized that inherited thrombophilia may increase the risk of PVIT.

Purpose. In preparation for a multi-center study of our hypothesis, we conducted a pilot study to estimate PVIT incidence, measure the prevalence of inherited thrombophilia, and pilot test the study procedures.

Methods. A prospective case-control study of 25 cases (patients with PVIT) matched on catheter duration to 25 controls. PVIT risk factors and inherited thrombophilia were assessed.

Results. PVIT incidence was 14 per 1000 catheter-days. There were no significant differences in the prevalence of the inherited thrombophilia disorders among cases and controls (32% vs. 48%). A previous history of PVIT was noted in 4 cases compared to 0 controls. Procedural problems included a high rate of non-consent and inadequate communication with the laboratory.

Conclusions. Though an association between PVIT and inherited thrombophilia was not shown, a previous history of PVIT among cases supports a biological predisposition to PVIT. Our pilot study did provide useful data on PVIT incidence and procedural issues used to design a more definitive study of inherited thrombophilia and PVIT.

Abrégé

Le role de la thrombophilie héreditaire dans le dévlopement de la thropmbophlébite intraveineuse périphérique: Une étude pilote.

Introduction. La thrombophlébite intraveineuse périphérique (TVIP) est une complication de la thérapie intraveineuse. Nous présumons que la thrombophilie héreditaire peut être un facteur important dans la pathogénèse du TVIP.

Objectifs. En préparation pour une étude multi-centrique, on a executé une etude pilote pour estimer l'incidence de TVIP, déterminer la prévalence de la thrombophilie héreditaire, et tester les procédures de l'étude.

Méthods. Ceci est une étude de cas-témoin, dont 25 cas (patients avec TVIP) seront comparés a 25 témoins. Les facteurs de risques du TVIP et la thrombophilie héreditaire seront evalués.

Résultats. L'incidence de TVIP était de 14 pour 1000 cathéter-jours. La prévalence de la thrombophilie hériditaire était comparable entre les cas et temoins (32% vs. 48%). 4 cas contre 0 temoin ont une histoire antérieure de TVIP. Les problèmes procéduraux incluèrent un taux elévé de refus de consentement et une communication inadéquate avec le laboratoire.

Conclusions. Nôtre étude nous a fourni de l'information utile pour planifier une étude plus définitive sur la thrombophilie hériditaire et le TVIP. Un lien entre le TVIP et la thrombophilie héreditaire n'a pas était demontré, mais une histoire antérieure de TVIP à travers les cas suggère une prédisposition biologique au TVIP.

Statement of originality

I performed all aspects of this study, which include: 1) design of study protocol, 2) design of case report forms, and 3) data collection (with assistance from Dr. Axel Tosikyan), entry, analysis, and interpretation. This thesis reports on this pilot study.

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Index of abbreviations

DVT = Deep vein thrombosis

ER = Emergency room

IQR = Interquartile range

ITD = Inherited thrombophilic disorders

IV = Intravenous

Kcl = Potassium chloride

MHA = Medical holding area

MSTU = Medical short term unit

MTHFR=Methylenetetrhydrofolate reductase

OR = Odds ratio

PT = Prothrombin time

PVIT = Peripheral vein infusion thrombophlebitis

SD = Standard deviation

SC = Subcutaneous

SVT = Superficial vein thrombosis

VTE = Venous thromboembolism

Chapter 1. Introduction

In this thesis I have undertaken to study the role of inherited thrombophilic disorders, a group of blood clotting disorders, in the development of peripheral vein infusion thrombophlebitis (PVIT), a common complication of intravenous therapy among hospitalized patients. By way of introducing this study, I shall briefly review some basic aspects of PVIT and the inherited thrombophilic disorders.

Intravenous (IV) devices are indispensable in modern-day medical practice, and constitute one of the most common invasive procedures experienced by hospitalized patients (1). Short peripheral venous catheters, the most commonly used IV devices (2,3), are usually inserted temporarily into the veins of the forearm or hand in order to administer fluids, medications, and blood products. An estimated 25 million patients receive infusion therapy through peripheral venous catheters each year in U.S. hospitals (4).

PVIT is the most common complication of peripheral venous infusion (2-5) and is characterized by pain, redness, swelling, and a palpable thrombosis (clot) of the cannulated vein (6). PVIT causes patient discomfort and often necessitates reinsertion of the catheter into another peripheral vein if IV therapy is to continue. Repeated episodes of PVIT during a hospitalization can lead to difficulties with venous access and may necessitate more invasive procedures such as placement of a larger venous catheter into central veins of the chest, neck, or groin. Less common complications of PVIT include local infection and sepsis (6,7).

Although the pathogenesis of PVIT has not been well studied, it is postulated that irritation of the vein wall leads to inflammation and thrombus formation in the vein, resulting in clinically manifest PVIT (2). There is some evidence to suggest that thrombus formation may be a necessary causative factor in the development of PVIT (8). Etiologic factors leading to PVIT can be divided into IV catheter- and patient-specific risk factors. From the available data, IV catheter-specific risk factors, such as duration of catheterization, catheter material, type of infusate, and catheter site infections, have consistently been shown to increase the risk of PVIT (4). To date, patient-specific risk factors that may promote PVIT have received little attention, but it appears evident that

individuals vary in biologic vulnerability to developing PVIT (4). This reported biologic vulnerability and the postulated casual role of thrombus formation in the pathogenesis of PVIT prompts the following research question: "Is the biologic vulnerability to developing PVIT explained, in part, by the presence of underlying inherited thrombophilia?"

In the last few years, identification and characterization of the inherited thrombophilic disorders has led to important advances in our understanding of the etiologic mechanisms of clinical thrombosis. Together, these disorders are present in about 10-12% of the general population (9). It has been well established that these disorders are strongly associated with an increased risk of deep vein thrombosis (DVT), which refers to the presence of a blood clot in the lumen of the deep veins of the body. It is biologically plausible that inherited thrombophilia may also be associated with PVIT, which is primarily a thrombotic process affecting the lumen of the catheterized superficial vein.

In the course of planning a study to address the above question, it became clear that a proper design crucially depended on several areas where information was lacking, and that a small pilot study was therefore required. It consisted of a case-control study of 50 hospitalized patients with an IV catheter. Although the sample size by design was not large enough to accurately estimate the extent of any association between PVIT and inherited thrombophilia, this study's main objectives were:

1) To pilot test the study methods in preparation for a larger two-center prospective study, designed to address the same research question more definitively. Because blood analyses for the inherited thrombophilic disorders are extremely expensive, it was essential to assess how well the study performed "in the field" on a small sample of patients before undertaking a larger study - especially since the proposed research question had not been previously studied.
2) To provide an estimate of the local PVIT incidence that was needed to calculate the sample size for the planned larger study.

This thesis reports on this pilot project and consists of 5 chapters, in addition to the references. Chapter 2 follows, which is a literature review of PVIT and the role of inherited thrombophilia in PVIT. Chapter 3 describes the study methods, and chapter 4 presents the results. Finally, chapter 5 presents a discussion of the important findings and study limitations, as well as concluding remarks. There are two labeling schemes for tables and figures in this thesis. Tables and figures are placed within the text and are labeled with numbers (eg. Table 2.2), if they present information not formally stated in the text. Tables and figures which aid in summarizing or depicting what already is stated in the text are placed at the end of the chapter and are labeled with letters (eg. Table 2a.).

Chapter 2: Literature Review

This review of the literature on peripheral vein infusion thrombophlebitis (PVIT) will focus on the incidence, pathogenesis, risk factors, and the evidence supporting a role for inherited thrombophilia in PVIT development. As well, a brief overview of the inherited thrombophilic disorders will be presented. Therefore, an appreciation of the clinical importance of PVIT and its relation to inherited thrombophilia will be gained. This is the background required for the chapters to follow.

2.1. CLINICAL SIGNIFICANCE OF PVIT

PVIT, the most frequent complication associated with short peripheral intravenous catheter use (10), causes patient discomfort and generally leads to catheter removal and insertion of a new catheter at a different site, which is painful and unpleasant and requires extra nursing time. Analgesics and local treatment with compresses are usually administered (11). Repeated episodes of PVIT can lead to venous access difficulties, often necessitating more invasive procedures such as central venous catheter placement (12). As a result, administration of parenteral medications may be unnecessarily delayed, and hospital stay lengthened. In a recent small prospective study of 90 hospitalized patients with peripheral IV catheters, 23 (26%) developed PVIT, among whom complications which resulted in either a delay in the current IV therapy, additional IV therapy, or an extended hospital stay (2-5 days), occurred in 8 of the 23 patients with PVIT, which represented an important "personal and financial cost to the patient and a financial cost to the hospital" (13).

Several medical complications are associated with PVIT. Occlusion of the vein by thrombus may lead to extravasation of fluids into tissues and consequent edema, thus limiting venous access in the affected arm (14). In addition, suppurative thrombophlebitis may occur if the intravascular thrombus becomes infected. Although occurring in only 0.2%-2% of peripheral vein catheter insertions (12,5), this is one of the most serious local complications of PVIT (16). The resultant intravascular abscess may lead to bacteremia even after the catheter has been removed (6).

Moreover, patients with PVIT have an 18-fold increased risk for catheter-related bloodstream infections such as bacteremia and sepsis (i.e. a bloodstream infection in the setting of sepsis-defining symptoms) (17). Although compared to central vascular catheters only a small proportion of patients with PVIT develop catheter-related bloodstream infections, there is evidence that up to 50% of patients with IV-related bloodstream infection have PVIT (18). Studies of central venous catheters have shown that several of the different protein components of a thrombus increase adherence of *Staphylococcus aureus* and *Staphylococcus epidermidis* to catheters (19).

Arnow and colleagues (20) retrospectively studied 94 patients with 102 episodes of IV catheter sepsis due to percutaneously inserted catheters over a 45-month period. They found that 44 (43%) of these episodes occurred with peripheral venous catheters, 52 (51%) with central vein catheters, and 6 (6%) with peripheral arterial catheters. Of the 44 episodes due to peripheral vein catheters, 16 were complicated by PVIT, cellulitis, and/or superficial abscess, and in addition, 7 were complicated by suppurative thrombophlebitis. The average cost per peripheral catheter episode was $4,830 (1991 US dollars) (includes laboratory costs, therapy, and hospital room). Hence, it is evident that PVIT is a frequent complication in hospitalized patients, with associated morbidity, patient suffering, and high total costs.

2.2. DIAGNOSIS OF PVIT

There is no single accepted criterion or group of criteria for the diagnosis of PVIT that has been shown to be valid and/or reproducible. One of the earliest definitions put forward by the British Medical Research Council in 1957 defined PVIT as "redness, tenderness, and edema of the vein" (2). Furthermore, they proposed a PVIT grading system for use as a clinical assessment tool in everyday IV care. Variations of this grading system have been developed over the past 20 years, for example the Maddox scale (21) in 1977 and more recently, the Baxter scale (22) in 1988 (Table 2.1). The Maddox or Baxter scales are similar except that pain and erythema are assigned equal importance in the latter because of studies showing that erythema can occur simultaneously with or may precede the development of pain. An important limitation in

the validity of both grading systems is that not all the signs may develop, or develop in the sequence indicated. As a result, many investigators simply define PVIT based on various combinations of pain, tenderness, warmth, erythema, swelling, and palpable venous cord (4,23,24) whereby the presence of at least two of any the above is required for the diagnosis.

More recently, however, in the largest prospective study to date on risk factors for PVIT, Maki (4) developed a quantitative, summative scoring system for PVIT. Points were assigned and then summed based on the presence of pain (0/1), tenderness (0/1), redness (0/1/2), purulence (0/1), swelling (0/1/2), and palpable cord (0/1). PVIT was defined by the presence of 2 or more of these characteristics and was considered to be severe if the sum total score was higher than the 77^{th} percentile of all scores. This cutoff appears to have been arbitrarily chosen. Using this definition for severe PVIT, additional risk factors were identified for severe PVIT that were not risk factors for non-severe PVIT. These included catheter-related infection, PVIT with a previous catheter, and anatomic site of catheter insertion (the hand (relative risk 0.71) or the wrist (relative risk 0.60) rather than forearm). To date, however, the utility of this scoring system as a diagnostic tool in the clinical setting has not been assessed.

Table 2.1. The Baxter Scale for grading the severity of phlebitis[22]

Grade	Phlebitis severity criteria
0	No pain at IV site, no erythema, no induration, no palpable venous cord.
1	Painful IV site or erythema, no swelling, no induration, no palpable venous cord.
2	Painful IV site with erythema or some degree of swelling or both, no induration, no palpable venous cord.
3	Painful IV site, erythema and swelling and with induration or a palpable venous cord less than 3 inches above the IV site.
4	Painful IV site, erythema, swelling, induration and a palpable venous cord greater than 3 inches above the IV site.
5	Frank vein thrombosis, along with all the signs of 4 above; IV infusion may have stopped running owing to thrombosis.

2.3. INCIDENCE OF PVIT

2.3.1. Methodological considerations

The cumulative incidence of PVIT reported in the literature varies widely, ranging from 2.3% to 53% (Table 2a). Most studies are not directly comparable largely due to differences in definition of PVIT, study design, and patient selection. Furthermore, earlier studies reflect incidence rates based on catheters made of steel, which since the early 1980s have been replaced by plastic catheters. Table 2a describes all English language prospective studies published between 1966 and 2001 that report PVIT incidence of small plastic peripheral IV catheters (steel catheters, central venous catheters, and peripherally inserted central venous catheters were excluded). I have chosen to discuss below the most methodologically robust studies from Table 2a. Problems with studies not discussed included small sample size and unclear patient selection criteria.

2.3.2. Studies reporting PVIT incidence

In 1983, Tager and colleagues conducted the largest prospective multi-center epidemiologic study of the risks associated with peripheral venous catheters. The cumulative incidence of PVIT was 2.3% among 5161 short catheters (1), which was much lower than the average rate of 25% reported in the literature (Table 2a). The authors commented that the discrepancy between their rate and that reported by other groups could have been due to underreporting of cases because of the difficulty of standardizing detection of PVIT among the large number of participating practitioners. Furthermore, the definition of PVIT was restrictive in that it did not include the presence of a palpable cord and 3 PVIT characteristics had to be present for the diagnosis.

Maki and colleagues (4) conducted the next largest study to date that prospectively evaluated PVIT incidence. In a randomized trial comparing the incidence of PVIT using two catheter materials, 1054 short peripheral catheters (2.5 cm and 3 cm) were studied in 714 patients, of whom 36% were admitted to medical wards and 64% to surgical wards. Among catheters inserted, the overall PVIT incidence was 41.8%, with

day-specific incidence rates of 30% by day 2 and 45% by day 3. It should be noted that a large proportion of the study patients (>75%) received IV antibiotics, a known risk factor for PVIT.

Recently, Monreal and colleagues prospectively studied 766 consecutive patients with acute pneumonia who had IV catheters inserted to administer IV antibiotic therapy (23). He reported an overall PVIT incidence of 39% among first catheters of all lengths inserted. Among patients with short (5 cm) catheters, the PVIT incidence was 53% per patient, which is greater than that reported by Maki for similar length catheters. This may be explained in part by universal exposure to IV antibiotics in Monreal's study population.

Interestingly, in the same hospital under similar study conditions, Monreal prospectively studied 400 consecutive pre-operative patients who received 5 cm catheters and found the PVIT incidence was only 15% per patient (20). These patients also had IV catheters inserted for IV antibiotic therapy prior to their surgery. This discrepancy compared to Monreal's earlier study was likely due to a longer duration of catheter insertion in a medical cohort (mean of 4 days) vs. a surgical cohort (mean of 3 days).

Tomford in 1984 and Soifer in 1998 conducted randomized clinical trials to determine if insertion of IV catheters by specialized IV teams resulted in lower PVIT incidence rates than insertion by the medical and/or nursing staff. Tomford (9) prospectively studied 863 peripheral IV catheters in 445 patients and demonstrated a PVIT incidence of 32% in catheters maintained by the ward staff vs. 15% in catheters maintained by a professionally trained IV team. While most catheters maintained by the IV team were left in place for < 48 hours, it was not stated how long catheters maintained by the ward staff were left in place. However, when Soifer (22) prospectively studied 875 peripheral IV catheters which remained in place for 72 hours or less, the incidence of PVIT was 1.4% in patients with catheters inserted by the housestaff and 0.1% in patients with catheters inserted by the IV team. The exact catheter duration for either group was not stated. The discrepancy in PVIT rates between the 2 studies is largely due to the strict definition employed by Soifer, which consisted of a complex point system (Table 2a). In fact, when he applied a PVIT definition in which 1-3 characteristics were sufficient to

make a diagnosis of PVIT, the incidence was 13% for house staff catheters and 6.6% for IV team catheters.

In summary, although incidence rates have varied in the literature, these studies suggest that PVIT is a common occurrence with an average incidence of 25%-35% per patient. The variability amongst studies is probably due to differences in patient populations and case ascertainment and not to the IV care delivered in the study hospitals, since most American and Canadian hospitals have adopted the Centers for Disease Control guidelines on the care and maintenance of peripheral IV catheters (10). Despite attempts at standardizing IV care, PVIT continues to be a common problem amongst hospitalized patients. The IV Nurses Society established guidelines in 1990 (14), which stated that an acceptable PVIT rate in any given patient population is 5% or less, a rate which is exceeded in almost all published studies (4,5,12,13,24,25,26,27,28,29).

2.3. PATHOGENESIS OF PVIT

The current model of the pathogenesis of PVIT is that catheterization of the peripheral vein results in inflammation and thrombus formation (2). However, the specific relationship between inflammation and thrombosis is unclear. It is commonly postulated that vein irritation, whether chemical due to the infusate (4,14), as a result of the catheter material (4,5,14), or due to bacterial colonization of the intravascular segment of the catheter, leads to prostaglandin-mediated activation of the inflammatory cascade (Figure 2a) (2). At sites where the endothelium is severely inflamed, clotting intermediates are activated and accumulate (2), and this, combined with stasis, can initiate thrombosis. Humoral agents released in response to vein irritation may also provoke constriction of the vein (14), leading to stasis in the catheterized vein, which along with vein wall injury may predispose to thrombus formation and PVIT. Histopathological studies of veins following PVIT demonstrate swelling of endothelial cells, leukocytic infiltration of the vein wall (2, 30) and other changes consistent with inflammation, along with fibrin deposition and thrombus formation (30).

A small study used ultrasonography to test the hypothesis that thrombus in the catheterized vein may be the progenitor of PVIT. B-mode ultrasonography was

performed serially on veins in the antecubital fossa that were catheterized with long (14 cm) 22 gauge peripheral catheters (8). An echogenic mass within the vein lumen, indicating thrombus, was visualized in 14 of 22 veins catheterized. Nine of the 14 veins with thrombus but 0 of the 8 veins without thrombus were accompanied by "clinical phlebitis". Furthermore, thrombus detected within 24 hours of catheter insertion was associated with early development of clinically manifest PVIT while thrombus detected after 24 hours was associated with later development of clinically manifest PVIT. Although the peripheral venous catheters studied were longer than those typically used in hospitalized patients for non-nutritional peripheral IV therapy, it is unlikely that the thrombus formation visualized on ultrasonography is unique to long catheters. This study was the first to implicate thrombus formation as a necessary causal factor in the pathogenesis of PVIT.

Lastly, a role for thrombosis in the development of PVIT is supported indirectly by recent evidence that heparin, an antithrombotic agent used to treat clotting disorders, may prevent PVIT. A recent meta-analysis was performed of 13 randomized controlled trials that evaluated infusion of heparin intermittently (flush technique of 1 ml every 6-8 hours) or continuously in both peripheral IV and intraarterial catheters (31). When the results of the two trials that examined 100units/ml flushes every 6 or 8 hours compared to 0.9% sodium chloride flushes were pooled, heparin flushes significantly decreased the risk of both PVIT (relative risk 0.61 (95% CI [0.42,0.88])) and catheter clotting, which was defined as clot adherent or occluding the catheter upon removal (relative risk 0.52 (95% CI [0.33,0.83])). Furthermore, a significant decrease in the risk of PVIT was also observed when the results of 7 trials comparing 1unit/ml continuous heparin infusions with 0.9% sodium chloride flushes were combined (relative risk of 0.55, 95% CI [0.39,0.77]). The authors concluded that further evaluation of heparin use in the prevention of peripheral catheter-related complications such as PVIT is warranted.

2.4. RISK FACTORS FOR PVIT

Many of the studies on risk factors for PVIT are limited by small sample sizes, lack of a control group, and the rare use of multivariate analyses. Nonetheless, certain

risk factors have been implicated in the genesis of PVIT. These may be categorized into catheter-specific and patient-specific risk factors (Table 2b).

2.5.1. Catheter-specific risk factors

To date, the most extensively studied risk factors for PVIT are catheter-specific risk factors, such as duration of catheterization, catheter material, catheter length, catheter colonization, and type of infusate.

2.5.1.1. Duration of catheterization

Catheter duration is consistently shown to be an important predictor of PVIT. As early as 1975, Collin (32) found that PVIT incidence increased dramatically with catheter duration, such that PVIT rates were 14%, 53%, and 75% with infusion durations of <36 hours, 36-72 hours, and > 72 hours respectively. In 1983, in a prospective study of 5161 peripheral plastic catheters, Tager (1) showed that there was a highly significant trend toward increasing PVIT incidence with increasing duration of catheterization from 1 to 6 days. Specifically, the incidence was 0.2% for one day or less of catheterization, 4% for catheters in place 3-4 days, and 5.6 % for catheters in place 5-6 days. Of interest, although the day-specific risk of PVIT increased with increasing duration of catheterization up to 6 days, the wide confidence intervals for the day-specific estimates beyond day 2 suggest that day-specific rates after the second day may be constant. Thus, much of the risk of PVIT with longer durations of catheterization may be due to the accumulation of a relatively constant day-specific risk rather than to a progressively increasing risk over time.

Other authors have also reported on the relationship between day-specific risk of PVIT and catheter duration. In a randomized clinical trial comparing two catheter materials, Maki showed that the incidence of PVIT increased markedly between day 1 and day 2 after catheterization (day 1:day 2 relative risk 0.44; $p<0.001$), whereas the risk for each remaining day was similar to that on day 2 (day 3:day 2 relative risk 1.05; day 4:day 2 relative risk 1.05; $p>0.05$ for each comparison)(4). Nonetheless, despite a constant day-specific risk after day 2, the incidence of PVIT in both groups rose

progressively with increasing periods of catheterization; the cumulative risk of PVIT was 30% by day 2, 39%-49% by day 3, and 50%-62% by day 4 (4). More recently, Brezenger and colleagues prospectively studied IV catheter-related complications, including PVIT (29). Of the 609 peripheral IV catheters, 120 developed PVIT (19.7%). Mean duration of catheterization was 4.4 days (SD = 4.0). The incidence density of PVIT was constant after day 2 of catheterization until day 15, suggesting that the 1996 recommendations by the Centers for Disease Control Working Group (10) for routine replacement of IV catheters every 48-72 hours needed to be re-evaluated.

In summary, duration of catheterization appears to be an important risk factor for PVIT, though a randomized clinical trial is warranted to definitively address whether periodic rotation every 48-72 hours has an impact on the risk of PVIT.

2.5.1.2. Catheter material

The association between catheter material and PVIT has also been studied extensively. Teflon® catheters (tetrafuoroethylene-hexafuoropropylene) and Vialon® catheters (polyurethane) are widely used in Canada and the United States (4). Both have similar rates of catheter-related infection (4). However, in a randomized trial comparing the newer Vialon® catheters to the older Teflon® catheters, Vialon® catheters were associated with a 30% overall reduction in the incidence of PVIT (4). Similarly, Gaukroger found a 46% reduction in PVIT incidence with Vialon® compared with Teflon® catheters (5).

2.5.1.3. Catheter-related infection

Catheter-related infection is also associated with PVIT. Infection can activate both the inflammatory and procoagulant cascades, which are closely linked (33). Various inflammatory cytokines, such as tumour necrosis factor-α and interleukin-6, are capable of activating coagulation and inhibiting thrombolysis (i.e. clot dissolution). In turn, thrombin, which is responsible for clot formation, can activate inflammatory pathways and promote further vein damage (34). Thus, the inflammatory and procoagulant mechanisms, in reaction to infection, can synergistically initiate and perpetuate PVIT.

It is postulated that microorganisms gain access to the intravascular catheter most

often through the patient's skin, and less commonly from a contaminated catheter hub, contaminated IV fluid, or via hematogenous seeding from a remote site of infection (Figure 2b). Between 5%-25% of IV catheters are colonized by skin organisms at the time of removal (6). Colonization, which in most instances is asymptomatic, is thought to provide the biologic setting for infection. There is some evidence linking catheter colonization with an increased risk of PVIT (4, 35,36). Maki first demonstrated an association between PVIT and catheter colonization during the evaluation of a semi-quantitative culture technique (roll technique) that attempted to distinguish between catheter colonization from contamination (35). Specifically, signs of local inflammation (defined as the presence of lymphangitis, purulence or at least 2 of the following: erythema, tenderness, increased warmth, or a palpable thrombosed vein) were present in 64% of 25 catheters yielding $\geq$ 15 colonies per plate (defined as colonization), but in only 18% of 225 catheters yielding < 15 colonies per plate (considered contamination). In a subsequent prospective study, Maki demonstrated that catheter colonization was associated with a 6-fold increased risk for severe PVIT (4). Similarly, in a prospective study of 876 peripheral IV catheters, Larson and colleagues showed that 68.7% of IV catheters that were colonized, as reflected by semiquantitative cultures, had associated PVIT (36).

In summary, given the recent evidence linking the inflammatory and pro thrombotic physiologic cascades (33,34), catheter-related infection as a possible casual element in the pathogenesis of PVIT deserves more rigorous study.

2.5.1.4. Catheter length and gauge

There are no clinical trials that have examined the association between catheter length or gauge and PVIT. Furthermore, the small number of prospective studies that address this association have methodological limitations.

A prospective study of 5161 catheters (1) was unable to demonstrate a statistically significant difference in the PVIT incidence rate between short catheters (defined as less than 7.5 cm) and long catheters (defined as greater than 7.5 cm). However, a disproportionately small number of long catheters were observed (n=111) compared to short catheters (n=6258).

More recently, in Monreal's study of 766 patients with pneumonia receiving peripheral IV antibiotic therapy (24), PVIT developed in 53% of patients with short lines (2.5 cm), 41% with mid-sized lines (5 cm), and 10% with long lines (7 cm). Compared to short lines, the hazard ratio for PVIT with midsized lines and long lines was 0.39 (95% CI [0.30,0.50]) and 0.042 (95% CI [0.022,0.08]) respectively. However, use of IV medications and fluids were not adjusted, which is important because rate of IV medication delivery, as well as type of medications, influence the size of the IV catheter to be inserted.

In addition, it has been suggested that smaller gauge catheters are associated with a higher risk of PVIT than large gauge catheters (14), possibly due to the physical trauma caused by the insertion of a small gauge catheter into a relatively short, narrow vein. However no prospective study has shown a significant association between PVIT risk and catheter gauge.

2.5.1.5. Infusate characteristics

The nature of the infusate administered through a peripheral IV catheter also may influence the occurrence of PVIT, though studies are limited by small sample sizes and lack of adjustment for infusate concentration or dosage. Generally, both low pH and high osmolality IV solutions medications are reported to be associated with the occurrence of PVIT (14). For example, glucose (dextrose)-containing admixtures and hypertonic glucose solutions are reported to be more thrombogenic than normal saline (4,16). In addition, various intravenously administered drugs, such as Kcl, barbiturates, phenytoin, furosemide, and many cancer chemotherapeutic agents can produce severe PVIT (4). IV antibiotics, such as vancomycin, amphotericin B, erythromycin, and most beta-lactams, have been shown to increase the risk of PVIT (overall relative risk 1.5-2.0) (4,13,24), which may be attributable to the presence of microparticulates in the antibiotic solutions.

2.5.2. Patient-specific risk factors

Patient-specific risk factors have not been well studied, and furthermore little data exist on their association with PVIT development. Increasing age, Caucasian race, female

gender, "poor quality" peripheral veins, and the presence of underlying medical disease have been suggested as possible risk factors (4,14). Tager and colleagues observed a 2.7-fold increased risk of PVIT in patients with diagnoses considered to be high risk of acquiring any nosocomial infection (hematological/lymphoreticular malignancies, metastatic disease, solid tumours, and immunodeficiency states) compared to patients with low risk diagnoses (1). However, the association between high risk medical conditions for nosocomial infection and PVIT may be confounded by catheter colonization. Specifically, the presence of a nosocomial infection is associated with an increased risk of bacteremia, which can lead to catheter colonization.

2.5.3. Other risk factors

Other reported risk factors for PVIT include insertion in the emergency room, where establishing access quickly is often necessary, and inexperience of the person inserting the catheter (3,4,14). For example, the availability of an IV therapy team to insert IV catheters and to assure close surveillance of infusions resulted in a 2-fold lower rate of PVIT and an even greater reduction in catheter-related sepsis (12,26). Furthermore, insertion in the forearm as compared to the hand or wrist is also a risk factor (4).

Disinfection of the skin site prior to peripheral IV catheter insertion either with alcohol, povidone-iodine, or chlorhexidine is associated with a reduced risk of PVIT (37). However, there are no comparative trials of different cutaneous antiseptics to prevent PVIT. Type of catheter site dressing (gauze vs. transparent) alone does not appear to influence PVIT rates (38,39). However, changing gauze dressings more frequently than every 48 hours has been shown to increase the risk of PVIT (40), presumably as a result of manipulation of the cannula during the dressing process.

2.6. ROLE OF HYPERCOAGULABILITY IN PVIT

It is interesting to consider how the risk factors described above might relate to what is known about PVIT pathogenesis, namely that thrombosis may be a significant

causal element. The etiology of venous thrombosis can still be conceptualized by Virchow's triad (1860) of pathophysiological factors that promote venous thrombosis, namely vein wall damage, stasis, and hypercoagulability. Catheter-specific risk factors, such as catheter material and catheter-related infection, are likely markers of vein wall damage and stasis. Infection can also promote hypercoagulability, the third component of the triad. However, little attention has been given to the potential contribution of patient-specific risk factors that relate to hypercoagulability in the genesis of PVIT. Specifically, the hypercoagulable state conferred by the inherited thrombophilias, a group of blood coagulation disorders associated with increased risk of venous thromboembolism (VTE), may play a causal role in the development of PVIT.

2.6.1. Inherited thrombophilia

Hypercoagulability may be inherited or acquired. The inherited type, termed inherited thrombophilia, is suspected when a patient with VTE has recurrent or life-threatening venous thromboembolism, has a family history of VTE, is younger than 45 years of age at the time of diagnosis, has no acquired risk factors to explain VTE (eg. recent surgery), or there is a history of multiple miscarriages, stillbirth, or severe preeclampsia (41). The inherited thrombophilias can be essentially divided into genetic polymorphisms and anticoagulant protein deficiencies. The genetic polymorphisms include factor V Leiden, prothrombin G20210A, and the MTHFR C677T polymorphism. The anticoagulant proteins include antithrombin, protein C, and protein S. More recently, elevated levels of the coagulation proteins factor VIII, factor IX and factor XI have also been associated with increased VTE risk (42,43,44).

2.6.2. Mechanism of thrombosis in inherited thrombophilia

Coagulation refers to a multitude of distinct physiologic mechanisms that promote and regulate clot formation. Coagulation, along with its counterpart, fibrinolysis, are responsible for maintaining the blood circulation as a closed system in a normal basal state of equilibrium, referred to as hemostasis (45). A complex network of coagulation

proteins, or clotting factors, participate in a cascade of events that lead to the production of the protein thrombin, which is the ultimate product of the clotting cascade and is responsible for the formation and stabilization of fibrin clots (Figure 2c.).

Inhibition or down-regulation of the coagulation cascade to prevent excessive clotting occurs at the level of thrombin, as a result of two distinct mechanisms (41): 1) the protein C pathway, which controls the generation of thrombin, and 2) antithrombin, which neutralizes thrombin. (Figure 2d.). In the latter, the anticoagulant, antithrombin, binds to heparin sulfate on endothelial cells of the vessel wall and neutralizes or renders ineffective several procoagulants, most notably thrombin. As a result, antithrombin deficiency leads to decreased neutralization of thrombin and thus an increased tendency for clot formation (45).

The protein C pathway is much more complex, involving key anticoagulants such as protein S, factor V, and factor VIII, which together interact to inhibit the generation of thrombin from prothrombin (Figure 2d.). Once thrombin binds to cells on the endothelial surface of the vessel, protein C is activated which in turn inactivates factor V and factor VIII in the presence of free protein S, thereby inhibiting the generation of thrombin (41). Protein S itself has anticoagulant properties in that it inhibits the conversion of prothrombin to thrombin (41). Consequently, deficiencies of protein C and S result in the up-regulation of thrombin formation, as do elevated levels of factor VIII, IX, and XI levels by up-regulating factor X, an important co-factor in the formation of thrombin (Figure 2d.).

The control of thrombin generation is also compromised by mutations in the genes coding for factor V and prothrombin. The Arg506Gln substitution in factor V Leiden leads to increased thrombin generation (45). Moreover, the mutant factor V has diminished ability to inactivate factor VIII via protein C (41), thus further enhancing thrombin formation. For unclear reasons, the G20210A mutation in the 3' untranslated region of the prothrombin gene is associated with an increased level of prothrombin, which promotes thrombin generation and impairs inactivation of factor V by protein C (Figure 2d.).

Homocysteine is an amino acid formed during the conversion of methionine to cysteine (45). Elevated levels of homocysteine, a risk factor for VTE, can be caused by

genetic disorders affecting the trans-sulfuration or remethylation pathways of homocysteine metabolism, or by deficiencies of necessary cofactors in its metabolism such as folic acid, vitamin B12, and vitamin B6 (45). In addition, hypothyroidism, renal failure, smoking and increasing age have all been associated with elevated levels of homocysteine. Hyperhomocyteinemia exerts a number of effects that are relevant in the pathogenesis of thrombosis. Most notably it induces endothelial cell damage, resulting in thrombin generation by the vessel wall (45).

2.6.3. Epidemiology of inherited thrombophilia

The prevalence of the inherited thrombophilias varies within healthy populations and among patients with venous thrombosis. The frequency of all inherited thrombophilias is significantly higher in unselected patients with venous thrombosis than in healthy subjects. Furthermore, factor V Leiden and the G20210A prothrombin mutation are common among healthy whites but are extremely rare among Asians and Africans. Table 2c provides a summary of the prevalence of the inherited thrombophilic disorders and relative risk for first VTE.

The heterozygous form of factor V Leiden is found in 5-7% of the general population and confers a 7-fold increased risk of VTE (46), while the homozygous form (population prevalence of 0.02%) confers an 80-fold increased risk (95%CI [22,289]) (47). Heterozygotes for the prothrombin G20210A mutation (population prevalence of 2-3%) have prothrombin antigen and activity measurements that are elevated by 30% compared to normal individuals (48), and have a 2.8-fold increased risk for VTE. The MTHFR C677T homozygous genotype, which is found in 10-12% of population, is associated with elevated homocysteine levels, and elevated homocysteine levels are associated with a 2.5-fold increased risk of VTE (50-52). However, a direct association between the MTHFR C677T genotype and thrombosis has yet to be demonstrated.

The genetic mutations for the deficient anticoagulant proteins, antithrombin, protein S, and protein C, are heterogeneous in nature. For example, 161 different mutations have been described for protein C deficiency, 131 for protein S deficiency, and 127 for antithrombin III deficiencies (41). Type I defects (low activity and low antigen

level) predominate in patients with a deficiency of protein C or S, whereas both type I and type II (low activity and normal antigen level) defects are common in patients with antithrombin deficiency. While rarer than the genetic mutations of prothrombin, factor V Leiden, and homocysteine, the relative risk of developing VTE for each of the three protein deficiencies (heterozygous forms) is increased by about 10-fold (57). Homozygous antithrombin deficiency is probably incompatible with life unless it is a type II defect, in which the susceptibility to VTE is indistinguishable from that of persons with heterozygous antithrombin deficiency (41). Similarly, homozygous deficiencies of protein C or S are exceedingly rare and are manifested by massive thrombosis soon after birth.

Elevated levels of factor VIII (> 90^{th} percentile) have been associated with a 7-fold increased risk of recurrent VTE (56). Similarly, elevated levels of factor XI and factor IX have been associated with a 2-fold increased risk of developing a first VTE (42,44). About 10% of the general population has elevated levels of one or more of these factors (42,44). Although no genetic alterations have been shown as of yet, family studies suggest that elevated levels of these factors are often genetically determined (58).

In summary, inherited thrombophilic disorders have an overall prevalence of 5% to 15% in the general population, with the genetic mutations being far more common than the anticoagulant protein deficiencies.

2.6.4. Evidence for a causal role of inherited thrombophilia in PVIT

There are no published studies that have specifically examined whether inherited thrombophilia is associated with PVIT, hence my thesis project is the first to explore this association. However, there are several lines of evidence that suggest that this association may exist.

Firstly, there appears to be an underlying host susceptibility to developing PVIT. Maki (4) demonstrated that patients who develop PVIT with a first catheter were 50% more likely to develop severe PVIT with a second catheter (RR 1.5, 95%CI [1.1,2.1]). He concluded that individuals vary in biologic vulnerability to developing phlebitis, and that

"the pathologic basis for such vulnerability is unknown, but would be an important subject for investigation".

Secondly, Monreal in two separate studies reported an increased risk of PVIT in patients with higher hemoglobin levels. Among 400 consecutive surgical patients, the PVIT hazard ratio for patients with hemoglobin levels >14.5 g/dl compared to < 12.2 g/dl was 2.5 (95% CI [1.2,5.5]) (25). Similarly, a hazard ratio of 2.3 (95% CI [1.6,3.3]) was found among medical patients with hemoglobin levels >13.9g/dl compared to levels < 10.5g/dl (24). He postulated that a high hematocrit might lead to "local activation of coagulation which may predispose thrombosis-susceptible patients to PVIT". Notably, high hemoglobin (hematocrit) levels have been associated with VTE. For example, in patients with polycythemia vera, a condition where the blood volume and hemoglobin levels are increased, arterial and venous thrombotic events are common (59). While the exact mechanism leading to VTE is unclear, stasis caused by increased blood viscosity is thought to be important.

Third, there is evidence that inherited thrombophilia has an etiologic role in central venous catheter-related thrombosis in children. Nowak-Göttl and colleagues (60) prospectively followed 163 children who had a central venous catheter placed. Among 18 children with clinically symptomatic central venous catheter-related thrombosis, 15 had inherited thrombophilia (mostly factor V Leiden or protein C deficiency). Among the children with a central venous catheter but no clinical and/or ultrasonographically documented thrombosis (n=145), 2 had inherited thrombophilia. The authors concluded that inherited thrombophilia plays an important role in central catheter-related VTE in children.

Fourth, links have been established between inherited thrombophilia and spontaneous superficial vein thrombosis (SVT). Martinelli (61) studied 63 patients with SVT of the lower extremities and 537 healthy controls. The prevalence of each thrombophilic state was higher in cases than controls (odds ratios of 6.1, 4.3, and 12.9 for factor V Leiden mutation, prothrombin mutation, and anticoagulant protein deficiencies, respectively). These risks did not change when the analysis was restricted to the 43 patients who had SVT as their only thrombotic manifestation (i.e., without a subsequent deep vein thrombosis which is known to be associated with inherited thrombophilia).

They concluded that screening for thrombophilia should be performed in patients with SVT in order to identify subjects at high risk for more serious thrombotic complications.

Lastly, Hanson and colleagues prospectively followed 3714 lower extremity venous duplex scans over 2 years and identified 17 patients with isolated saphenous vein (i.e. superficial) thrombophlebitis (without concomitant deep vein thrombosis) and no underlying malignancy (62). Ten of the 17 patients were found to have inherited thrombophilia, however, a control comparison group was not studied.

Hence, while the evidence for a link between PVIT and inherited thrombophilia is mostly indirect at present, this association deserves more definitive study because of the high prevalence of PVIT and inherited thrombophilia. The next two chapters describe the methods and results of a pilot study that I conducted, which will lead to a more definitive study that will explore the possible association between PVIT and inherited thrombophilia.

Chapter 2: Tables and Figures

Figure 2a. Pathogenesis of PVIT

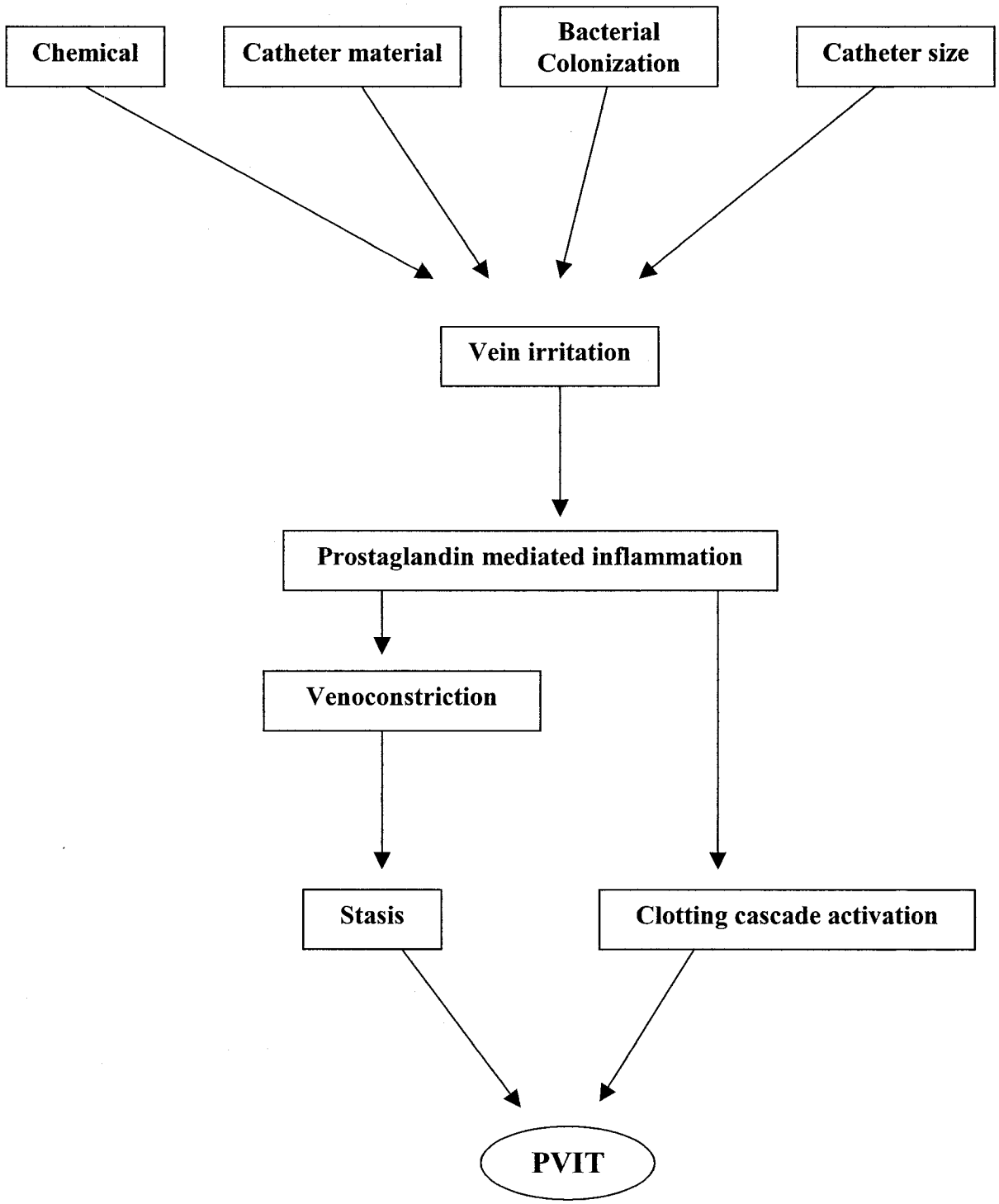

Figure 2b. Potential sources for access to intravascular catheter by microorganisms (ref 3)

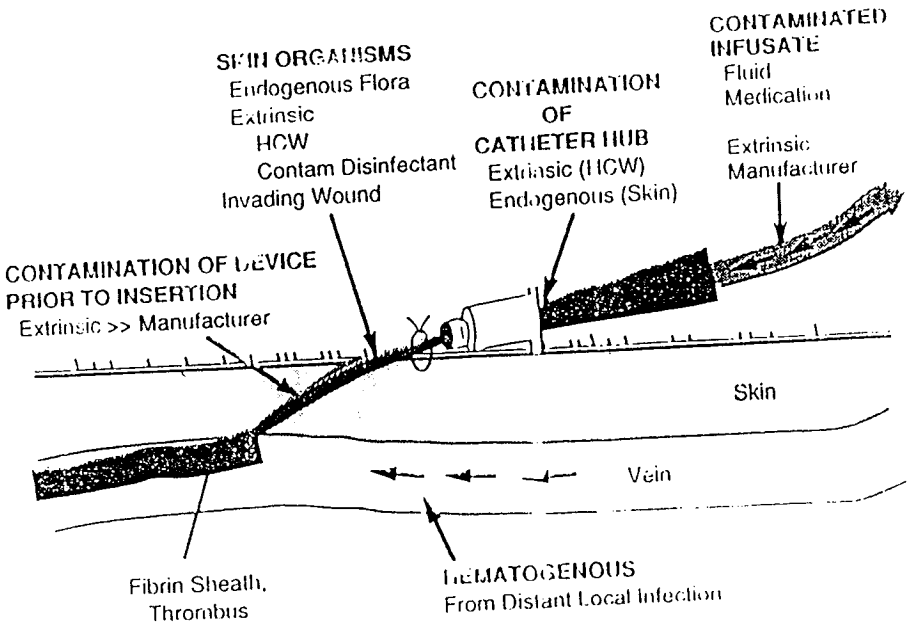

Figure 2c. Coagulation cascade (ref 45)

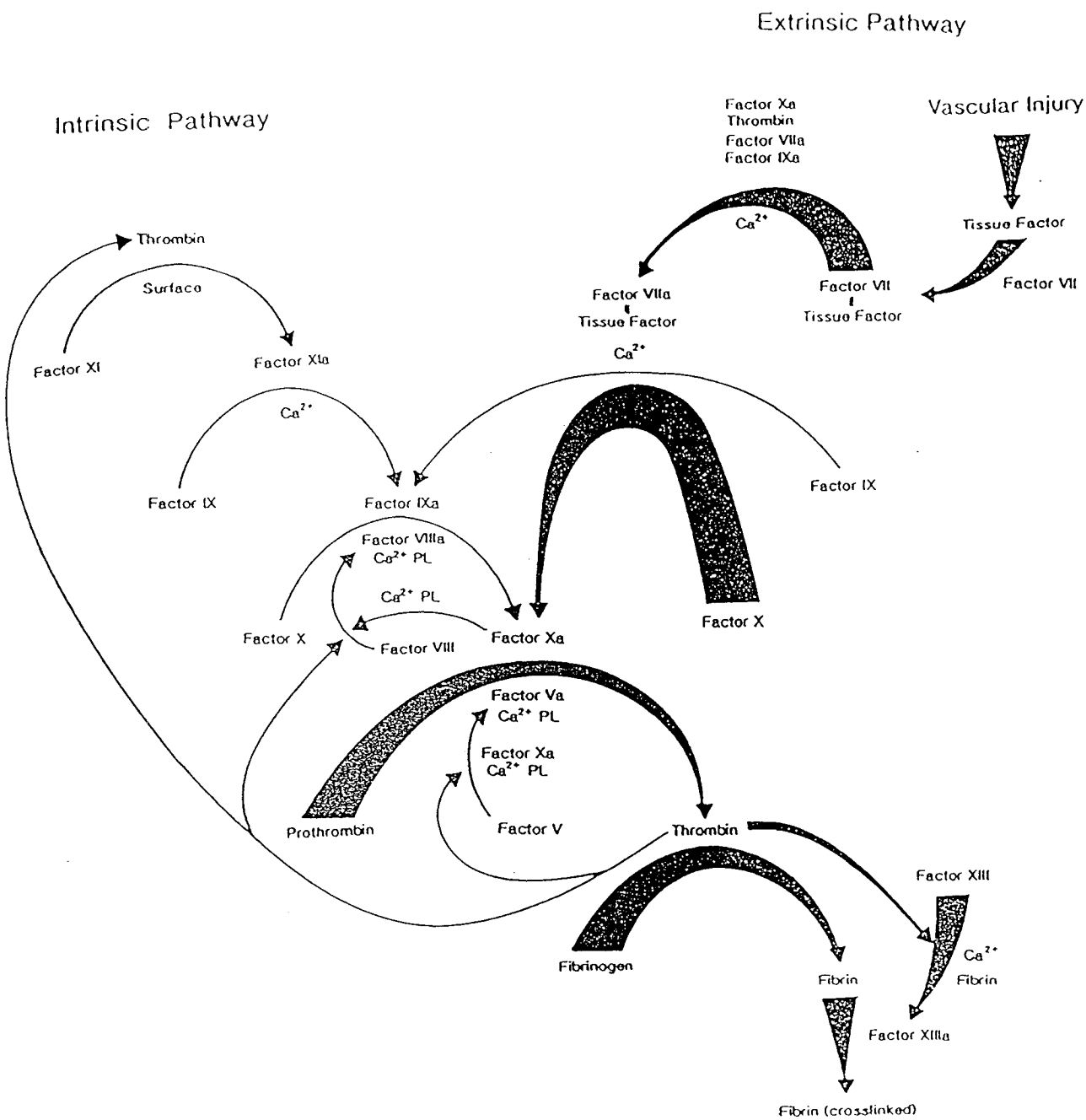

Figure 2d. Mechanisms involved in the normal control of coagulation and inherited thrombophilia (ref 41)

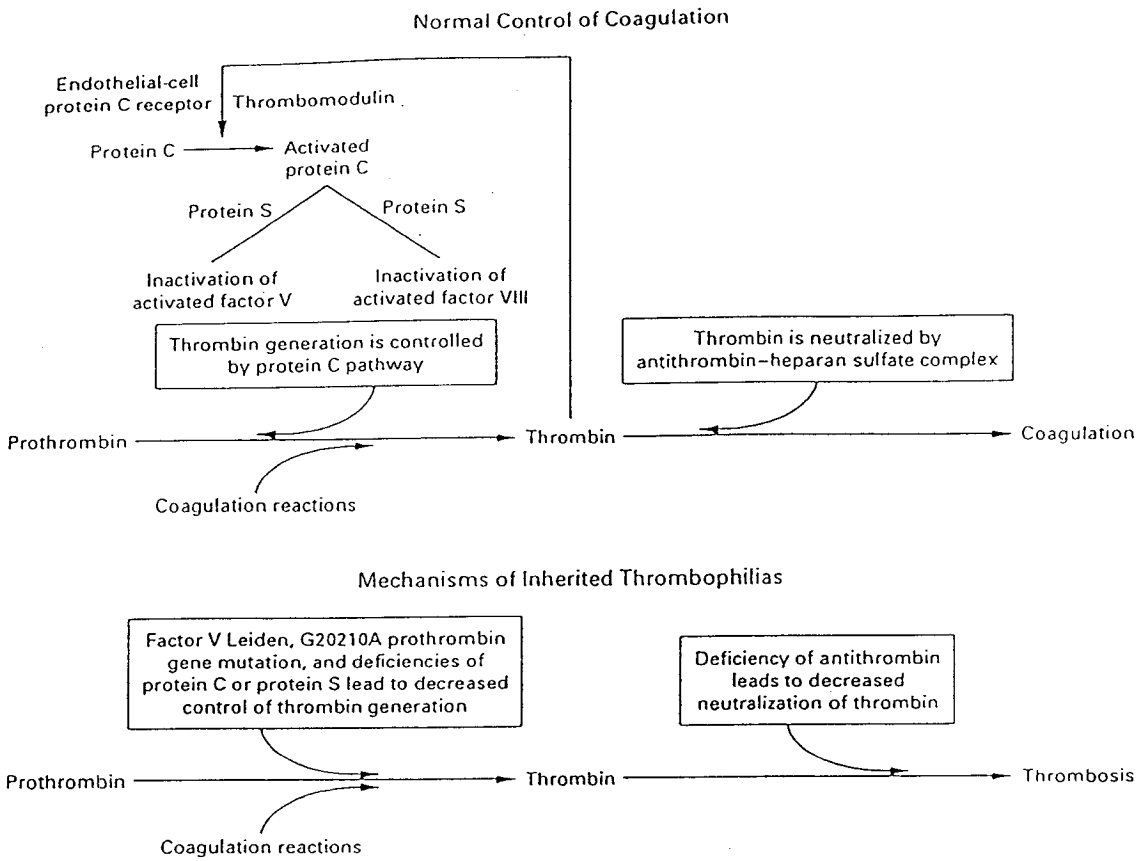

Figure 1. Major Mechanisms Involved in the Normal Control of Coagulation and Inherited Thrombophilias.

Control of coagulation is achieved by the protein C pathway and antithrombin. In the protein C pathway thrombin bound to thrombomodulin activates protein C, which in turn inactivates activated factor V and factor VIII in the presence of protein S, thereby down-regulating the generation of thrombin. The neutralization of thrombin is achieved by antithrombin bound to heparin sulfate. In the inherited thrombophilias, a deficiency of antithrombin, protein C, or protein S, aberrant activity of factor V, or increased activity of prothrombin results in decreased neutralization of thrombin or increased generation of thrombin.

Table 2a. Prospective studies reporting incidence of PVIT

STUDY	STUDY DESIGN	PATIENT POPULATION	PVIT DEFINITION	MEAN CATHETER DURATION	CUMULATIVE PVIT INCIDENCE
Tager 1983	Prospective observational	N=5161 catheters	Erythema, heat and swelling with or without tenderness; cord not included	2 days	2.3% per catheter
Tomford 1984	Randomized trial comparing IV team vs. medical house staff; 2.5 month duration	N=794 catheters; 100% medical	3 of the 4 following: pain, redness, induration, or cord of at least 2.5 cm	Not specified	·32% per catheter (medical housestaff) ·14% per catheter (IV team)
Adams 1986	Randomized trial comparing in line filtration vs. no in line filtration[1]; duration not stated	N= 102 patients; 100% surgical; Number of catheters not indicated	Maadox scale[2]	2.1 days	·30.6% per patient (in line filtration) ·26.4% per patient (no in line filtration)
Hoffman 1988	Randomized trial comparing 2 types of IV dressings	N= 490 patients; 54.5% medical; 45.5% surgical	Warmth and redness over an indurated or tender vein	Not specified	·9.8% per patient (gauze dressing) ·7.6% per patient (polyurethane dressing)

[1] In line filtration: microfilters placed in IV catheter to filter infusing particulate matter.
[2] Similar to the Baxter scale

Table 2a. (continued) Prospective studies reporting incidence of PVIT

STUDY	STUDY DESIGN	PATIENT POPULATION	PVIT DEFINITION	MEAN CATHETER DURATION	CUMULATIVE PVIT INCIDENCE
Gaukroger 1988	Randomized trial comparing Vialon® to Teflon® catheters	N=645 catheters; 100% surgical	Standard[3]	1.5 days	·63.5% per Teflon® catheter ·40.9% per Vialon® catheter
Maki 1991	Randomized trial comparing Vialon® to Teflon® catheters	N=1054 catheters; 36% medical patients, 64% surgical	Standard[3]	59 hours (SD=2) (Teflon®); 65 hours (SD=2) (Vialon®)	41.8% overall per catheter
Soifer 1998	Randomized trial comparing IV team vs. medical house staff	N=875 catheters; 100% medical	Point system devised by author[4]	Not stated	·1.4% per catheter (house staff) ·0.1% per catheter (IV team)
Monreal 1999	Prospective observational	N=400 patients (catheters); 100% surgical	As in Soifer 1998	2.0 days (SD=1.5)	15% per catheter

[3] PVIT defined as 2 or more of the following: pain, tenderness, swelling, erythema, and a palpable cord.
[4] A definition of PVIT was established on a point system using these local complications: warmth-1 point; erythema 3-6 cm from site (1 point); erythema >6 cm from site (2 points); and induration and/or swelling (2 points). PVIT was defined as 3 or more points in any combination.

Table 2a. (continued) Prospective studies reporting incidence of PVIT

STUDY	STUDY DESIGN	PATIENT POPULATION	PVIT DEFINITION	MEAN CATHETER DURATION	CUMULATIVE PVIT INCIDENCE
Campbell 1998	Prospective observational	N=90 patients (catheters); 100% medical	Baxter scale[5]	1.5 days	26% per catheter
Monreal 1999	Prospective observational	N=308 patients (308 catheters); 100% medical	Cord or any of the following two at least 3 cm from the IV site: warmth, erythema, tenderness, or induration	4.6 days (SD=3.4)	53% per catheter
Bregenzer 1998	Observational	N=451 patients N=609 catheters; 80% medical, 20% Intensive Care Unit	Standard	4.4 days (SD =4)	11% per catheter
Summary Statistic		**Σ 9936 catheters[6]**			**Average: 25% per catheter[7]**

[5] See page table 2.1 on page 9.
[6] Excluding studies by Adams and Hoffman because catheter sample size not indicated.
[7] Weighted average PVIT incidence

Table 2b. Risk factors for PVIT (References)

Catheter-specific
Catheter duration (1,4,24,17)
Catheter material (4,5)
Catheter size (21,27,28)
Intravenous infusate (4,9,10,13,21)
Catheter-related infection (4,27,29,30)
Site of catheter insertion (4)
Patient-specific
Poor quality peripheral veins (5)
Sex (4,5)
Underlying medical disease (1,4)
Biologic vulnerability (4)
Other
Experience of person inserting catheter (4, 8, 32)
Insertion in the emergency room (4)
Daily intravenous gauze changing (33)

Table 2c. Inherited thrombophilia: prevalence and risk of first venous thromboembolism

Inherited Thrombophilia (References)	**General population prevalence (%)**	**Relative risk of first venous thrombo-embolism***
Genetic Polymorphisms		
Factor V Leiden		
Heterozygous (46)	5-7	7
Homozygous (47)	0.02	80
Prothrombin G20210A gene mutation (48,49)	2-3	2-3
Homozygous C677T mutation in the MTHFR gene (50,51,52)	10-12	2.5†
Anticoagulant protein deficiencies		
Antithrombin III deficiency (53,54)	0.02	8
Protein C deficiency (54,55)	0.4	7
Protein S deficiency (41,54)	0.2-0.4	8.5
Elevated factor VIII levels (56)	11	4.8

* Compared to healthy control population.

† Risk observed with elevated blood levels of homocysteine, which can be due to the C677T mutation in the MTHFR gene.

Chapter 3: Study Methods

3.1. HYPOTHESIS

Inherited thrombophilia may be an important risk factor for PVIT, and consequently hospitalized patients with peripheral IV catheters who have inherited thrombophilia are at higher risk for PVIT than those without inherited thrombophilia.

3.2. OBJECTIVES

In preparation for a future prospective multi-center study to definitively address the above hypothesis, my pilot study had the following objectives:

1. To pilot test the study procedures.
2. To provide a preliminary estimate of the incidence of PVIT amongst patients with IV catheters, which will be useful in calculating the sample size required for the larger, future study.
3. To describe both patient-specific and IV catheter-specific characteristics of patients with PVIT in comparison to the literature.
4. In a preliminary fashion, to provide a rough estimate of the prevalence of inherited thrombophilic disorders in patients who develop PVIT vs. patients without PVIT.

3.3. ETHICS APPROVAL

The study was approved by the McGill University Institutional Review Board (see appendix for letter of approval). All participating patients provided informed signed consent.

3.4. OVERALL DESIGN

This was a hospital based case-control study of patients (n=50) hospitalized on 3 medical wards at the SMBD-Jewish General Hospital (JGH). Patient recruitment began January 23, 2001 and ended August 11, 2001. Cases (n=25) were patients with clinically documented new onset PVIT. Controls (n=25), who had a peripheral IV catheter but no PVIT, were selected from among patients on the same hospital ward as cases. Furthermore, controls were matched to cases on duration of peripheral intravenous catheterization. For cases and controls, (1) data were collected on patient specific characteristics (co-morbid conditions, medications, thrombosis risk factors, known thrombophilia, prior personal and/or family history of thrombosis) and catheter-specific characteristics (size, site, duration, infusate, order), and (2) blood samples were obtained and analyzed for markers of inherited thrombophilia.

3.5. STUDY POPULATION

The SMBD-JGH is a 637-bed McGill University-affiliated hospital in Montreal, Quebec. It is a tertiary care referral center that also serves the population in its catchment area. The source population from which cases and controls were recruited consisted of all patients admitted to hospital wards who had a peripheral IV catheter in place on their arrival to the ward or had a peripheral IV catheter inserted during their stay on the ward. Specifically, three general medicine wards were selected to provide the patient population from which the cases and controls were recruited. These were 7-West (7W) (32 beds), 7-Northwest (7NW) (28 beds), and medical short term unit (MSTU) (16 beds). These wards were chosen because they are representative of the source population, namely typical hospitalized patients at risk for PVIT. The following types of wards were excluded: (1) orthopedic surgery and cardiology wards because of the high rate of heparin use in these areas, either for prophylaxis or treatment, which could conceivably decrease the incidence of PVIT in patients hospitalized in these areas; (2) surgical wards, where

patient turnover is high, making recruitment difficult; and (3) intensive care areas, because of potential difficulties in obtaining consent from severely ill patients.

3.5.1. Patient survey

Two to three times a week (Monday-Friday 9:00-17:00), I performed an on-site survey of all patients admitted to the three study wards. Although the survey days and times were not randomly pre-selected before the study commenced, the decision to survey on a particular day was based on my availability, and thus was independent of any prior knowledge related to the wards, such as patient census and number of IV catheters. During the survey, patients who were available for an IV site assessment were questioned about pain at the insertion site, and the site was inspected and palpated for tenderness. For each of the study wards, the following was documented in a log on each survey day: 1) the total number of patients available for an IV site inspection, 2) the number of patients who had a peripheral IV catheter, and 3) for those patients with an IV catheter, the duration of catheterization (in days), and the presence or absence of PVIT. Every attempt was made to follow the IV catheter through subsequent survey days by recording salient features of the catheter such as catheter gauge and anatomic location. If a patient had more than one catheter simultaneously or in succession, then each catheter was considered in the calculation of PVIT incidence. However, in the case-control study, once a patient was enrolled as case or control, then he or she was no longer eligible to be a case or control with a subsequent catheterization.

With respect to patients with more than one catheter, we included each catheter. If a catheter was removed and another inserted in the same patient, then we considered the subsequent catheter as a new catheter.

Consent from the ward patients surveyed was not necessary since no nominal information was recorded and these patients did not participate in the case-control study. Furthermore, the SMBD-JGH Ethics Committee viewed the survey as standard medical care, since the SMBD-JGH nursing policy on IV care stipulates that all IV catheters be inspected daily.

3.5.2. PVIT diagnosis

The diagnosis of PVIT was made according to the following pre-defined criteria; Presence of two or more of the following symptoms or signs at the catheter insertion site: pain as reported by the patient, tenderness on palpation of the site, erythema, swelling, purulence, and a palpable venous cord. Because there is no single accepted criterion or group of criteria for the diagnosis of PVIT, the above-stated definition was chosen because it is the one most often used by prior investigators.

In order to ensure high inter- and intra-rater reliability for the diagnosis and grading of PVIT, in a run-in period to the study, I and Dr Axel Tosikyan, a medical resident at McGill University who participated in case and control enrollment, attended a one hour training session given by Dr. Michael Libman, an infectious disease specialist at the Montreal General Hospital, who used 3 live patients to demonstrate the clinical criteria used to diagnose PVIT.

3.5.3. Identification of cases

I identified PVIT cases during the on-site survey. According to availability, one of the investigators then proceeded to enroll the cases. Informed consent was sought from the patient. The number and reasons for non-consent among the patients with PVIT who did not wish to participate in the study were documented, with their permission.

3.5.4. Identification of controls

On the day that a case was identified, the next patient on the ward roster list who had a peripheral IV catheter in place for the same number of days as the case but had not developed PVIT was selected to be a control patient (Figure 3a.). If a control with the same duration of catheterization as the case could not be found, then the next patient on the ward roster list with a peripheral IV insertion of longer duration by one day was selected as a control. If a control could still not be found for the case, then on the next survey day, the first patient on the ward list who met the matching criterion was selected

as the control for that case. Because increasing catheter duration is a powerful predictor of PVIT, by matching cases to controls of only longer rather than shorter duration, an attempt is made to ensure that PVIT development in the case is not primarily the result of longer catheter duration.

Control enrollment was performed by either one of the investigators. Informed consent to participate in the case-control study was sought from the patient. The numbers and reasons for non-consent among patients asked to serve as controls were recorded, with their permission.

3.5.5. Rationale for matching procedure

Random sampling from the study base, where controls are chosen independently of characteristics of the cases (i.e. not matched on any criteria), is the simplest strategy for control selection (63). However, matching is an option that is often used to improve efficiency in the estimation of the effect of the exposure by protecting against an unbalanced distribution of a known strong confounder among cases and controls (63). This allows for a more efficient stratified analysis.

Although catheter duration has been consistently shown to be a strong predictor of PVIT, it is not a confounder because any foreseeable relation to inherited thrombophilia is derived secondarily from the association between PVIT and inherited thrombophilia. In other words, it can be argued that patients with inherited thrombophilia may have shorter catheter durations because they develop PVIT faster than the source population. Nonetheless, cases and controls were individually matched on catheter duration not to limit possible confounding, but to avoid any unbalanced distribution of catheter duration between the two groups that could obscure associations between PVIT and other predictor variables, given the known strong association between catheter duration and PVIT. This should improve upon study efficiency (not likely for this study because its very small sample size renders it extremely inefficient to begin with, but possibly for the future, larger study).

Negative consequences to the study as a result of the matching are unlikely. Information on catheter duration was already being collected during the patient survey, so

matching did not add complexity to the study design. Furthermore, the alternative option of increasing the number of study subjects to ensure similar distribution of catheter duration among cases and controls is not feasible, since the inherited thrombophilia laboratory tests are too expensive ($200.00 per subject). However, a limitation to matching is that it precludes investigation of the association between catheter duration and PVIT, as well as interactions between duration and inherited thrombophilia or other covariates. With a larger sample size, it would be possible to study catheter duration as a modifier of relative risk by observing how the odds ratio varies across strata of durations.

3.6. STUDY PROCEDURES

As soon as a case or a control was identified and written consent obtained, (1) data collection and (2) blood sample collection were performed.

3.6.1. Data collection

The investigators documented the following patient-related and IV catheter-related characteristics on a standardized case report form (see appendix). The data were collected by a bedside interview (patient-related information) and medical chart review (IV catheter-related information).

1. <u>Patient-Specific Characteristics</u>

A) <u>Demographic data</u>:

- Age
- Sex
- Admitting ward [7W/7NW, MSTU]

B) <u>Admitting diagnosis</u>:

- Reason for admission (cancer-related*, cardiovascular disease, infection, other)

* Cancer-related diagnosis includes diagnoses related to a complication or a consequence of cancer (malignant pleural effusion, ascites, spinal cord compression, hypercalcemia, etc.)

C) Presence of risk factors for venous thromboembolic disease:

Patient-specific

- Paralysis
- Active cancer
- Inflammatory bowel disease
- Nephrotic syndrome
- Pregnancy
- Known thrombophilic disorder (including type)

Situation-specific

- Surgery in the last 3 months (post-surgical)
- Immobility greater than 4 days in the last 3 months
- Fracture of the pelvis, hip, or leg in the last 3 months

D) Prior personal and family history of venous thromboembolism:

- Prior history of PVIT
- Prior history of venous thromboembolism (deep venous thrombosis and/or pulmonary embolism)
- Family history of venous thromboembolism (first degree relative: mother/father, sister/brother, child)

E) Use of the following medications (pro-thrombotic or anti-thrombotic) while IV was in place

Anti-thrombotic

- Aspirin
- Clopidogrel
- Ticlopidine
- Warfarin
- Unfractionated Heparin subcutaneous injection
- Low Molecular Weight Heparin

Pro-thrombotic

- Oral Contraceptives
- Hormone Replacement Therapy

2. <u>IV Catheter-Specific Characteristics</u>

- IV catheter duration (days)
- IV gauge
- IV anatomic location (hand/wrist or forearm/antecubital fossa)
- Patient location when IV inserted (ward, emergency, out patient clinic)
- Infusions administered through the IV (heparin, steroids, furosemide, potassium chloride (Kcl), morphine, antibiotics, blood, dextrose solution (D_5W))
- IV catheter inserter (nurse or medical resident)

3.6.2. Blood sample collection

On the day of enrollment, the ward nurse responsible for the care of the study patient collected 2 tubes of venous blood from the study patient, which then were sent to the hematology lab of the JGH. Plasma was isolated within 30 minutes of blood collection by centrifugation at 2000G for 20 minutes, and then aliquoted and stored individually at $-70^{o}C$ until analysis. Samples were analyzed in batches during the enrollment phase of the study. Antithrombin III activity by chromogenic assay, protein C activity by chromogenic assay, and the STACLOT protein S clotting activity were all measured on an MDA 180 Analyzer from Organon Teknika. The study investigators were blinded to the results of the analyses until the end of patient enrollment so as to avoid information bias.

Polymerase Chain Reaction (PCR) methodology with appropriate primers and probes was used for assessment of the genetic polymorphisms: factor V Leiden, prothrombin 20210, and MTHFR C677T. Genomic DNA was isolated from the buffy coat of patient blood and analyzed in the Molecular Diagnostics Laboratory at the Jewish General Hospital. The prothrombin G20210A polymorphism was detected by amplification of a 345-bp fragment and digestion with *HindIII* as previously described

(47). The factor V G1691A mutation was determined after amplification of a 223 bp fragment and subsequent digestion with *MnlI*. The presence of the factor V Leiden mutation resulted in the loss of an *MnlI* restriction site as described by Bertina et al (64). The MTHFR C677T genotype was detected by amplification of a 198 bp fragment and subsequent digestion with *HinF* (50).

3.6.3. Data entry

Once all 50 patients were enrolled, a research assistant, who was blinded to the study hypothesis, entered the data from the case report forms into an Excel file (Microsoft Word, Inc), which was later transferred into SAS (release 6.8e for Windows, SAS Systems, Inc) for analysis. Because of limited funds, there was no double entry of data, which is a technique used to limit misclassification bias from coding errors. Once the data was entered, I screened the database for coding errors by checking each variable for impossible or unusual values. This was feasible because of the small sample size and small number of variables.

3.7. OUTCOME VARIABLE

The outcome variable was PVIT, thus cases had PVIT and controls had no PVIT. Table 3a describes the outcome variable name and how it was coded. Furthermore, describes the coding for the PVIT scoring scheme.

3.8. EXPOSURE VARIABLES

3.8.1. Main exposure variable

The main exposure variables were the inherited thrombophilic disorders: factor V Leiden, prothrombin G20210A mutation, MTHFR C677T mutation, protein S deficiency, protein C deficiency, and antithrombin III deficiency. Table 3b describes the main exposure variable names and how they were coded.

3.8.2. Covariates

Tables 3c and 3d describe the patient-related and IV catheter-related characteristics respectively and how they were coded.

3.9. SAMPLE SIZE CALCULATION

The sample study was limited to 50 subjects (25 cases and 25 controls) based on feasibility and economic restraints (eg. thrombophilia assays cost on average $200.00 per patient). This restricts the accuracy by which parameters could be estimated. The main aim of this pilot study, however, was to provide preliminary information that would be useful to the design of the future larger PVIT study, and to provide a very rough estimate of PVIT incidence needed for sample size calculation for the larger study. While formal justification is difficult, 50 subjects should be sufficient for pilot testing study procedures, and given the wide range of PVIT incidence estimates in the literature, even a rough estimate will be helpful in planning a larger study.

However, based on sample size calculations for a case-control study and given a PVIT incidence of 15% in unexposed patients and 30% in exposed patients and a 95% confidence interval of 0.25, a total sample size of 350 would be required to detect a clinically meaningful odds ratio of 2.

3.10. STATISTICAL ANALYSIS

As a result of the small sample size of the study, the statistical analysis was limited to univariate and bivariate analyses. A trivariate analysis resulted in extremely small strata, and similarly a multivariate analysis resulted in unstable estimates as a result of extremely small numbers of observations for the independent variables. SAS© software (SAS© release 6.8e for Windows, SAS Systems, Inc) was used for the univariate and bivariate analyses.

3.10.1. Univariate analysis

Cases and controls were compared on all baseline variables. Because of the small sample size, I chose not to assume a normal distribution for continuous variables, hence results for continuous variables are presented as medians with interquartile ranges. However for the sake of completeness, means and standard deviations are also presented. Differences in means and medians are reported, as well as the 95% confidence interval for the mean and median* differences (65).

Dichotomous variables are presented as proportion (percent) affected in each outcome group. Differences in proportions are reported, as well as the associated 95% confidence interval for the difference $[p_1-p_2 \pm 1.96^* \sqrt{(p_1q_1/n_1 + p_2q_2/n_2)}]$. While this formula depends on a normal approximation, unlike single proportions, the difference of two proportions converges to normality very rapidly.

3.10.2. Bivariate analysis

Given the results of the univariate and correlation analyses, as well as prior knowledge of known predictors of PVIT, a crude Mantel-Haenszel odds ratio with 95% confidence intervals was determined for the association between PVIT and selected exposure variables, including the inherited thrombophilic disorders. The Mantel-Haenszel odds ratio was estimated to reflect the matched design (66). Because of the small sample size, we often have results with zero cells. In such cases, it is possible to add an arbitrary number of subjects to each cell, in order to produce variances for binomial distributions and odds ratio estimates. Popular choices include adding ½ or 1 to each cell. Under conditions of very small sample sizes, however, there is a very large difference in point estimates and confidence intervals, depending on whether ½ or 1 is used, and in all cases, the confidence intervals are so wide as to be non-informative. Therefore, we have chosen not to estimate these parameters in the cases of zero cells.

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* 95% confidence interval for median difference was calculated using a boostrap program on Splus© version 4 for Windows, Mathsoft, Seattle, 1997.

Chapter 3: Figures and Tables

Figure 3a. PVIT control selection strategy (eg. 7W)

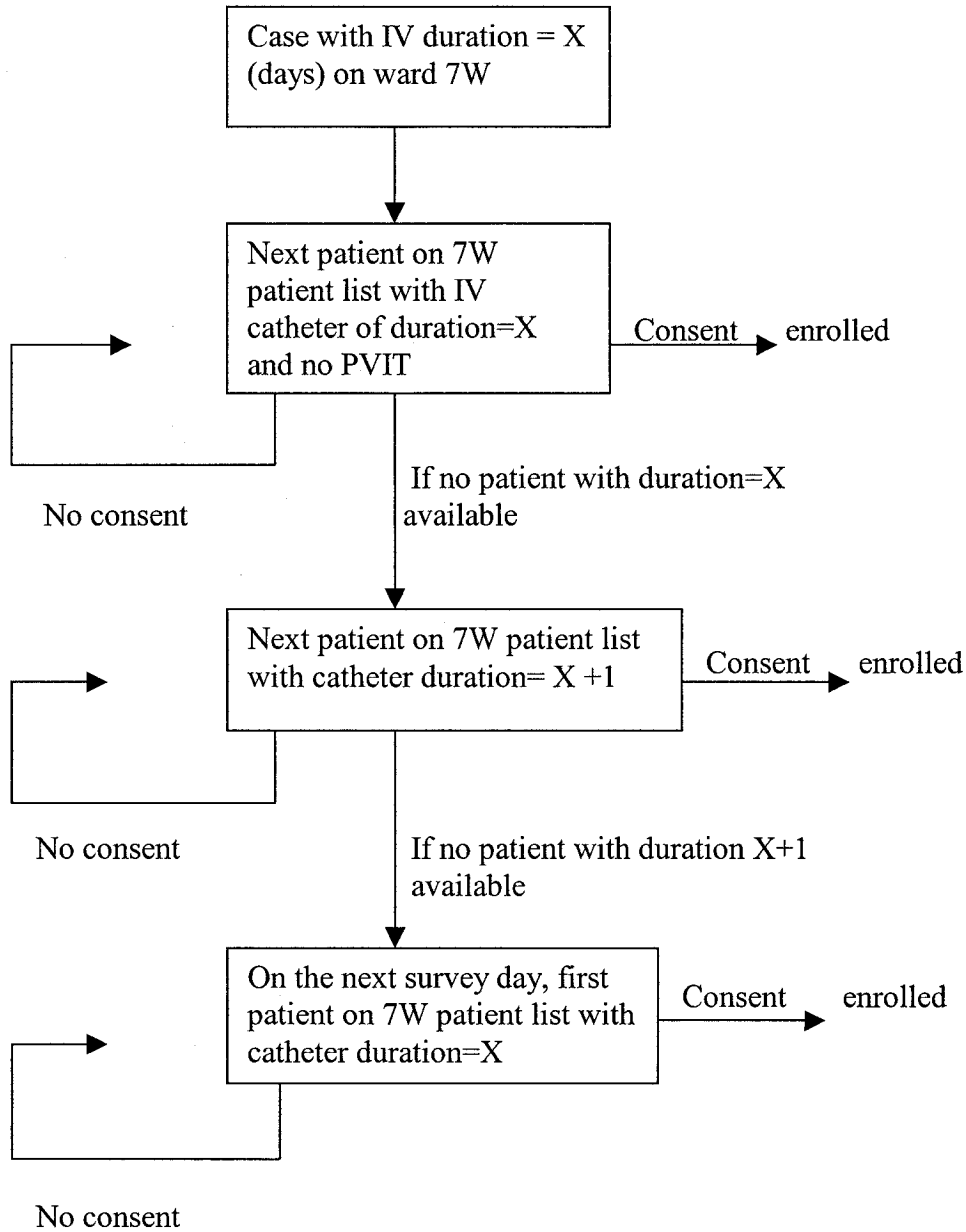

Table 3a. Outcome variable

VARIABLE DESCRIPTION	VARIABLE CODING	VARIABLE TYPE
Case status for PVIT	Case=1 Control=0	Dichotomous

Table 3b. Main exposure variables

VARIABLE DESCRIPTION	VARIABLE CODING	VARIABLE TYPE
Factor V Leiden	Absent=0 Present*=1	Categorical
Prothrombin G20210A	Absent=0 Present*= 1	Categorical
MTHFR C677T	Absent=0 Present†=1	Categorical
Protein S deficiency	Absent=0 Present=1	Categorical
Protein C deficiency	Absent=0 Present=1	Categorical
Antithrombin III deficiency	Absent=0 Present=1	Categorical

*Present = mutation that is either heterozygous or homozygous

† Present = homozygous mutation (Absent = normal or heterozygous mutation)

Table 3c. Covariates: Patient-specific characteristics

VARIABLE DESCRIPTION	VARIABLE CODING		VARIABLE TYPE
Patient age	Age, in years		Continuous
Gender	Female=0	Male=1	Dichotomous
Admitting ward	7W/7NW=0	MSTU=1	Dichotomous
Smoking	Never=0	Ever=1	Dichotomous
Reason for admission	Cancer-related=0 Cardiovascular disease=1 Infection=2 Other=3		Categorical
VTE risk factors (patient-specific and situation-specific)	No=0	Yes=1	Dichotomous
PVIT history	No=0	Yes=1	Dichotomous
Personal history of VTE	No=0	Yes=1	Dichotomous
Family history of VTE	No=0	Yes=1	Dichotomous
Oral medications (anti-thrombotic)	No=0	Yes=1	Dichotomous
Oral medications (pro-thrombotic)	No=0	Yes=1	Dichotomous

Table 3d. Covariates: IV catheter-specific characteristics

VARIABLE DESCRIPTION	VARIABLE CODING	VARIABLE TYPE
IV duration	days	Continuous
IV gauge	18 G (1.2 mm)=0 20 G (1.0 mm)=1 22 G (0.8 mm)=2	Categorical
Anatomic location	Hand/wrist=0 Forearm/antecubital fossa=1	Dichotomous
Patient location when IV inserted	Ward=0 ER/MHA*=1 Outpatient clinic=2	Categorical
IV inserter	Nurse=0 Medical resident=1	Dichotomous
IV medications	No=0 Yes=1	Dichotomous

* ER = Emergency Room; MHA = Medical Holding Area (where ER patients wait to be admitted to hospital)

Chapter 4: Results

In this chapter, statistical results and study procedure-related issues highlighted by the pilot study are reported.

4.1. STATISTICAL RESULTS

Results are presented separately for the patient survey and the case-control study.

4.1.1. Patient survey

A total of 44 PVIT episodes were observed (7W/7NW: 39 and MSTU: 5) during 41 non-consecutive survey days. During the first 13 survey days, number of catheters and catheter duration were not recorded. As a result, table 4.1 shows the total number of catheters, catheter-days, and PVIT episodes observed during the last 28 survey days.

Because 7W patients were re-located to 7NW and vice-versa twice during the study period (due to renovations), it was time-consuming and labor-intensive to keep track of each patient's ward allocation. The results for 7W and 7NW have therefore been combined.

4.1.1.1. MSTU PVIT incidence

During 28 non-consecutive survey days, amongst 139 peripheral IV catheters, 2 episodes of PVIT were observed among 477 catheter-days. This translates into a PVIT rate of 4.2 per 1000 catheter-days (95% CI [0.2,8.2] per 1000 catheter-days)*.

4.1.1.2. 7W/7NW PVIT incidence

During 28 non-consecutive survey days, amongst 532 peripheral IV catheters, 29 episodes of PVIT were observed among 1673 catheter-days. This translates into a PVIT rate of 17 per 1000 catheter-days (95% CI [0.8,33.2] per 1000 catheter days).

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* 95%CI for poisson parameter, $(x-1.96\sqrt{x}, x+1.96\sqrt{x})$ where x=count of events in time (normal approximation)

4.1.1.3. Total sample PVIT incidence

A total of 31 PVIT episodes were observed among 2150 catheter days over 28 days. This results in a total per–catheter PVIT rate of 14 per 1000 catheter-days (95% CI [6.7,21.3] per 1000 patient-catheter days).

Table 4.1. Survey statistics

WARD	% OF PATIENTS WITH CATHETER PER DAY	TOTAL NUMBER OF CATHETERS	TOTAL NUMBER OF CATHETER-DAYS	TOTAL NUMBER OF PVIT EPISODES	CUMULATIVE PVIT INCIDENCE*	PVIT INCIDENCE (per 1000 patient-catheter-days)
MSTU	38%	139	477	2	1.4%	4.2
7NW/7W	34%	532	1673	29	5.5%	17
TOTAL	36%	671	2150	31	4.6%	14

Note: *Cumulative PVIT incidence = (Total PVIT episodes/ total catheters) X 100

4.1.2. Case-control study

The statistical analyses for the matched case-control study are presented below. Due to the small sample size, most parameters of interest were not accurately estimated. However, it is worthwhile to examine these analyses for clinically interesting results that would merit further attention in the larger study.

4.1.2.1. Patients excluded

In all, 31 patients, consisting of 19 cases and 12 controls, were excluded from the study because they did not provide informed consent. Of the 19 cases, 14 were not willing to participate and 5 were not competent to give consent. Of the 12 controls, 10 were not willing and 2 were not competent.

As seen in Table 4.2, study cases and excluded cases were relatively similar in age and sex distribution. In contrast, compared to study controls, the excluded control patients were younger and a higher proportion were female (Table 4.3).

Table 4.2. Comparison of study cases vs. non-consenting cases

VARIABLE	CASES N=25	NON-CONSENTING CASES N=19
Age (years), median (IQR)	72 (28-89)	71 (36-86)
Male sex (n (%))	11 (44%)	7 (37%)

Table 4.3. Comparison of study controls vs. non-consenting controls

VARIABLE	CONTROLS N=25	NON-CONSENTING CONTROLS N=12
Age (years), median (IQR)	72 (29-90)	64 (50-72)
Male sex (n (%))	11 (44%)	3 (25%)

4.1.2.2. Univariate analysis

4.1.2.2.1. Patient Characteristics

1. Demographic variables (Table 4.4)

Cases and controls were similar in age and sex distribution, and 84% of cases and 85% of controls were admitted to 7W or 7NW compared to MSTU.

Table 4.4. Demographic data on cases and controls

VARIABLE	CASES N=25	CONTROLS N=25	PER CENT DIFFERENCE [95% CI]
Age (years), median (IQR)	72 (28-89)	72 (29-90)	0 [-23,7]
mean (SD)	69.8 (13.6)	64.5 (19.7)	5.3 [-4.3,14.9]
Sex (%male)	11 (44%)	11 (44%)	0%[-28,28]
Admitting ward (% 7W/7NW)	21 (84%)	23 (92%)	-8% [-9,36]

2. Admitting medical diagnosis (Table 4.5)

More controls than cases were admitted with a cancer-related diagnosis, though the difference was not significant. Cases were more likely than controls to be admitted

because of cardiovascular disease or infection. Because of the small sample size, I could not study specific types of cancer or infection.

Table 4.5. Admitting medical diagnosis in cases and controls

VARIABLE	CASES N=25	CONTROLS N=25	PER CENT DIFFERENCE [95% CI]
Cancer-related	8 (32%)	13 (52%)	-20%[-47,6.8]
Cardiovascular disease	5 (20%)	3 (12%)	8%[-12,28]
Infection	6 (24%)	3 (12%)	12%[-9,33]
Other	6 (24%)	6 (24%)	0% [-23, 23]

3. Risk factors for VTE

i. Patient Specific (Table 4.6)

Active cancer, paralysis, and inflammatory bowel disease were equally present among cases and controls.

Table 4.6. Patient specific risk factors for VTE in cases and controls

VARIABLE	CASES N=25	CONTROLS N=25	PER CENT DIFFERENCE [95% CI]
Active cancer	12 (48%)	13 (52%)	-4[-32,24]
Paralysis	2 (8%)	1 (4%)	4%[-9,17]
Inflammatory bowel disease	1 (4%)	1(4%)	0%[-11,11]
Nephrotic syndrome	0	0	---
Pregnancy	0	0	---
Previously known inherited thrombophilic disorder	0	0	---

ii. Situation Specific (Table 4.7)

Sixteen percent of cases compared to 4% controls had surgery in the 90 days prior to study enrollment. The type of surgery was not recorded. Immobilization was equally present among cases and controls.

Table 4.7. Situation specific risk factors for VTE in cases and controls

VARIABLE	CASES N=25	CONTROLS N=25	PER CENT DIFFERENCE [95% CI]
Immobilization	5 (20%)	5 (20%)	0%[-22,22]
Post-surgical	4 (16%)	1 (4%)	12%[-4,28]
Fracture	0	0	---

4. Family and personal history of thrombosis (Table 4.8)

With respect to personal and family history of VTE, the difference among cases and controls is very small. However, because the confidence intervals are very wide, the effect of these two variables on PVIT is inconclusive and will have to be studied further in the larger study.

Among cases and controls reporting ever having an IV catheter in the past, 18% of cases compared to none of the controls had a prior PVIT episode. This difference is important given the confidence interval does not include zero and its upper limit of 34% is clinically important.

Table 4.8. Family and personal history of thrombosis in cases and controls

VARIABLE	CASES N=25	CONTROLS N=25	PER CENT DIFFERENCE [95% CI]
History VTE	4 (16%)	3 (12%)	4%[-15,23]
Family VTE history	2 (8%)	1 (4%)	1%[-9,17]
PVIT history with prior IV	4 (18%) (n=22)*	0 (n=23)*	18%[2,34]

Note: *22 cases and 23 controls reported prior IV catheter insertion.

5. Oral medications (Table 4.9)

i. Anti-thrombotic medications

An equal proportion of cases and controls were taking warfarin, an oral anticoagulant. Aspirin use was relatively similar among cases and controls. More cases than controls were administered heparin subcutaneously for VTE prophylaxis while the IV catheter was in place. The confidence interval is too wide for definitive conclusions, but a potential difference of up to 28% is clinically interesting.

Table 4.9. Anti-thrombotic medications in cases and controls

VARIABLE	CASES N=25	CONTROLS N=25	PER CENT DIFFERENCE [95% CI]
Aspirin	6 (24%)	7 (28%)	-4%[-28,20]
Warfarin	2 (8%)	2 (8%)	0%[-15,15]
Unfractionated heparin subcutaneous	5 (20%)	3 (12%)	8%[-12,28]
Low Molecular Weight Heparin	0	0	
Ticlodipine	0	0	
Clopidogrel	0	0	

ii. Pro-thrombotic medications

None of the cases or controls were taking oral contraceptive medications or hormone replacement therapy while the IV catheter was in place.

4.1.2.2.2. Catheter-related characteristics (Table 4.10)

The catheter duration varied between 1 and 6 days (median 4 days, mean 3.5 days ± 1.6). The most common site for IV catheter insertion in the study population was the forearm or antecubital fossa compared to the hand or wrist. Moreover, 92% of cases had their IV inserted in the forearm or antecubital fossa compared to 68% of controls. This difference is important since the confidence interval does not include zero, and a possible difference of up to 45% is clinically significant.

Table 4.10. Catheter-specific characteristics in cases and controls

VARIABLE	CASES N=25	CONTROLS N=25	PER CENT DIFFERENCE [95% CI]
Catheter duration (days), median (IQR)	4 (1-6)	4 (1-6)	---
mean (SD)	3.5(1.5)	3.5(1.5)	---
Anatomic location of IV			
Hand or wrist	2 (8%)	8 (32%)	-24%[-45,-3]
Forearm or antecubital fossa	23 (92%)	17 (68%)	24%[3,45]
IV gauge			
18	6 (24%)	5 (20%)	4%[-19,27]
20	8 (32%)	8 (32%)	0%[-26,26]
22	11 (44%)	12 (48%)	-4%[-27,19]
IV inserter			
Nurse	25(100%)	25(100%)	0%[0,0]
Medical resident	0	0	---
Patient location when IV inserted			
Ward	16 (64%)	14 (56%)	8%[-19,35]
ER/MHA	7 (28%)	8 (32%)	-4%[-29,21]
Outpatient Clinic	2 (8%)	3 (12%)	-4%[-21,13]
IV dextrose solution	15(60%)	13 (52%)	8%[-19,35]
IV antibiotic	12 (48%)	9 (36%)	12%[-15,39]
IV heparin	1 (4%)	5 (20%)	-16%[-33,2]
IV furosemide	4(16%)	2(8%)	8%[-10,26]
IV steroid	3(12%)	3(12%)	0%[-18,18]
IV blood	0	3(12%)	-12%[-25,1]
IV Kcl	3 (12%)	0	12%[-1,25]

A nurse inserted all catheters. Among cases and controls, the differences in IV gauge and in the patient's hospital location when the IV catheter was inserted are very

small. Nonetheless, given the very wide confidence intervals, further study is needed to conclude on their effect on PVIT risk.

More cases than controls were exposed to IV furosemide, dextrose solutions, Kcl, and antibiotics. However, no definitive conclusions on their effect on PVIT can be made. As a result of the small sample size, I could not investigate which types of antibiotic were associated with case status. Compared to cases, IV heparin and blood transfusions were more common among controls. Though the confidence intervals for both variables include zero, a difference of up to 33% for IV heparin and 25% difference for blood transfusions is clinically significant, and hence, a larger data set is needed to definitively study the effect of these two variables on PVIT risk.

4.1.2.2.3. Inherited thrombophilic disorders (Table 4.11)

Gene mutations

A large proportion of cases and controls (52% and 56% respectively) had the MTHFR heterozygous gene mutation, but only two cases and three controls had the more clinically meaningful homozygous mutation. The heterozygote factor V Leiden gene mutation was present among 12% of controls compared to none of the cases, and the prothrombin gene mutation occurred in only one case and one control.

Table 4.11. Inherited thrombophilic disorders in cases and controls

VARIABLE	CASES N=25	CONTROLS N=25	PER CENT DIFFERENCE [95% CI]
Factor V Leiden			
Heterozygote	0	3 (12%)	-12%[-25,0.7]
Homozygote	0	0	---
Hetero or Homo	0	3 (12%)	-12%[-25,0.7]
Prothrombin G20210A mutation			
Heterozygote	1 (4%)	0	4%[-4,12]
Homozygote	0	1 (4%)	-4%[-12,4]
Hetero or Homo	1 (4%)	1 (4%)	0%[-11,11]
MTHFR C677T mutation (homozygote)	2 (8%)	3 (12%)	-4%[-13,21]
Antithrombin III deficiency	2 (8%)	3 (12%)	-4%[-13,21]
Not on heparin therapy	1 (4%)	1 (4%)	0%[-11,11]
On heparin therapy	1 (4%)	2 (8%)	-4%[-65,15]
Protein S deficiency	8 (32%)	4 (16%)	16%[-7,39]
PT* < 13.5 sec	4 (16%)	4 (16%)	0%[-20,20]
PT* ≥13.5 sec	4 (16%)	0	16%[2, 30]
Protein C deficiency	(N=20)	(N=18)	
	1 (5%)	1 (6%)	-1% [-14,15]

Note: *PT = prothrombin time

Anticoagulant protein deficiencies

Five cases and seven controls (24% of the study population) did not have testing for protein C deficiency. Around the time of the start of the pilot study, the JGH Hematology Laboratory Director instituted a new policy restricting testing for protein C deficiency to patients whose prothrombin time was less than 13.5 seconds. Unfortunately, neither I nor my supervisor were advised. The reason for the new policy is as follows: Prothrombin time measures the time required for a clot to form in a blood sample. It is a screening procedure for overall evaluation of extrinsic coagulation factors V, VII, and X, and of prothrombin and fibrinogen (67), and is used to monitor oral anticoagulant therapy (warfarin). A prothrombin time ≥ 13.5 seconds may indicate deficiencies in fibrinogen, prothrombin, or factors V, VII, or X; vitamin K deficiency; liver disease; or it may result

from ongoing oral anticoagulant therapy (67). Protein C is synthesized in the liver and requires vitamin K for its synthesis. Thus, vitamin K deficiency, hepatic disease, as well as oral anticoagulant therapy can result in depressed levels of protein C, resulting in acquired protein C deficiency (67). Consequently, a positive test for protein C deficiency in the setting of a prothrombin time ≥ 13.5 seconds is not specific for inherited protein C deficiency, i.e. it can also be indicative of an acquired protein C deficiency. By restricting protein C testing to patients with a prothrombin time < 13.5 seconds, the laboratory hopes to decrease the number of false positive tests for inherited protein C deficiency, especially since the test is expensive.

Protein S testing was not restricted during this study, but will be in the near future. Acquired protein S deficiency can result from vitamin K deficiency, oral anticoagulant therapy, and liver disease (67). Furthermore, the following conditions, although they do not alter prothrombin time, also lead to depressed levels of protein S: oral contraceptive use, pregnancy, nephrotic syndrome, inflammatory conditions, and acute VTE (67). Thus, a clotting assay test for protein S deficiency in the setting of a prothrombin time ≥ 13.5 seconds is also not specific for an inherited deficiency.

Twice as many cases as controls were protein S deficient (8 vs. 4 respectively). None of these patients were pregnant or taking oral contraceptive medications; as well, none had an acute VTE episode or were diagnosed with nephrotic syndrome. However, the prothrombin time was ≥ 13.5 seconds in 4 of the 8 cases who were protein S deficient and none of the 4 controls. Of these 4 cases with an elevated prothrombin time, 1 was taking warfarin.

As a result, the presence of protein S deficiency was stratified according to prothrombin time, since protein S deficiency in patients whose prothrombin time is ≥ 13.5 seconds may be indicative of either an inherited or acquired deficiency. Among protein S deficient patients with prothrombin times < 13.5 seconds, which is more specific for an inherited deficiency, there were 4 cases and 4 controls.

Antithrombin III deficiency can also be acquired. Low molecular weight or IV heparin, liver disease, acute inflammatory conditions, or active VTE can lead to depressed levels of antithrombin III (67). Hence, a positive test for antithrombin III deficiency is not specific for an inherited deficiency in the setting of heparin or any of the

above factors. Although none of the 5 patients with a positive test for antithrombin III deficiency had known liver disease or acute VTE, 1 case and 2 controls were exposed to IV heparin therapy, the most common cause of acquired antithrombin III deficiency. No study patients were taking low molecular weight heparin.

4.1.2.3. Bivariate analysis

Bivariate analyses were performed to assess, in a preliminary fashion, the association between PVIT and each of the inherited thrombophilic disorders, as well as to explore potential associations between PVIT and selected independent variables. Protein C deficiency was not assessed because of the large amount of missing data.

4.1.2.3.1. PVIT and the inherited thrombophilic disorders

The results of the crude bivariate analyses between PVIT and the genetic mutations are presented in table 4.12. No useful information is derived from the analyses involving Factor V Leiden, prothrombin and MTHFR gene mutation because of the extremely small cell numbers (uniformly less than 5 positives).

Table 4.12. Bivariate analysis comparing PVIT with the inherited thrombophilic disorders

VARIABLE	CASE STATUS		ODDS	95% CI
	CASE	CONTROL	RATIO	
Factor V Leiden present*	0	3	---	
Factor V Leiden absent	25	22		
Prothrombin mutation present*	1	1	1.0	[0.05,16.9]
Prothrombin mutation absent	24	24		
MTHFR gene mutation present†	2	3	0.6	[0.1,4.2]
MTHFR gene mutation absent	23	22		

Note: *Heterozygote and homozygote mutations have been combined.
†Homozygote mutation

The PVIT odds ratios for protein S deficiency and antithrombin III deficiency were, for reasons discussed already, stratified according to prothrombin time and IV heparin use, respectively. The positive crude association between protein S deficiency

and PVIT (odds ratio 2.5) is entirely due to the effect of patients with a prothrombin time ≥ 13.5 seconds, since the association is nullified in patients with a prothrombin time < 13.5 seconds (Table 4.13). Similarly, among patients with no heparin therapy, the association of PVIT and antithrombin III deficiency tends toward the null (Table 4.14).

Table 4.13. Protein S deficiency in cases and controls stratified by prothrombin time

VARIABLE	PROTEIN S DEFICIENT		NOT PROTEIN S DEFICIENT		ODDS RATIO	95% CI
	CASE	CONTROL	CASE	CONTROL		
CRUDE	8	4	17	21	2.5	[0.6,9.6]
PT* < 13.5	4	4	15	15	1.0	[0.2,4.8]
PT* ≥ 13.5	4	0	2	6	---	

Note: * PT = prothrombin time

Table 4.14. Antithrombin III deficiency in cases and controls stratified by heparin therapy

VARIABLE	ANTITHROMBIN III DEFICIENT		NOT ANTITHROMBIN III DEFICIENT		ODDS RATIO	95% CI
	CASE	CONTROL	CASE	CONTROL		
CRUDE	2	3	23	22	0.6	[0.1,4.2]
NO HEPARIN	1	1	23	19	0.8	[0.04,13.6]
HEPARIN	1	2	0	3	---	

4.1.2.3.2. PVIT and selected covariates

The choice of variables for the bivariate analyses were driven by prior knowledge of known predictors of PVIT, specifically the catheter-specific risk factors, and the results of the univariate analysis. For the purpose of this analysis, age was dichotomized at the median.

1. Known catheter-specific risk factors (Table 4.15)

Of the known catheter-specific risk factors, IV furosemide, IV antibiotics, and IV dextrose solutions were predictive of PVIT, though the 95% confidence intervals for each

estimate were wide and crossed one. In particular, PVIT was strongly associated with placement of the IV catheter in the forearm. Specifically, patients with PVIT were 5.4 times more likely than controls to have the IV catheter in the forearm or antecubital fossa as opposed to the wrist or hand. With respect to IV heparin, PVIT patients were 0.2 times as likely as controls to be receiving IV heparin, suggesting a protective effect of heparin against PVIT, but again the confidence interval is very wide.

Table 4.15. Bivariate analysis comparing PVIT with known catheter-specific risk factors

VARIABLE	CASE STATUS		ODDS RATIO	95% CI
	CASE	CONTROL		
IV dextrose solution given	15	13	1.4	[0.5,4.2]
IV dextrose solution not given	10	12		
IV heparin given	1	5	0.2	[0.02,1.6]
IV heparin not given	24	21		
IV Kcl given	3	0	---	---
IV Kcl not given	22	25		
IV antibiotic given	12	9	1.6	[0.5,5.1]
IV antibiotic not given	13	16		
Blood transfusion given	0	3	---	---
Blood transfusion not given	25	22		
IV furosemide given	4	2	2.2	[0.4,13.2]
IV furosemide not given	21	23		
Arm or antecubital fossa placement	23	17	5.4	[1.0,28.8]
Hand or wrist placement	2	8		

2. Other co-variates (Table 4.16)

With respect to other potential predictors of PVIT, of note was the strong association observed between PVIT and surgery in the preceding 90 days (odds ratio 4.6). Of further note, cases were more likely than controls to be paralyzed (odds ratio 2.1) and to have a family history of VTE (odds ratio 2.1). There was also a trend toward a

positive association between PVIT and an infection-related diagnosis on admission (odds ratio 2.3). However, this may be explained by the fact that all 6 cases and 1 of the 3 controls with an infection-related diagnosis were taking IV antibiotics, a risk factor for PVIT. Nonetheless, all the confidence intervals for these estimates were very wide, so at best all these analyses will have to be redone in the future, larger data set.

Table 4.16. Bivariate analysis comparing PVIT with other co-variates

VARIABLE	CASE STATUS		ODDS RATIO	95% CI
	CASE	CONTROL		
Age >72	12	11	1.2	[0.4,3.6]
Age<=72	13	14		
Infection-related diagnosis	6	3	2.3	[0.5,11]
No infection-related diagnosis	19	22		
Active cancer present	12	13	0.9	[0.3,2.6]
Active cancer absent	13	12		
Paralyzed	2	1	2.1	[0.2,24.6]
Not paralyzed	23	24		
Post-surgical	4	1	4.6	[0.5,44.2]
Not post-surgical	21	24		
History PVIT	4	0	---	---
No history of PVIT	22	23		
History of VTE	4	3	1.4	[0.3,7.0]
No history of VTE	21	22		
Family history of VTE	2	1	2.1	[0.2,24.6]
No history of VTE	23	24		
Heparin SC* given	5	3	1.8	[0.4,8.7]
Heparin SC* not given	20	22		
Taking aspirin	6	7	0.8	[0.2,2.9]
Not taking aspirin	19	18		

Note: *SC = subcutaneous

4.2. STUDY PROCEDURE -RELATED RESULTS

Three important issues related to study procedures were highlighted by this pilot study. They are presented here as part of the study's objective findings and will be discussed in further detail in the following chapter. These issues do not represent the study limitations, which will be discussed in the next chapter, but rather important information that will help in the optimal design of the larger two-center study.

1. Inadequate communication with the JGH Hematology Laboratory.
2. The need to draw a blood sample was an important factor resulting in unwillingness to consent.
3. Underestimation of time needed to survey the medical wards.

4.2.1. Communication with the JGH Hematology Laboratory

The restriction of protein C testing that was instituted midway through the study resulted in 24% of the study population not having protein C testing. This was not realized until data entry, when the study investigators were unblinded to the results.

During the planning phase of the study, the director and head technician of the hematology laboratory were extensively involved in advising the study investigators on blood sample processing and analysis. However, once the study began, there was little communication between the laboratory and study investigators, likely the result of limited resources, both monetary and personnel, which had been allocated to this study.

However, the impact of the missing protein C information is not as significant as it would have been had this occurred during the larger two-center study because the pilot study was not powered to detect a statistically significant difference in protein C among cases and controls. Nonetheless, it does highlight the importance of establishing good

lines of communication between the study investigators and the hematology laboratory, and providing regular updates to all collaborators on the study progress

4.2.2. Blood taking and unwillingness to consent

Of the 31 non-consenting study patients, 24 patients were not willing to participate (14 cases and 10 controls) and 8 were not able to provide informed consent. Of the 24 unwilling patients, 46% (8 controls and 3 cases) refused to participate because they did not want to provide a blood sample. The two most common reasons given were the following: 1) just had their blood taken and would rather not have it re-taken again, and 2) blood taking is too painful. The remaining 64% of patients who were unwilling to consent refused because they were too ill or tired to participate.

Since drawing of blood is essential to the study, refusal to consent because of blood taking is an important issue that has to be addressed in the design of the larger two-center study. If almost ½ of the non-consenting subjects are refusing because of blood taking, this impacts on the feasibility of conducting the larger study. Generally, the higher the rate of non-consent, the longer it takes to recruit, which is a problem for most studies as operational budgets need to be calculated according to a specific timeframe.

Furthermore, non-consent can bias the results of a study, if the reason for non-consent is related to the exposure. This is unlikely in this study because patients with inherited thrombophilia disorders are not aware they have these disorders.

4.2.3. Underestimation of surveying time

On average, 45 minutes were needed to survey the IV catheters on 7W and 7NW and 20 minutes to survey in MSTU. The original pilot study protocol and a preliminary budget for the larger study allocated 30 minutes for surveying of 7W and 7NW. The extra 15 minutes per ward amounts to an extra 2 hours for the larger two-center study since 8 wards will be surveyed in total. This extra time has a significant impact on the projected budget for the larger study, specifically on the budget allocated for nursing salary, which is based on an hourly fee.

Time needed to survey was under-estimated because of failure to consider the following: 1) 10-15% of IV catheters per ward were not dated (date of insertion not noted on the catheter) and 2) 3-4 patients per ward were medically isolated for infection control reasons, necessitating the investigator to put on a gown and mask before entering the patient's room. In the former case, the investigator had to search for the patient's nurse and ask her to consult her personal nursing notes to find the date of catheter insertion. This was extremely time consuming since the nurse was not always available. Consequently, this issue will have to be addressed in the final design of the larger study in an attempt to limit the budget and improve nursing efficiency. With respect to medical isolation of patients, there is little that can be done to reduce time spent "gowning" and "un-gowning".

Chapter 5: Discussion

PVIT is an important problem in hospitalized patients receiving IV therapy. Catheter-specific risk factors have been well elucidated but patient-specific risk factors have received little attention to date. Given emerging biologic and indirect clinical evidence suggestive of a causal role for thrombosis in the pathogenesis of PVIT, it seems biologically feasible that the inherited thrombophilic disorders, which are strongly associated with an increased risk of DVT, may also play an important role in the development of PVIT. These disorders may possibly represent, at least in part, the as yet undefined "biologic vulnerability" to developing PVIT (4).

In this thesis, I describe a pilot study whose objective was to collect information useful to the design of a much larger study that would ultimately address the postulated association between PVIT and the inherited thrombophilic disorders.

5.1. OVERVIEW OF IMPORTANT FINDING

5.1.1. Patient survey statistics

The PVIT incidence varies in the literature between 0.1% to 53% (see Table 2a). The overall cumulative incidence of PVT for our study population was 4.6%. The per-catheter PVIT incidence rate was 4.2 per 1000 catheter-days (95% CI [0.2,8.2] per 1000 catheter-days) on MSTU, 17 per 1000 catheter-days (95% CI [0.8,33.2] per 1000 catheter days) on 7W/7NW, and 14 per 1000 catheter-days (95% CI [6.7,21.3] per 1000 patient-catheter days) for the combined wards. Because surveying occurred on non-consecutive days, undoubtedly catheters as well as PVIT cases were missed. However, because the decision to survey on a particular day was dependent on investigator availability and not on any prior information related to number of inserted IV catheters or likelihood of observing PVIT, it is unlikely that the PVIT rate among missed IV catheters would differ from that observed. In fact, in 1996 Dr. Mark Miller, the chief of the Division of Infectious Disease at the JGH, performed a small survey of 4 medical wards (including

7W and 7NW) over 40 consecutive days and observed a similar PVIT incidence rate of 15 per 1000 catheter-days (personal communication).

The reason for the discrepancy between the 7W/7NW and MSTU rates is unclear. The difference may be due entirely to chance, since the confidence interval for the estimate of the 7W/7NW rate is very wide (95% CI [0.8,33.2] per1000 catheter-days), and includes the MSTU estimate. However, it is well known that 7W/7NW patients and MSTU patients are different. Patients admitted to MSTU are relatively medically stable and typically have only one medical problem, whereas, patients admitted to 7W/7NW tend to have multiple medical problems. Specifically, they are more likely than MSTU patients to be immunocompromised and/or have cancer, which have been linked to an increased risk of PVIT (1,4). As a result, they are more likely to be exposed to multiple IV medications such as antibiotics and chemotherapeutic drugs, which are also known to be important PVIT risk factors.

Because the future study will not include short stay wards like MSTU, the 7W/7NW PVIT cumulative incidence estimate of 5.5% was provided to the statistician of for sample size calculations. Though the future study is similar to the pilot study in its methodology, it will have a nested case-control design rather than a simple case-control format. In other words, an underlying cohort of IV catheters will be defined and surveyed daily. From this cohort, all cases will prospectively be identified, and controls will be randomly selected from cohort members at risk for PVIT at the tine the case occurs. This ensures that no cases are missed and permits estimation of the absolute risk of PVIT in patients with and without inherited thrombophilic disorders. As such, the sample size calculation was carried out as for a cohort study under a proportional hazards model because nested case-control studies are only slightly less efficient than cohort studies (due to not using the whole cohort) and there is no specific literature on sample size calculations for nested case-control studies.

5.1.2. Case-control analysis

Though the statistical analysis for the pilot study was limited to univariate and bivariate analyses, and parameters were not accurately estimated, a few interesting,

hypothesis-generating findings were observed nonetheless, which will be addressed more definitively in the larger study.

5.1.2.1. Catheter-specific factors

There was a trend toward an association between case status and several previously described catheter-specific factors. They are presented below as possibly predictive and protective for PVIT. Of course, for most of these factors, confidence intervals were too wide for definitive conclusions.

5.1.2.1.1. Possible predictive factors for PVIT

Consistent with previous studies (4,9,10,13,21), cases were estimated to be 1.4 times more likely to be receiving IV dextrose solution, 1.6 times more likely to be receiving IV antibiotics, and 2.2 times more likely to be receiving IV furosemide, compared to controls. Furthermore, 3 cases compared to 0 controls were receiving IV Kcl through the IV catheter.

Similar to Maki's findings (4), we estimated that cases were 5.4 times more likely than controls to have the IV catheter placed in the forearm or antecubital fossa than the hand or wrist (95% CI [1.0,28.8]). It remains unclear if this potential association is a reflection of vein size (forearm or antecubital veins are bigger in diameter than hand veins) or rather the gauge of catheter, since the choice of catheter gauge is dependent on the planned IV insertion site. For example, smaller gauge IV catheters (larger diameter) are usually placed in larger veins and vice versa. In the future study, any association between PVIT and catheter site will be adjusted for catheter gauge.

5.1.2.1.2. Possible protective factors for PVIT

Firstly, we estimated that controls were 5 times more likely to be receiving IV heparin compared to cases. This is in agreement with Randolph's meta-analysis on the benefit of heparin in peripheral IV catheters, which showed a decreased risk of PVIT with heparin IV flushes (31). Furthermore, given heparin's anti-thrombotic effect, our finding is suggestive of a role for thrombosis in PVIT development.

Receiving a blood transfusion also showed a trend toward a protective effect, since 3 controls and 0 cases had received blood through the IV catheter. No prior studies have linked blood transfusion to PVIT. However, it is recognized that during storage of frozen donated blood there is a relatively rapid loss of some clotting factors (68). For example, factor XI and factor VII fall to about 20% of their original level within the first week of storage. As a result, decreased levels of activated clotting factors may occur when more than the patient's blood volume (10-12 units) is replaced by banked blood within a 24 hour-period (68). Such a large volume of blood transfusion is rare, but has been described in cases of severe trauma. The number of blood transfusions received through the IV catheter was not recorded in this study, but as a result of our finding, data on number of units of blood transfused will be collected in the future larger study.

5.1.2.2. Patient-specific factors

Some patient-specific risk factors showed an interesting trend toward an association with PVIT. However, definitive conclusions are not possible given the wide confidence intervals.

With respect to previously described patient-specific risk factors, in this study, sex did not show an association with PVIT, though some studies have shown female sex to be a risk factor. However, given the wide confidence intervals, we cannot rule out such an association. Patients with cancer and/or immunodeficiency states are at an increased risk for PVIT (1,4), but in our small sample, cases and controls were equally likely to report active cancer. Compared to controls, cases were 2.3 times more likely to be admitted with an infection-related diagnosis. This has not been described in previous studies. However, the association between infection-related admitting diagnosis and PVIT may be explained, at least in part, by IV antibiotics, since 7 of the 9 patients with this diagnosis received IV antibiotics.

Of particular interest is the reporting of at least one PVIT episode with a prior IV catheter in 4 cases compared to 0 controls (difference of 18% [2,34]) This lends support to a "biologic vulnerability" to PVIT, which, though unproven, could be linked to the inherited thrombophilic disorders. However, because data on the number of prior IV catheterizations was not collected, this finding may simply reflect an increased rate of

catheterization among cases, and as a result, a greater opportunity (i.e. exposure) to develop PVIT compared to controls. In the future study, in patients reporting a prior PVIT episode, we plan to further specify number of prior catheterizations and PVIT episodes. However, the information on number of prior catheterizations may not be reliable, since insertion of an IV catheter is such a common procedure among hospitalized patients, hence it is difficult for patients to recall the number of catheterizations per hospitalization. Furthermore, hospitalized patients, if very ill, may not be aware of the IV catheter.

Of known risk factors for VTE, only surgery in the 90 days prior to IV catheter insertion showed an interesting trend. Of course, trends could not be ruled out for many of the other VTE risk factors, given the wide confidence intervals. With respect to surgery, however, cases were 4.6 times more likely than controls to have had surgery in the past 90 days. Patients recovering from surgery, particularly orthopedic and abdominal surgery, are at high risk of DVT of the lower extremities (eg., 71% DVT incidence after total knee replacement, 25% after major abdominal surgery (69)) due to clotting factor activation during surgery, endothelial damage to veins, and venous stasis as a result of prolonged bed-rest. Interestingly, DVT of the upper extremity has never been linked to post-surgical status. In our study, the observed trend toward an association between PVIT (all episodes occurred in the upper extremity) and post-surgical status may possibly be confounded by risk factors for PVIT, such as catheter gauge. Specifically, anesthesiologists usually insert large gauge IV catheters in surgical patients, so that fluids, blood, and medications can be delivered quickly in case of an emergency during the surgery. In the future study, the association between PVIT and post-surgical status will have to be adjusted for catheter gauge, as well as type of surgery and time since surgery.

5.1.2.3. Inherited thrombophilic disorders

With respect to the inherited thrombophilic disorders, the pilot study did not show a trend toward an association between PVIT and any of the inherited thrombophilic disorders. In fact, 3 controls compared to 0 cases were heterozygote for the factor V Leiden mutation. Furthermore, the association observed between protein S deficiency and

PVIT (OR 2.5) was entirely due to the effect contributed by those patients who had an elevated prothrombin time (≥13.5 seconds), for whom decreased protein S clotting activity assay is not specific for the inherited protein S deficiency. Thus, in the future study, the association between protein S and protein C will be adjusted for prothrombin time and other variables that cause acquired deficiencies of these proteins. Similarly, the association between PVIT and antithrombin III will be adjusted for concurrent heparin therapy, as well as liver disease and acute VTE. Alternatively, for the future study we could exclude patients on heparin or oral anticoagulant therapy, the two most common causes of acquired anticoagulant deficiencies. However, this would not allow us to assess the impact of these drugs as covariates on PVIT risk, which would be of interest to study given the lack of definitive evidence for the protective effect of heparin on PVIT.

In our sample of 25 controls, the prevalence of heterozygous factor V Leiden, prothrombin G20210A mutation, and homozygous MTHFR C677T mutation was 12%, 4%, and 12% respectively. These are relatively similar to the general population prevalences (Table 2c). However, the estimated prevalence of the inherited anticoagulant protein deficiencies in our sample were 10 to 200 times greater than those reported in the literature (protein S deficiency 16%*, antithrombin III deficiency 4%†, and protein C deficiency 5.5%‡) (Table 2c.). This discrepancy may be due to misclassification of the inherited protein deficiencies. Though prothrombin time was measured in all study patients, diseases such as nephrotic syndrome and acute VTE, and medications such as oral contraceptives can also lead to acquired protein deficiencies, despite a normal prothrombin time. In our study, information on these covariates was sought out by patient interview, but confirmation from another source, such as the patient's medical chart could have helped to reduce the possibility of misclassification errors.

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* 16% = (4 protein S deficient patients with PT <13.5 sec / 25 patients) x 100
† 4% = (1 antithrombin III deficient patients on no heparin therapy / 25 patients) x 100
‡ 5.5%=(1 protein C deficient patients/18 patients) X 100

Finally, another possible explanation for the higher-than-expected prevalences of anticoagulant protein deficiencies may be related to the source population of the JGH. Four years ago, a Thrombosis Clinic was established at the JGH, which has evolved into a referral center for patients with VTE and other thrombotic problems across the province of Quebec. As a result, if these patients were also more likely to be hospitalized at the JGH for reasons not necessarily related to VTE, then the prevalence of the inherited thrombophilic disorders in the JGH patient population would be higher compared to the general population. However, this is likely not the case given that the prevalence of the genetic mutations were comparable to those in the general population. There is no plausible reason as to why patients with genetic mutations would be less likely to be referred to the JGH Thrombosis clinic than patients with anticoagulant protein deficiencies. Nonetheless, in the future study, the Montreal General Hospital (MGH), which is not a thrombosis referral center, will also be used for patient recruitment, and as a result, the prevalence proportions of the thrombophilic disorders at the JGH and MGH can be directly compared.

5.1.3. Study procedure-related issues

The pilot study provided a unique opportunity to pilot test the procedures and methods in preparation for the larger study. As such, three issues were highlighted that necessitate changes to the procedures and methods of the future study. Furthermore, the matching scheme, an important aspect of the study, will also be discussed

5.1.3.1. Communication with JGH Hematology Laboratory

The inadequate communication between the study investigators and the JGH Hematology Laboratory resulted in almost ¼ of the study patients not having had protein C testing. I have since met with Director of the Hematology Lab who has assured me that potential changes in policy that could impact on the thrombophilia assays will be communicated to investigators.

As a result, in the future study, all blood samples will be processed and stored at the MGH and JGH laboratories until the end of patient recruitment, at which time they

will be transported to the JGH where all of the analyses will be performed. As a result, if there is a change in protocol with respect to the assays (eg. change in company supplying the reagents), all of the samples will be affected by this change, thus limiting the potential for misclassification. Moreover, before the analyses are to be performed, a meeting has now been scheduled with the Chief laboratory technician and Director of the JGH laboratory to ensure that the assays are performed as per protocol. Another advantage to performing the analyses at the end of patient recruitment is that all study personnel will be blinded to the results. Blinding to thrombophilic states during patient recruitment prevents biases that could potentially affect subsequent assessment of PVIT by the investigator and/or study nurse (eg. ascertainment bias).

5.1.3.2. Consent

The second issue highlighted was the high proportion of patients unwilling to consent due to the need to give a blood sample. Specifically, 46% of patients who refused consent did so because of the need for blood taking, either because they had just had their blood drawn or because the procedure is aversive. Because a high rate of non-consent lengthens recruitment time and thus impacts on a study's feasibility and cost, to try to improve upon this in the future study, we will offer to take the extra blood needed at the same time that regular bloods are scheduled to be drawn, despite the extra time and coordination that will be required of the study nurse. The time delay between study enrollment and study blood drawing should not bias the results because the presence of inherited thrombophilic disorders in the blood do not change over time.

5.1.3.3. Underestimation of time needed to survey

Time spent surveying also severely impacts on study feasibility and cost. To try to improve upon time spent determining the date of IV catheter insertion, the investigators will meet with all 8 study ward Head Nurses before the study begins to re-enforce the importance of the existing nursing policy of labeling all IV catheters with the date of insertion. If necessary, the investigators will also issue regular reminders to the Head Nurses during the study period.

5.1.3.4. Feasibility of matching

Finally, an important aspect of the study design was the matching scheme (i.e. matching on IV duration in days) (Figure 3a.). In general, there was no difficulty finding matched eligible controls. For 15 of the 25 cases, the control was found on the same day as the case. For the remaining 10 cases, the control was enrolled on the next survey day. For 5 of these cases, this was due to a lack of eligible controls meeting the matching criteria on the day of case enrollment, and for the remaining 5 cases, an eligible control was found, but the patient could not or was not willing to consent. The matching process did not incur added costs in time or effort, since catheter duration information was already being collected for the survey statistics.

5.2. STUDY LIMITATIONS

This study has several limitations, which will be discussed under the headings of sample size and validity.

5.2.1. Sample size

As already mentioned, because of the small sample size by design, the study did not provide accurate estimates of the parameters of main interest. Consequently, the analysis was fairly straightforward, restricted to univariate and bivariate statistics, and the results were extremely imprecise, as reflected by the wide confidence intervals. Moreover, I could not effectively explore for potential confounders and effect modifiers, as any stratified analysis resulted in extremely small strata.

5.2.2. Validity

Validity (lack of systematic error) is usually separated into 2 components: the validity of the inferences drawn as they apply to the source population of the study subjects (internal validity), and the validity of inferences as they pertain to people outside the source population (external validity or generalizability) (70). Internal validity is

required before external validity can be considered. In other words, in order to generalize findings of a study to the greater population, the inferences made to the source population of the study participant must be valid, or free of bias.

5.2.2.1. Internal validity

Both selection bias and misclassification bias may have impacted on the internal validity of this study.

5.2.2.1.1. Selection bias

In any case-control study, control selection is particularly vulnerable to selection bias. This is because intentional or unintentional selection forces often operate during recruitment of controls, and as a result, the sample of controls may not be representative of the study base that generated the cases.

This study was hospital-based. As such, the source population consists of all individuals who would be admitted to the JGH and have a peripheral IV catheter inserted. As mentioned previously, because the JGH is a referral center for VTE, a higher proportion of hospitalized JGH patients could have had potentially inherited thrombophilic disorders, which are important predictors of VTE, compared to the source population. Thus, the association between inherited thrombophilia and PVIT may be different for those who participated in the study, compared to those theoretically eligible but did not participate. As already discussed, in the future study, study subjects will be equally recruited from the JGH and MGH, which is not a referral center for VTE.

The surveying itself might have caused selection bias. Though the decision to survey was dependent only on investigator availability and not on any prior knowledge associated with exposure or outcome, because the survey occurred on non-consecutive days during the week, patients with short length of stays and thus short catheter durations (i.e. 1-2 days) may have been missed. In other words, patients with short catheter durations were less likely to participate in the study than patients with longer catheter durations. If the hypothesized association between PVIT and inherited thrombophilia exits, then it is biologically plausible that patients with inherited thrombophilia would develop PVIT within a short time of IV insertion than patients without inherited

thrombophilia. Since PVIT occurrence necessitates removal of the catheter, short catheter duration may be a marker of underlying inherited thrombophilia. Hence, the surveying procedure would tend to differentially select patients without inherited thrombophilia. In the future study, surveying will occur on a daily basis, thus avoiding this type of bias.

Although common to case-control studies, diagnostic bias or detection bias was not likely an important bias in this study because the association between inherited thrombophilic disorders and PVIT has never been suggested in the literature, and most patients with inherited thrombophilia are not aware they have these disorders, hence whether a patient has an inherited thrombophilic disorder would not influence the decision to insert an IV catheter or to be diagnosed with PVIT once a catheter is in place.

5.2.2.1.2. Information bias

Information bias can occur in case-control studies whenever there are errors in the measurement of the exposure variables, but the consequences of these errors are different, depending on whether the distribution of errors is similar among cases and controls (66). Simply, for discrete variables, measurement error is usually called misclassification (70). Misclassification that is different among cases and controls is called differential misclassification, and misclassification that is similar among cases and controls is referred to as nondifferential misclassification (70). The reason for this distinction is that nondifferential misclassification of a variable is predictable in the direction of the resulting bias, namely toward the null value, whereas the direction of the bias introduced by a differential misclassification cannot be easily predicted (i.e. the bias can either exaggerate or underestimate the effect) (66). It is the predictable direction of nondifferential misclassification bias that has contributed to the consideration of nondifferential misclassification as a more benign bias among the various types of possible biases in epidemiologic research (66).

In our study, differential misclassification, in the form of recall bias, may have occurred, since 4 cases and 0 controls reported a prior history of PVIT. Patients with current PVIT (cases) may be more likely to remember prior episodes of PVIT than control patients. Even though cases and controls were given the same verbal description of PVIT, it is possible that current disease experience affected recall of prior PVIT.

Differential recall can occur in any case-control study that relies on a subject's memory (70). In the future study, we will use a photograph of PVIT as a better stimulus to recall prior PVIT episodes.

As previously discussed, misclassification of protein S and antithrombin III deficiency could also have occurred in our study. Although most, but not all reasons, for an acquired anticoagulant protein deficiency are represented by an elevated prothrombin time, which was measured in all subjects, it is still possible that patients were falsely classified as having an inherited deficiency of protein S and antithrombin III, because information on potential causes of acquired protein deficiencies was collected by patient interview. However, because no links have been suggested between PVIT and conditions which can lead to acquired anticoagulant protein deficiencies (eg. oral contraceptive use, inflammatory conditions, etc.), this classification error should be similar among cases and controls, and hence represent a nondifferential misclassifcation bias. In the future study, to reduce this bias, information on potential causes of acquired anticoagulant protein deficiencies will be collected from the medical chart and factored into the analysis.

5.2.2.2. External validity

As mentioned, internal validity is a prerequisite to some degree (no study is 100% internally valid) for the study to contribute usefully to the general population. However, it may still be worth mentioning our study's restrictions to generalizability, so that they can be appropriately addressed in the future study:

1. The study was conducted at a single tertiary care hospital which is a referral center for VTE, hence the generalizability to other types of centers is unknown.
2. Surgical patients were not studied, hence the generalizability to a population of surgical patients is unknown.
3. The prevalence of protein S (16%), protein C (5.5%), and antithrombin III (4%) deficiency was higher than that reported for the general population, suggesting that our population was not representative of the general population of hospitalized patients.

The future study will not be as restrictive, since the source population will include a second tertiary care hospital that is not a referral center for VTE and surgical patients.

5.3. CONCLUSIONS

Though limited by a small sample size, this pilot study was important in several ways. Firstly, it was the first study to address whether there is an association between PVIT and inherited thrombophilia. Secondly, it suggested a potential protective effect for IV heparin, which can be directly estimated in future studies of strategies to prevent PVIT. Thirdly, some suggestions of effects between PVIT and catheter-specific risk factors were observed, such as IV dextrose, antibiotics, and site of catheter insertion, confirming previously established data on these associations. Fourthly, it added support to the possibility of an underlying "biologic vulnerability" to developing PVIT. Finally, and most importantly, it provided invaluable information relating to procedural issues, methodology, and PVIT incidence that was used in the design and calculation of sample size of the larger multi-center study.

Since the completion of the pilot study, this larger study was successfully funded in May of 2001 as an operating grant by the Fonds de la recherche en santé du Québec ($120,000.00 for 2 years). It is a case-control study, nested among hospitalized patients with IV catheters on a total of 8 wards (4 medical and 4 surgical) at the JGH and MGH. A total of 300 patients (100 cases to 200 controls) will be recruited over 13 months at both centers (150 per center). As of submission of this thesis, 50% of the required sample size has been enrolled, and the study is running smoothly, in part due to lessons learned from the pilot study. Furthermore, the background of this pilot study was published as a manuscript in the American Journal of Medicine in August, 2002 (71), becoming the first peer-reviewed article to introduce the possibility of a link between inherited thrombophilia and PVIT.

Chapter 6: References

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Appendix

McGill

Faculty of Medicine
3655 Promenade Sir William Osler
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler
Montréal, QC, H3G 1Y6

June 1, 2001

Dr. Vicky Tagalakis
Clinical Epidemiology and Community Studies
Jewish General Hospital
3755 Cote Ste. Catherine Road, Room A-130
Montreal, Quebec H3T 1E2

Dear Dr. Tagalakis,

Thank you for submitting the research proposal entitled "PVIT Pilot: The Role of Inherited Thrombophilia in Peripheral Vein Infusion Thrombophlebitis" for review by the Institutional Review Board of the Faculty of Medicine.

As this study involves no more than minimal risk we are pleased to inform you that approval for the study (June 2001) and Case and Control Consent forms (June 2001) was provided via an expedited review by the Chair on June 1, 2001, valid until June 2002. The study proposal will be presented for corroborative approval at the next meeting of the Institutional Review Board on June 18, 2001 and a certificate of approval will be issued to you at that time.

A review of all research involving human subjects is required on an annual basis in accord with the date of initial approval. Should any modification to the study occur over the next twelve months, please advise IRB appropriately.

We ask you to take note that it is the responsibility of the investigator to deposit a copy of the approved research protocol and consent form with the Research Ethics Board of each hospital where patients are enrolled or study data is collected.

Sincerely,

J. Lawrence Hutchison, M.D.
Chair
Institutional Review Board

cc: A06-M48-01A

Last Name (maiden) _____ First Name_____
U-# |__|__|__|__|__|__|__|__| Study ID # |__|-|__|__|__|
Today's date: |__|__|_____| Ward |_____| ❑Case or ❑Control

PATIENT CHARACTERISTICS

A. DEMOGRAPHICS

1. Date of birth (dd/mm/yyyy) |__|__|_____| 2. Sex: ❑ M ❑ F
3. Smoking: ❑ smoker ❑ ex-smoker ❑ non-smoker

B. PAST AND PRESENT MEDICAL HISTORY

1. Reason for admission? _____
_____

2. Does the patient have past or present medical history of the following?

CONDITION (yes/no)	Diagnosis date (dd/mm/yyyy)	Still Present? (yes/no)	Give Details (i.e. specify type, location, currently in treatment)
Liver Disease			
Renal Disease			
Pneumonia			
COPD &/or Emphysema			
CAD			
CHF			
Atrial Fib.			
Diabetes			
Stroke			
Peripheral Vascular Dz			
Other:			

Last Name (maiden) _____ First Name_____
J-# |__|__|__|__|__|__|__|__| Study ID # |__|-|__|__|__|

3. Does the patient <u>currently</u> have any of the following known risk factors for thromboembolic disease?

CONDITION Y/N		Duration of condition (years, months, weeks or days)	Give details (i.e. specific type, currently in treatment)
	Thrombophilic Disorder		
	Immobility		
	Fracture of the leg, hip, pelvis		
	Is post-operative?		
	Pregnancy		
	IBD		
	Malignancy		
	Nephrotic Syndrome		
	Paralysis		

4. Does the patient have a prior history of PVIT?

❑No

❑Yes, specify how many_____

❑Never had an IV before

Last Name (maiden) _____ First Name_____
U-# |__|__|__|__|__|__|__|__| Study ID # |__|-|__|__|__|

5. History of prior venous thromboembolism (VTE)?

- ❑ No
- ❑ Yes, specify below
- ❑ Do not know

Date of diagnosis	Specify type of VTE (i.e. PE , DVT)	Give Details (i.e. treatment, precipitating event)

6. If female, history of more than one spontaneous abortion?

- ❑No
- ❑Yes, specify how many_____

7. Is there a family history of VTE?

- ❑ No
- ❑ Yes, specify
- ❑ Do not know

8. While the iv catheter is (or was) in place, is (or was) the patient on any of the following medications?

	Yes	No
Warfarin	❑	❑
Heparin SQ	❑	❑
Low Molecular Weight Heparin	❑	❑
ASA	❑	❑
Plavix	❑	❑
Dipyridamole	❑	❑
Ticlid	❑	❑
Oral Contraceptive	❑	❑
Hormone Replacement Tx	❑	❑

Last Name (maiden) _____ First Name_____
U-# |__|__|__|__|__|__|__|__| Study ID # |__|-|__|__|__|

9. Was the patient on any of the above medications in the 2 weeks prior to the placement of the iv catheter? (i.e. not including the period during which the iv catheter is/was in place)

- ☐ No
- ☐ Yes, if yes specify the medication(s) and date that it was stopped?

_____

_____

_____

_____

Last Name (maiden) _____ First Name_____
U-# |__|__|__|__|__|__|__|__| Study ID # |__|-|__|__|__|

INTRAVENOUS CHARACTERISTICS

1. Date IV placed |__|__|_____| 2. Time of day placed __:__ pm or am

3. IV number |__|

4. Is IV in place currently? ❑ Yes → ❑NS lock or ❑Infusion
   time of assessment __:__ pm or am
   ❑ No → date removed |__|__|_____|
   time removed __:__ pm or am

5. Guage of catheter
   ❑ 14
   ❑ 16
   ❑ 18
   ❑ 20
   ❑ 22
   ❑ 24
   ❑ other _____

6. Anatomic location
   ❑ hand
   ❑ wrist
   ❑ lower arm
   ❑ antecubital fossa
   ❑ upper arm
   ❑ foot

7. Hours in place
   ❑ </= 12 hours
   ❑ 13-24 hours
   ❑ 25-36 hours
   ❑ 37-48 hours
   ❑ 49-60 hours
   ❑ 61-72 hours
   ❑ >73 hours

Last Name (maiden) _____ First Name_____
U-# |__|__|__|__|__|__|__|__| Study ID # |__|-|__|__|__|

8. Patient location when catheter inserted
- ❑ Ward
- ❑ Emergency Department
- ❑ CCU/ICU
- ❑ Operating room
- ❑ Dialysis
- ❑ Other _____

9. Inserted by
- ❑ Nurse
- ❑ Medical resident
- ❑ Anesthesiologist
- ❑ Other_____

10. Any comment on ease or difficulty of catheter insertion?

❑No

❑Yes, specify ❑very easy ❑easy ❑moderately difficult ❑very difficult

Last Name (maiden) _____ First Name_____
U-# |__|__|__|__|__|__|__|__| Study ID # |__|-|__|__|__|

11. Which of the following IV medications/solutions were administered through the catheter?

			YES	NO
KCL solutions			❑	❑
Dextrose containing solutions			❑	❑
Antibiotics			❑	❑
If yes,	Erythromycin	→ ❑		
	Cephalosporin	→ ❑		
	Aminoglycoside	→ ❑		
	Fluroquinolone	→ ❑		
	Penicillins	→ ❑		
	Ampicillin	→ ❑		
	Metronidazole	→ ❑		
	Clindamycin	→ ❑		
	other_____			
	_____			
	_____			
Corticosteroids			❑	❑
Blood transfusion			❑	❑
Heparin			❑	❑

Other IV meds._____
_____
_____
_____