We critically assessed studies on the clinical importance, diagnosis, incidence, and pathogenesis of peripheral vein infusion thrombophlebitis, including catheter-related and patient-related risk factors. We reviewed the evidence linking thrombosis, particularly prothrombotic states such as the inherited thrombophilic disorders, with peripheral vein infusion thrombophlebitis. Peripheral vein infusion thrombophlebitis occurs in 25% to 35% of hospitalized patients with peripheral intravenous catheters and has both patient-related implications (e.g., sepsis) and economic consequences (e.g., extra nursing time). Although duration of catheterization, catheter-related infection, and catheter material are important risk factors for peripheral vein infusion thrombophlebitis, patient-related risk factors are not well elucidated. Am J Med. 2002;113:146–151. ©2002 by Excerpta Medica, Inc.

METHODS
A computer search of the MEDLINE database from 1966 to 2001 was performed to identify English-language articles on the incidence of peripheral vein infusion thrombophlebitis, risk factors for its occurrence, pathophysiology, diagnostic criteria, and associations with thrombophilic disorders. Either the term phlebitis, thrombophlebitis, infusion thrombophlebitis, infusion phlebitis, peripheral catheter-related phlebitis, or peripheral catheter-related thrombophlebitis was combined with one or more of the following terms: risk factors, pathophysiology, diagnosis, treatment, prevention, heparin, thrombosis, protein S deficiency, protein C deficiency, antithrombin deficiency, factor V Leiden, prothrombin, and factor VIII. In addition, the bibliographies of all relevant articles were reviewed to obtain additional references not identified by the MEDLINE search. All randomized clinical trials, case-control studies, and cohort studies retrieved by our search were included for critical review, except for those that involved central venous catheters, steel needles, and peripherally inserted central catheters.

RESULTS
Clinical Importance
Peripheral vein infusion thrombophlebitis, the most frequent complication associated with peripheral catheter use (7), causes patient discomfort and generally leads to catheter removal and insertion of a new catheter at a different site. Repeated episodes can lead to venous access difficulties and more invasive procedures, such as central venous catheter placement (8). As a result, administration of parenteral medications may be unnecessarily delayed, and hospital stay lengthened. In a recent prospec-
Table 1. Grading Scale for Peripheral Vein Infusion Thrombophlebitis*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Pain or erythema at intravenous site</td>
</tr>
<tr>
<td>2</td>
<td>Pain at intravenous site with erythema or swelling</td>
</tr>
<tr>
<td>3</td>
<td>Pain at intravenous site with erythema, and swelling or a palpable venous cord</td>
</tr>
<tr>
<td>4</td>
<td>Pain at intravenous site with erythema, swelling, and a palpable venous cord</td>
</tr>
<tr>
<td>5</td>
<td>Purulent discharge at intravenous site, along with all the signs of grade 4 thrombophlebitis</td>
</tr>
</tbody>
</table>

* From references 17 and 18.

tive study of 90 hospitalized patients with peripheral intravenous catheters, 23 (26%) developed peripheral vein infusion thrombophlebitis, among whom one third had complications that resulted in a delay in intravenous therapy, additional intravenous therapy, or an extended hospital stay of 2 to 5 days (9).

Several medical complications are associated with peripheral vein infusion thrombophlebitis. Occlusion of the vein by thrombus may lead to extravasation of fluid into surrounding tissues, which may limit venous access in the affected limb (10). Suppurative thrombophlebitis, which may occur if the intravascular thrombus becomes infected (11), occurs following 0.2% to 2% of peripheral vein catheter insertions (8,12), and is one of the most serious local complications of peripheral vein infusion thrombophlebitis (13). The resultant intravascular abscess may lead to bacteremia even after the catheter has been removed (6). Furthermore, patients have an increased risk of catheter-related bloodstream infections (14). Up to 50% of patients with intravenous-related bloodstream infection have peripheral vein infusion thrombophlebitis (15).

Arnow and colleagues (16) studied 94 patients with 102 episodes of sepsis due to percutaneously inserted catheters and found that 44 (43%) of these episodes occurred with peripheral venous catheters; the remaining episodes were due to central vein and peripheral arterial catheters. Of the 44 episodes, 16 were accompanied by peripheral vein infusion thrombophlebitis, cellulitis, or superficial abscess, and 7 were complicated by suppurrative thrombophlebitis. The average cost per episode, in 1991 U.S. dollars, was $4830, including laboratory, therapy, and hospital stay.

**Diagnosis**

No diagnostic criterion or group of diagnostic criteria has been shown to be valid or reproducible. One of the earliest definitions, suggested by the British Medical Research Council in 1957, defined peripheral vein infusion thrombophlebitis as “redness, tenderness, and edema of the vein” (2). The council proposed a grading system as a clinical assessment tool. Variations of their grading system have evolved during the past 20 years, including the Maddox scale (17) and the Baxter scale (18). All scales grade peripheral vein infusion thrombophlebitis according to severity of physical signs and symptoms (Table 1). An important limitation of grading systems is that not all the signs may develop, or they may not develop in the sequence indicated. As a result, many investigators define peripheral vein infusion thrombophlebitis based on two or more of the following: pain, tenderness, warmth, erythema, swelling, and a palpable cord (4,19,20).

**Incidence**

The incidence of peripheral vein infusion thrombophlebitis varies widely due to differences in definition, study design, patient selection, and follow-up time. In the largest randomized trial comparing two catheter materials (4), Maki and Ringer studied 1054 short peripheral catheters (2.5 cm and 3 cm) in 714 patients. The overall incidence was 42% of catheter insertions, with rates of 30% by day 2 and 45% by day 3 of catheterization. These rates are similar to previously reported rates of 25% to 35% per catheter (5,8,9).

In contrast, in a multicenter epidemiological study of the risks associated with peripheral venous catheters, Tager et al. found an incidence of only 2.5% among 5161 short catheters (1). The authors suggested that the discrepancy between the incidence rate they observed and that reported by other groups could have been due to the difficulty of standardizing diagnosis among the large number of participating practitioners, and because they used a stricter definition, in which redness, swelling, and heat had to be present, with or without tenderness.

The Intravenous Nurses Society established guidelines in 1990 that stated that an acceptable incidence of peripheral vein infusion thrombophlebitis should be 5% or less (10). This rate has been exceeded in almost all published studies (4,5,8,9,19,21–24).

**Pathogenesis**

The currently accepted model of the pathogenesis of peripheral vein infusion thrombophlebitis is that catheterization of the vein results in inflammation and thrombus formation (2). However, the specific relation between inflammation and thrombosis remains unclear. Irritation of the vein, whether due to the infusate (4,10), the catheter material (4,5,10), or bacterial colonization of the intravascular segment of the catheter, is thought to cause prostaglandin-mediated activation of the inflammatory cascade (2). At sites where the endothelium is severely inflamed, clotting intermediates are activated and accumulate (2); combined with stasis, this can initiate thrombosis. Histopathologic studies of veins following peripheral vein infusion thrombophlebitis demonstrate swelling of endothelial cells, leukocytic infiltration of the vein wall (2,25), and other changes consistent with inflamma-
A small study tested the hypothesis that thrombus in the catheterized vein may be the progenitor of peripheral vein infusion thrombophlebitis. B-mode ultrasonography was performed serially on veins in the antecubital fossa that were catheterized with long (14-cm) 22-gauge peripheral catheters (26). An echogenic mass within the vein lumen, indicating thrombus, was visualized in 14 of the 22 veins that were catheterized. Nine of the 14 veins with thrombus, but none of the eight veins without thrombus, were accompanied by “clinical phlebitis.” Thrombus detected within 24 hours of catheter insertion was associated with early peripheral vein infusion thrombophlebitis, whereas thrombus detected after 24 hours was associated with later development of peripheral vein infusion thrombophlebitis. Although the peripheral venous catheters studied were longer than those typically used in hospitalized patients for non-nutritional peripheral intravenous therapy, it is unlikely that thrombus formation is unique to long catheters. Thus, this study suggests that thrombus formation may be a necessary step in the pathogenesis of peripheral vein infusion thrombophlebitis.

**Risk Factors**

Many of the studies on the risk factors for peripheral vein infusion thrombophlebitis are limited by small sample size, lack of a control group, use of retrospective design, and inadequate analyses. Nonetheless, several catheter-specific and patient-specific risk factors have been identified (Table 2).

**Table 2. Risk Factors for Peripheral Vein Infusion Thrombophlebitis**

<table>
<thead>
<tr>
<th>Risk Factor (Reference)</th>
<th>Risk Factor (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter-specific</td>
<td></td>
</tr>
<tr>
<td>Catheter duration (1,4,24,17)</td>
<td></td>
</tr>
<tr>
<td>Catheter material (4,5)</td>
<td></td>
</tr>
<tr>
<td>Catheter size (21,27,28)</td>
<td></td>
</tr>
<tr>
<td>Intravenous infusate (4,9,10,13,21)</td>
<td></td>
</tr>
<tr>
<td>Catheter-related infection (4,27,29,30)</td>
<td></td>
</tr>
<tr>
<td>Patient-specific</td>
<td></td>
</tr>
<tr>
<td>Poor-quality peripheral veins (5)</td>
<td></td>
</tr>
<tr>
<td>Site of catheter insertion (4)</td>
<td></td>
</tr>
<tr>
<td>Sex (4,5)</td>
<td></td>
</tr>
<tr>
<td>Underlying medical disease (1,4)</td>
<td></td>
</tr>
<tr>
<td>Biologic vulnerability (4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Experience of person inserting catheter (4,8,31)</td>
<td></td>
</tr>
<tr>
<td>Insertion in the emergency room (4)</td>
<td></td>
</tr>
<tr>
<td>Daily intravenous gauze changing (32)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. The Centers for Disease Control and Prevention Recommendations for Preventing Peripheral Vein Infusion Thrombophlebitis**

- Select catheter based on the intended purpose and duration of use, and known complications (e.g., phlebitis); consider a polyurethane catheter
- Aseptic technique for insertion
- Disinfection of the site before insertion, with alcohol, povidone-iodine, or chlorhexidine
- Secure catheter with sterile gauze or transparent dressing
- Use an upper extremity site in preference to a lower extremity site
- Observe catheter site and palpate for tenderness at least daily
- Replace catheters and rotate peripheral venous sites every 48 to 72 hours
- Remove catheters placed in emergency room within 24 hours and insert a new catheter at a different site
- Change tubing no more than every 72 hours unless clinically indicated; change tubing used to deliver blood, blood products, or lipid emulsions within 24 hours of initiating the infusion
- Replace dressing when the catheter is removed or replaced, or when dressing becomes damp, loosened, or soiled

* From reference 7.

**Catheter-Specific Risk Factors**

Duration of catheterization is the most important predictor of peripheral vein infusion thrombophlebitis (1,4,24,27), and the Centers for Disease Control and Prevention recommends rotation of catheter sites every 48 to 72 hours to “minimize the risk of phlebitis” (Table 3). This recommendation has been questioned (24), because recent evidence suggests that after 2 days of catheterization, the day-specific risk of peripheral vein infusion thrombophlebitis is constant (4,24).

Catheter material and size may also affect risk. Although both have similar rates of catheter-related infection (4), the newer polyurethane (PEU) catheters have been associated with a 30% to 45% reduction in the incidence of peripheral vein infusion thrombophlebitis compared with tetrafluoroethylene-hexafluoropropylene (Teflon) catheters (4,5). Both long and short peripheral intravenous catheters have been associated with peripheral vein infusion thrombophlebitis (21,27). However, large-gauge catheters are associated with an increased risk compared with small-gauge catheters (28), possibly due to the physical trauma caused by the insertion of a large-gauge catheter into a relatively short, narrow vein.

Infusate characteristics also influence the occurrence of peripheral vein infusion thrombophlebitis. Both low pH and high-osmolality intravenous solutions, such as hypertonic glucose, confer a higher risk (10,13). In addition, intravenously administered medications, such as...
potassium chloride, barbiturates, phenytoin, and many cancer chemotherapeutic agents, have been implicated (4). Intravenous antibiotics, such as vancomycin, amphotericin B, and most β-lactams, have been associated with a twofold increased risk (4,9,21), which may be attributable to the presence of microparticulates in the antibiotic solutions.

Catheter-related infection may cause peripheral vein infusion thrombophlebitis (4,27,29,30). Between 5% to 25% of peripheral catheters are colonized by skin organisms at the time of removal, as reflected by semiquantitative cultures of the intravascular portion of the removed catheter or its tip (6,13). Colonized catheters are up to six times more likely to be associated with peripheral vein infusion thrombophlebitis (4).

**Patient-Specific and Other Risk Factors**

Female sex, “poor-quality” peripheral veins, insertion in the lower extremity, and the presence of underlying medical disease (cancer, immunodeficiency) appear to increase the risk of peripheral vein infusion thrombophlebitis (4,10). Other risk factors may include inexperience of the person inserting the catheter (4,8,31), and insertion in the emergency room, where establishing access quickly is often necessary (4). Although the type of catheter site dressing (gauze vs. transparent) does not appear to influence peripheral vein infusion thrombophlebitis rates (22,33), changing gauze dressings more frequently than every 48 hours has been shown to increase the risk (32), presumably because of manipulation of the cannula during the dressing process.

**The Potential Role of Hypercoagulability**

Although the etiology of venous thrombosis can still be conceptualized by Virchow’s triad of vein wall damage, stasis, and hypercoagulability, little is known about the potential contribution of patient-specific risk factors related to hypercoagulability, including those related to inherited thrombophilias (Table 4). Published studies have not examined whether inherited thrombophilia is associated with peripheral vein infusion thrombophlebitis, but there are several lines of evidence that suggest that this association may be present. First, Maki and Ringer (4) demonstrated that patients who develop catheter-related thrombophlebitis are more likely to develop a severe recurrent episode. Second, Monreal et al. (19,21) reported that higher hemoglobin levels were associated with an increased risk of peripheral vein infusion thrombophlebitis, perhaps due to local activation of coagulation in susceptible patients. Third, inherited thrombophilias increase the risk of spontaneous superficial vein thrombosis by six- to 13-fold (45). Finally, there is evidence that heparin may prevent peripheral vein infusion thrombophlebitis. A recent meta-analysis (46) of randomized trials concluded that the risk of peripheral vein infusion thrombophlebitis was decreased significantly with 100-U/mL heparin flushes through the catheter, as compared with normal saline (relative risk [RR] = 0.6; 95% confidence interval [CI]: 0.4 to 0.9). The use of 1-U/mL continuous heparin infusions also significantly decreased the risk compared with saline flushes (RR = 0.6; 95% CI: 0.4 to 0.8).

**CONCLUSION**

Peripheral vein infusion thrombophlebitis is a frequent complication of peripheral intravenous catheter use, with an incidence between 25% and 35%, which is well above the 5% rate targeted by the Intravenous Nurses Society’s standards of practice. Along with increased attention to catheter-specific risk factors, better characterization of

<table>
<thead>
<tr>
<th>Inherited Thrombophilia (Reference)</th>
<th>Prevalence in Population (%)</th>
<th>Relative Risk of First Venous Thromboembolism*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic polymorphisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterozygous (34)</td>
<td>5–7</td>
<td>7</td>
</tr>
<tr>
<td>Homozygous (35)</td>
<td>0.02</td>
<td>80</td>
</tr>
<tr>
<td>Prothrombin G20210A gene mutation (36,37)</td>
<td>2–3</td>
<td>2–3</td>
</tr>
<tr>
<td>Hyperhomocysteinemia (38,39)</td>
<td>10–12</td>
<td>2.5</td>
</tr>
<tr>
<td>Anticoagulant protein deficiencies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombin III deficiency (40,41)</td>
<td>0.02</td>
<td>8</td>
</tr>
<tr>
<td>Protein C deficiency (41,42)</td>
<td>0.4</td>
<td>7</td>
</tr>
<tr>
<td>Protein S deficiency (41,43)</td>
<td>0.2–0.4</td>
<td>8.5</td>
</tr>
<tr>
<td>Elevated factor VIII levels (44)</td>
<td>11</td>
<td>4.8</td>
</tr>
</tbody>
</table>

* Compared with healthy control population.
biologic factors will improve our understanding of the pathogenesis of peripheral vein infusion thrombophlebitis, and may allow development of better management strategies. In view of the ultrasonographic evidence for thrombosis as a possible causal factor, a recent meta-analysis demonstrating the benefits of heparin, and the associations between inherited thrombophilia and deep and superficial venous thrombosis, underlying prothrombotic states may explain, at least in part, the biological vulnerability to peripheral vein infusion thrombophlebitis. Studies should determine whether screening for thrombophilia in patients with peripheral vein infusion thrombophlebitis is worthwhile, and whether anti-coagulant therapy is warranted in these patients to prevent future episodes.

REFERENCES


