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Risk Factors for Infusion-related Phlebitis with Small Peripheral Venous Catheters

A Randomized Controlled Trial

Dennis G. Maki, MD, and Marilyn Ringer, BSN, MS

Objective: To identify risk factors for infusion-related phlebitis with peripheral intravenous catheters.

Design: A randomized trial of two catheter materials, with consideration of 21 potential risk factors.

Setting: A university hospital.

Patients: Hospitalized adults without granulocytopenia who received a peripheral intravenous catheter.

Interventions: House officers or ward nurses inserted the catheters, and each insertion was randomized to a catheter made of tetrafluoroethylene-hexafluoropropylene (FEP-Teflon) or a novel polyetherurethane without leachable additives (PEU-Vialon).

Measurements: Research nurses scored insertion sites each day for inflammation and cultured catheters at removal.

Results: The Kaplan-Meier risk for phlebitis exceeded 50% by day 4 after catheterization. Intravenous antibiotics (relative risk, 2.00), female sex (relative risk, 1.88), prolonged (> 48 hours) catheterization (relative risk, 1.79), and catheter material (PEU-Vialon: FEP-Teflon) (relative risk, 0.73) strongly predicted phlebitis in a Cox proportional hazards model (each, $P < 0.003$). The best-fit model for severe phlebitis identified the same predictors plus catheter-related infection (relative risk, 6.19), phlebitis with a previous catheter (relative risk, 1.54), and anatomic site (hand: forearm, relative risk, 0.71; wrist:forearm, relative risk, 0.60). The low incidence of local catheter-related infection was comparable with the two catheter materials (5.4% [95% CI, 3.8% to 7.6%] and 6.9% [CI, 4.9% to 9.6%]); none of the 1054 catheters prospectively studied caused bacteremia.

Conclusions: Multiple factors, including the infusate and the duration of cannulation, contribute to the development of infusion-related phlebitis. The use of peripheral intravenous catheters made of PEU-Vialon appears to pose the same risk for catheter-related infection as the use of catheters made of FEP-Teflon, and PEU-Vialon can permit longer cannulation with less risk for phlebitis.

The risk for catheter-related bacteremia with FEP-Teflon and PEU-Vialon catheters is sufficiently low that it no longer seems justifiable to recommend the use of small steel needles for most peripheral intravenous therapy.

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Infusion phlebitis, defined as the inflammation of the cannulated vein, is a frequent cause of pain and discomfort to the estimated 25 million patients who receive infusion therapy through peripheral intravenous cannulas each year in U.S. hospitals. Studies over the past two decades have shown that 27% to 70% of patients receiving peripheral intravenous therapy develop phlebitis that requires the removal of the cannula, the insertion of a new cannula in a different site, and, often, local treatment and analgesic drugs (1-5). Guidelines for the management of intravenous therapy have recommended daily surveillance of cannula sites and, to reduce the risk for phlebitis and infection, the rotation of cannula sites every 24 to 48 hours (1-6). This practice adds considerably to the costs of intravenous therapy.

Most investigators have concluded that infusion phlebitis is primarily a physicochemical phenomenon. On the basis of clinical studies, most with major limitations, such as small study samples, the assessment of relatively few risk factors (and the infrequent assessment of cannula-related infection), and incomplete statistical analyses (and the rare use of multivariate techniques), many factors have been reported to increase the risk for infusion phlebitis substantially ($P < 0.05$). These factors include cannula material, length, and bore size; operator skill in insertion; the anatomic site of cannulation; the duration of cannulation; the frequency of dressing changes; the character of the infusate; and host factors, such as patient age, Caucasian race, female gender, and the presence of underlying diseases (1-5). No reported study has examined the influence of the many potential host and therapeutic factors, particularly the influence of catheter material and catheter-associated infection, on the occurrence of infusion phlebitis in a large sample of peripheral intravenous catheters that are used clinically.

Although most peripheral intravenous catheters used in the United States at present are made of a Teflon, catheters made of polyurethanes are available. A novel catheter material, polyetherurethane (PEU) (PEU-Vialon, Becton Dickinson, Franklin Lakes, New Jersey) is based on polytetramethylene ether glycol, 4,4'-diphenylmethane diisocyanate, and 1,4-butanediol. It does not require catalysts or stabilizers in its manufacture, has a smoother microsurface, and is thermoplastic and more hydrophilic, becoming much more flexible than Teflon at body temperature. It also induces less platelet adherence in vitro and less thrombosis and inflammation in experimental animals (7, 8).

We report the results of a randomized clinical trial with 1054 peripheral intravenous catheters inserted in

Table 1. *Characteristics of Patients and Catheters in the Two Catheter Groups*

Characteristic	FEP-Teflon (n = 574)	PEU-Vialon (n = 480)
Patients		
Mean age, y	52	51
Men:women, %	57:43	57:43
Service, %		
Medical	36.2	39.0
Surgical	63.8	61.0
Intensive care unit, %	17.2	14.0
Blood glucose level > 8.3 mmol/L (> 150 mg/dL), %	25.4	23.5
Neoplastic disease, %	22.6	22.7
Receiving antibiotic therapy, %	75.3	75.4
Urinary catheter, %	40.9	35.4
Active noncatheter-related infection, %	10.8	12.5
Catheter, *n (%)*		
First catheter	398 (69.3)	316 (65.8)
Subsequent catheter	176 (30.7)	164 (34.2)
Insertion		
Mean hospital day	7.6	7.2
By nurse:house officer, %	60:40	70:30*
Difficult insertion, %	11.2	12.1
In operating room:patient care unit, %	38:62	27:73
Reason for catheter, %		
Fluids	51.4	57.1
Blood products	10.3	6.7†
Intravenous drugs	17.8	22.1
Removal for infiltration, leakage, or clotting, %	25.5	28.1
Hours in place		
12-24, %	17.6	13.1‡
25-48, %	34.1	32.5
49-72, %	20.2	23.5
> 72, %	28.0	30.8
Mean ± SE (range), *h*§	59 ± 2 (12-281)	65 ± 2 (12-262)†
Adherence of dressing at removal, %		
Adheres well	98.6	97.9
Edges up	1.2	1.7
Nonocclusive	0.2	0.4
Moisture on dressing at removal, %	7.8	9.6
Moisture or blood on skin under dressing at removal, %	9.9	11.9

* $P < 0.01$.
† $P < 0.05$.
‡ $P = 0.042$ by test for linear trend across four categories.
§ SE = standard error.

patients in a university hospital. The study was done to determine the relative risk for phlebitis and catheter-associated infection with catheters made of PEU-Vialon as compared with catheters made of FEP-Teflon and to identify risk factors that predict an increased (or decreased) risk for phlebitis. Twenty-one candidate risk factors were prospectively evaluated for their contribution to the occurrence of infusion phlebitis with discrete proportional hazards models.

Methods

Sources of Data

At the University of Wisconsin Hospital, Madison, a 450-bed referral hospital, house officers, nurses, and medical students insert peripheral venous catheters. Patients with infusions receive care in accordance with reported guidelines (6, 9).

Patients older than 18 years without granulocytopenia scheduled to have a peripheral intravenous catheter inserted were informed of the nature and purpose of the study before they were requested to provide written consent to participate. We studied the role of catheter material in predisposition to infusion phlebitis by randomizing each new insertion of a peripheral catheter to a 3.2-cm (1.25-inch) catheter (Jelco, Critikon, Tampa, Florida) made of tetrafluoroethylene-hexafluoropropylene (FEP-Teflon, DuPont, Wilmington, Delaware) or a 2.5-cm (1-inch) catheter made of PEU-Vialon (Insyte, Deseret Medical, Sandy, Utah).

Ten percent povidone-iodine (Triad Medical, Franklin, Wisconsin) was used for cutaneous antisepsis before catheter insertion. Topical antimicrobial or antiseptic ointments were not used on any catheters in this study. Catheters were dressed with a 5.1 × 5.1 cm^2 piece of sterile gauze (Hermitage Hospital Products, Niantic, Connecticut) and tape (Transpore, 3M, St. Paul, Minnesota).

Catheters were inserted percutaneously into a new site by a house officer or nurse. Research nurses (who were on call 24 hours a day) randomized each insertion to the appropriate catheter material and obtained a baseline culture of the skin at the insertion site before insertion. To assess individual biologic vulnerability as a risk factor for phlebitis, all of the peripheral intravenous catheters that patients received were studied; however, each new catheterization was randomized to a catheter made of one of the two catheter materials.

Each patient was seen daily by a member of the research team. The patient was questioned about pain at the insertion site, and the site was palpated. Every other day, when the patient had pain or discomfort at the insertion site, or when the dressing adhered poorly, the dressing was removed, the site was inspected and recleansed with povidone-iodine, and the site was redressed. Daily and at all dressing changes and at

catheter removal, the site was quantitatively scored for pain (0, 1), tenderness (0, 1), erythema (0 to 2), purulence (0, 1), swelling (0 to 2), and a palpable cord (0, 1).

Decisions to remove catheters were made independently by patients' physicians. At catheter removal, the skin around the catheter site was again cultured, the catheter hub and a sample of intravenous fluid were cultured, and the catheter was removed and cultured.

The study was restricted to catheters that were in place for at least 12 hours. For each catheter, the demographic characteristics of the patient and information on underlying medical conditions, infection, and antimicrobial therapy were obtained. The person who inserted the catheter, the catheter gauge, the anatomic site, the difficulty of insertion (whether three or more venipunctures were required), the condition of the site, and the period that the catheter remained in place were also recorded. Patients were followed for 3 days after catheter removal to detect latently expressed local inflammation related to the catheter (10).

Microbiologic Methods

As previously described, the skin around the catheter (10 cm^2) was cultured quantitatively using a sterile template; catheters were removed aseptically and cultured semiquantitatively; and catheter hubs were cultured using a cotton-tipped applicator (11, 12). Fluid (7 mL) was aspirated from the administration set and cultured quantitatively (9).

Catheter-related Infection

A positive semiquantitative culture of the catheter (≥ 15 colony-forming units [CFUs]) was considered to be synonymous with colonization of the catheter (12). A semiquantitative catheter culture and blood cultures that were positive for the same species, with a negative culture of infusate and with no clinical, autopsy, or microbiologic data identifying another apparent source for the septicemia, indicated catheter-related septicemia (11, 12).

Septicemia from Contaminated Infusate

The isolation of the same species from both infusate and separate percutaneously drawn blood cultures, with semiquantitative culture of the catheter negative for the infecting organism and with no other identifiable source for the septicemia, indicated septicemia from contaminated infusate (9, 11).

Table 2. *Colonization and Contamination at Catheter Removal in the Two Catheter Groups*

Variable*	FEP-Teflon (n = 574)	PEU-Vialon (n = 480)
Colonization of skin at insertion site		
Before disinfection, *mean log CFU ± SE*	1.82 ± 0.08	1.93 ± 0.09
After disinfection, *mean log CFU ± SE*	0.52 ± 0.05	0.49 ± 0.05
At removal, *mean log CFU ± SE*	0.95 ± 0.07	0.99 ± 0.08
> 10 CFUs, *n (%)*	98 (17.1)	90 (18.8)
Site colonization, %		
Coagulase-negative staphylococci	16.2	18.3
Staphylococcus aureus	0.2	0.2
Gram-negative bacilli	0.2	
Yeasts		0.2
Contamination (> 10 CFUs) of catheter hubs at catheter removal		
Number (%)	43 (7.5)	26 (5.4)
Mean log CFU ± SE	0.40 ± 0.05	0.39 ± 0.05
Intravenous fluid		
Contaminated (> 10 CFUs)	6 (1.0)	4 (0.8)

* No difference between groups was statistically significant at $P < 0.05$. CFU = colony-forming unit; SE = standard error.

Table 3. *Catheter-related Infection in the Two Catheter Groups*

Variable*	FEP-Teflon (n = 574)	PEU-Vialon (n = 480)
Catheter-related infection, *n (%)*		
Local (≥ 15 CFUs)	31 (5.4)	33 (6.9)
Bacteremia	0	0
Infecting organisms, *n*		
Coagulase-negative staphylococci	27	32
Staphylococcus aureus	1	0
Gram-negative bacilli	0	0
Yeasts	0	1
Mean log CFU ± SE on infected catheters	4.60 ± 0.04	4.48 ± 0.06

* No difference between groups was statistically significant at $P < 0.05$. CFU = colony-forming unit; SE = standard error.

Phlebitis

The presence of two or more of the following signs or symptoms on examination of the catheter insertion site indicated phlebitis: pain, tenderness, erythema, swelling, purulence, and a palpable venous cord (11, 12).

Severe Phlebitis

Using a quantitative scoring scale based on the sum total of all measures of inflammation (maximal score, 9), phlebitis with a score higher than in the 77th percentile of all phlebitis scores indicated severe phlebitis.

Statistics

Based on an expected rate of local catheter-related infection of at least 5% and on an expected rate of catheter-related phlebitis of 30% (11), we calculated that approximately 500 catheters would be needed in each catheter material group to show with strong statistical certainty (both alpha and beta < 0.05) a 50% difference in the rate of local infection and a 25% difference in the rate of phlebitis between the catheter groups (13).

For categoric data, the significance of differences was determined using the chi-square test or the Fisher exact test, and, for continuous data, using the Student t-test. For ordered categoric data, differences were tested using a chi-square test for linear trend (14). The cumulative risk for developing phlebitis or catheter-related infection in each catheter material group was compared using a log-rank test on the Kaplan-Meier estimates (13).

To assess which risk factors predicted the occurrence of phlebitis, 21 variables were evaluated using discrete proportional hazards modeling (15): catheter material, catheter episode (first or subsequent), phlebitis with a previous catheter, season (winter [January through March] or spring [April and May]), catheter diameter (14 to 18 gauge or 20 to 22 gauge), anatomic site (the hand, the wrist, or the forearm), the person inserting the catheter (house officer or nurse), the service (surgical or nonsurgical), the hospital location (emergency room, operating room, intensive care unit, or ward), the difficulty of insertion, the use of the catheter for the administration of intravenous antibiotics, the hospital day of insertion, the patients' age and sex, diabetes or blood glucose measurements of 11.1 mmol/L (200 mg/dL) or higher. The following variables were modeled as time-dependent covariates: the number of dressing changes (excluding the day of catheter removal) and the presence of moisture or blood under the dressing, catheter-related infection (≥ 15 CFUs), site colonization (> 10 CFUs), colonization of the catheter hub (> 10 CFUs), and fever (≥ 38 °C).

Variables were included in the model equation by interactively fitting a hierarchy of model equations representing increasing degrees of complexity, with each additional model

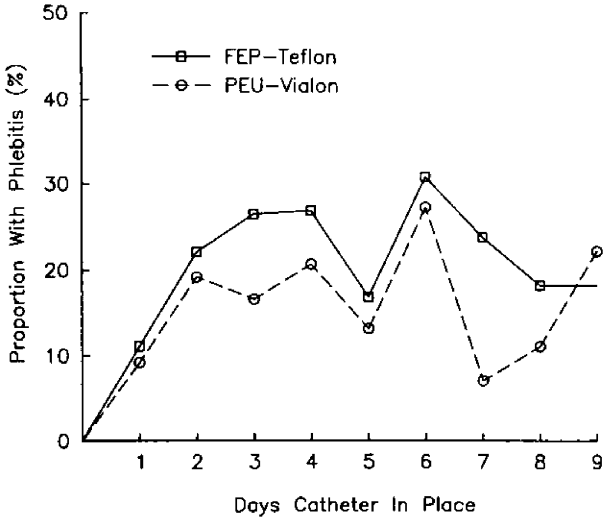

Figure 1. The day-specific risk for phlebitis associated with the two catheter materials.

being compared with the previous one using a likelihood ratio test (16). The resulting models were compared with models using forward and backward automated stepping routines to guard against variable selection bias and were compared with comprehensive models containing all the variables to guard against confounding (15).

Studying several catheters per patient permitted the study of individual biologic vulnerability to phlebitis as a risk factor. Making several observations per patient, however, raises the question of statistical independence of observations. The independence assumption was assessed by comparing models based on the entire study sample (n = 1054) with models based on each patient's first catheter only (n = 714).

The multiplicative hypothesis (proportional hazards assumption) of the models was tested by the inclusion of [time × factor] interaction terms. The significant interaction terms were included in the final models to relax the strict proportional hazards assumption (16). All P values were determined using two-tailed tests of significance. Confidence intervals (CIs) of 95% are provided where appropriate.

Results

Characteristics of the Study Sample

Over 95% of patients invited to enroll in this trial participated; complete data were obtained for 1054 catheters from 714 patients. The two catheter groups were very similar (Table 1). Two thirds of the catheters studied in each catheter group were the patient's first catheter. Most catheters in each group were used in patients who were more susceptible to nosocomial infection: A relatively high proportion of patients had surgery and high frequencies of hyperglycemia, neoplastic disease, and intensive care unit placement; approximately 10% of patients in each group had an infection that was not related to the catheter.

Every catheter was inserted in a peripheral arm vein, usually in the forearm or hand. Approximately two thirds of the catheters were inserted by a nurse. Insertion was judged to be difficult in 11% to 12% of the catheters in each group. Approximately one third of the catheters were inserted in the operating room; the rest were inserted in the emergency room or, more often, in a patient care unit. In both groups, catheters were inserted for similar reasons, mainly for the administration of fluids, blood products, or intravenous drugs (most frequently antibiotics).

Catheters remained in place an average of 10% longer in the PEU-Vialon group (65 compared with 59 hours; P = 0.029) (Table 1). In both groups, more than one half of the catheters were in place for longer than 48 hours, and nearly one third were in place for 72 hours or longer.

Site Colonization and Contamination of Hubs and Infusate

Baseline skin cultures obtained before catheter insertion showed approximately $10^{1.8}$ CFUs per 10 cm^2 before skin disinfection and $10^{0.5}$ CFUs per 10 cm^2 after skin disinfection in each group (Table 2). Colonization at catheter removal also was similar in the two groups (approximately $10^{1.0}$ CFUs). Nearly all cutaneous site colonization was with coagulase-negative staphylococci; colonization by *Staphylococcus aureus*, gram-negative bacilli, or yeasts was infrequent.

At catheter removal, 43 (8%) of FEP-Teflon catheter hubs and 26 (5%) of PEU-Vialon catheter hubs showed microbial contamination with more than 10 CFUs, and virtually all showed contamination with small numbers of coagulase-negative staphylococci (Table 2). Infusate was found to be contaminated only 10 times during the study (Table 2); in every instance, fluid was contaminated by small numbers of coagulase-negative staphylococci (< 10^2 CFU/mL). No catheter with a contaminated hub or infusate was associated with concordant bacteremia.

Catheter-related Infection

The incidence of local catheter-related infection was low and was comparable in the two catheter material groups (5.4% [CI, 3.8% to 7.6%] compared with 6.9% [CI, 4.9% to 9.6%]; $P > 0.05$) (Table 3). None of the 1054 prospectively studied catheters was considered to

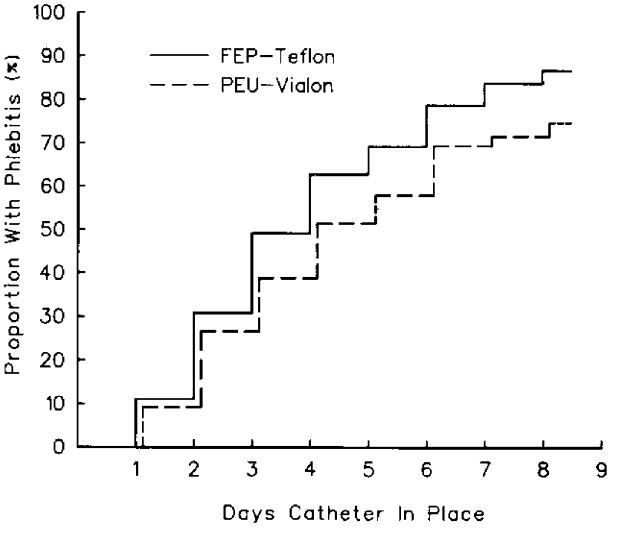

Figure 2. The cumulative risk for phlebitis associated with the two catheter materials. By log-rank test, P = 0.005.

Table 4. *Predictors of Phlebitis in the Study Sample of 1054 Peripheral Intravenous Catheters**

Predictor†	Regression Coefficient	Standard Error‡	Relative Risk	95% CI	*P* Value
Time index variable					
Intercept (days 1, 2)	−2.473	0.147	0.08	0.06 to 0.11	< 0.001
> 48 hours (days 3-9:days 1, 2)	0.585	0.110	1.79	1.45 to 2.22	< 0.001
Sex (female:male)	0.631	0.108	1.88	1.52 to 2.32	< 0.001
Use of intravenous infusion (antibiotics:other)	0.695	0.131	2.00	1.55 to 2.59	< 0.001
Catheter material (PEU-Vialon:FEP-Teflon)	−0.320	0.107	0.73	0.59 to 0.90	0.003

* According to a Cox discrete proportional hazards model.
† These variables, of 21 factors studied, form the best-fit model.
‡ Of the regression coefficient.

have caused bacteremia. Survival analysis comparison by log-rank test did not show a difference in the cumulative risk for infection between the two catheter materials ($P > 0.2$).

Phlebitis

Phlebitis occurred with 441 catheters overall (41.8%). The day-specific incidence of phlebitis is displayed in Figure 1, and the actuarial risk for phlebitis is displayed in Figure 2. The influence of catheter material on the incidence of phlebitis increased with extended placement of catheters; survival analysis by log-rank test showed a reduced risk for phlebitis with PEU-Vialon catheters ($P = 0.005$) (Figure 2).

The discrete proportional hazards model is a multiple-predictor variable survival analysis. The best-fit model, using the 21 factors examined as potential predictors of phlebitis, showed the duration of catheter placement (> 2 days:≤ 2 days, relative risk, 1.79; $P < 0.001$), sex (female:male, relative risk, 1.88; $P < 0.001$), use of the catheter for the administration of intravenous antibiotics (relative risk, 2.00; $P < 0.001$), and catheter material (PEU-Vialon:FEP-Teflon, relative risk, 0.73; $P = 0.003$) to be important predictors of infusion phlebitis in the study sample (Table 4).

The best model for severe phlebitis identified the same predictors as well as catheter-related infection (relative risk, 6.19; $P < 0.001$), phlebitis with a previous catheter (relative risk, 1.54; $P = 0.009$), and the placement of the catheter in the hand (relative risk, 0.71; $P = 0.05$) or the wrist (relative risk, 0.60; $P = 0.01$) rather than the forearm (Table 5). Individually, catheter insertion in the emergency room or operating room (relative risk, 1.39; $P = 0.06$) and an intensive care unit (relative risk, 0.59; $P = 0.08$) rather than a ward approached statistical significance. As a set, they were statistically significant ($P = 0.013$). Best-fit models for phlebitis and severe phlebitis based solely on first catheters identified the same risk factors, except for individual biologic vulnerability, with similar magnitudes of relative risk.

What the optimal, but safe, duration of catheter placement for intravenous therapy is should be of interest to clinicians, because it is relatively easy to control. A proportional hazards model, containing only the day-indicator variables as predictors, was used to compare the day-specific risk for phlebitis with the risk on day 2. As shown in Figure 1, the incidence of phlebitis increased markedly between 24 and 48 hours after catheterization (day1:day2, relative risk, 0.44; $P < 0.001$), whereas the risk for each remaining day was similar to that on day 2 (day3:day2, relative risk, 1.05; day4:day2, relative risk, 1.19; day5:day2, relative risk, 0.67; day6-9:day2, relative risk, 1.03; $P > 0.05$ for each comparison). Similarly, for severe phlebitis, the incidence at 48 hours was greater than that at 24 hours (day1:day2, relative risk, 0.42; $P < 0.001$), whereas the remaining risk for each day thereafter remained constant.

Discussion

Evidence is accumulating that catheter material plays an important role in the pathogenesis of device-related infection; some materials provide a more attractive surface for adherence by pathogenic organisms, such as staphylococci or yeasts (17). Intravascular catheters made of Teflon are more resistant to microbial adherence than are catheters made of polyvinylchloride or polyethylene and appear to be less prone to becoming colonized in vivo and to causing infection (18-20). Most central venous catheters used in the United States are made of polyvinylchloride, polyethylene, or siliconized elastomer.

The small Teflon catheters that are now used widely for peripheral intravenous therapy appear to be associated with far less infection than were the polyvinylchloride or polyethylene catheters used a decade ago, which were associated with a 2% to 5% risk for bacteremia (1). We encountered no catheter-related bacteremias in a recent prospective study of 2088 peripheral venous catheters made of FEP-Teflon, even though 25% had been in place for more than 72 hours (11). Other reports have confirmed a very low risk for bacteremia, far less than two cases per thousand catheters, with small peripheral intravenous catheters made of Teflon (21-24).

Limited data are available on the safety of using peripheral intravenous catheters made of polyurethanes, especially on the infection rate. Catheters were not cultured routinely in the three previous clinical studies of a polyurethane catheter (25-27). In our prospective randomized trial, we sought to determine whether using PEU-Vialon would be associated with a comparable rate of catheter-related infection. The rate of local catheter-related infection, defined as a positive semiquantitative culture (≥ 15 CFUs [12]), was very low in both groups, (5.4% and 6.9%, respectively) and was not statistically significant between the two groups (Table 3). None of the 1054 catheters caused bacteremia. The

Table 5. *Predictors of Severe Phlebitis**

Predictor†	Regression Coefficient	Standard Error‡	Relative Risk	95% CI	*P* Value
Time index variable					
Intercept (days 1, 2)	−3.433	0.291	0.03	0.02 to 0.06	< 0.001
> 48 hours (days 3-9:days 1, 2)	1.380	0.271	3.97	2.34 to 6.76	< 0.001
Sex (female:male)	0.492	0.149	1.64	1.22 to 2.19	< 0.001
Reason for intravenous infusion (antibiotics:other)	0.904	0.198	2.47	1.68 to 3.64	< 0.001
Catheter material (PEU-Vialon:FEP-Teflon)	−0.544	0.149	0.58	0.43 to 0.78	< 0.001
Phlebitis with previous catheter (yes:no)	0.432	0.165	1.54	1.12 to 2.13	0.009
Catheter-related infection (yes:no)	1.822	0.302	6.19‖	3.42 to 11.77	< 0.001
Season (winter:spring)§	0.130	0.255	1.14	0.73 to 1.77	NS
Season-time interaction§	−0.989	0.318	0.37	0.20 to 0.69	0.002
Anatomic site					
Hand:forearm	−0.346	0.179	0.71	0.50 to 1.00	0.053
Wrist:forearm	−0.513	0.199	0.60	0.41 to 0.88	0.010
Other:forearm	−0.389	0.357	0.68	0.34 to 1.36	> 0.2
Hospital location					
Emergency room or operating room:ward	0.326	0.174	1.39	0.99 to 1.95	0.061¶
Intensive care unit:ward	−0.522	0.298	0.59	0.33 to 1.06	0.079

* According to a discrete proportional hazards model. NS = not significant.
† These variables, of the 21 factors studied, form the best-fit model.
‡ Of the regression coefficient.
§ Season and season-time interaction are interpreted jointly. The relative risk for season (winter or spring) when the catheter is in place for less than 48 hours thus is 1.14. For more than 48 hours, it is 1.14 × 0.37 = 0.42. To find the ad hoc average relative risk, take (1.14 + 0.42)/2 = 0.78.
‖ This figure is likely to be overestimated. A conservative estimate of relative risk is 1.84 using a logistic regression model on the same set of variables.
¶ As a set, these two variables were significant for inclusion in the model using the more reliable likelihood ratio test (P = 0.013).

power of these data to identify a 50% difference between the groups in local infection is 0.42. For each group, the upper bound of the 95% CI for bacteremia is 0.8%; for the entire study sample, it is 0.4%. These data indicate that using peripheral intravenous catheters made of PEU-Vialon is much safer than using those made of polyvinylchloride or polyethylene and that PEU-Vialon and FEP-Teflon catheters pose a comparable risk for catheter-related infection.

Our study also confirms the findings of a recent large prospective study of peripheral intravenous catheters (11): Although the hubs of peripheral intravenous catheters are commonly contaminated at removal, hub contamination rarely causes infusion-related bacteremia in peripheral intravenous therapy. It also confirms the findings of recent studies showing a very low risk for extrinsic contamination of in-use intravenous fluid and, especially, bacteremia arising from such contamination, even when intravenous administration sets are not routinely replaced more frequently than every 72 hours (9). Because most U.S. hospitals strive to replace peripheral intravenous catheters every 48 to 72 hours, replacing the administration set and the catheter simultaneously every third day can permit substantial cost savings (9).

Our study and other recently reported studies of peripheral intravenous catheters indicate clearly that the major complication of peripheral intravenous therapy is now infusion-related phlebitis (11, 21-24). The prime impetus to continue to periodically rotate sites for peripheral venous access is to reduce the risk for phlebitis.

In our study, we prospectively sought to identify factors associated with an increased risk for infusion phlebitis that might be amenable to preventive strategies. Although many studies (cited in reviews 1-5) have identified such factors, in only a handful were the data subjected to multivariate analysis (21, 22, 24, 25, 28-32), and, of the many studies purporting an important role for catheter material in the genesis of phlebitis, few have been based on randomized clinical trials with cannulas made of different materials (21, 25-27, 33-35) (Table 7). In our study, in which the role of catheter material was addressed in a randomized trial, discrete proportional hazards modeling identified seven predictors of a statistically significant increased risk for infusion-related phlebitis (Tables 4 and 5).

Duration of Catheter Placement

The incidence of phlebitis in both catheter groups rose progressively with increasing periods of cannulation: The Kaplan-Meier risk for phlebitis was approximately 30% by day 2 and 39% to 49% by day 3 in the two groups (Figure 2); for severe phlebitis, the corresponding figures were 10% to 18% and 19% to 32%. The unchanging nature of the day-specific risk after day 1, however, suggests that if rotating the insertion site on day 2 were not feasible because of limited superficial peripheral veins for access, the day-specific risk for phlebitis each day thereafter would remain relatively constant (Figure 1). The cumulative risk would nonetheless ultimately become quite high (Figure 2). Better strategies for periodic site rotation to reduce the incidence of phlebitis are needed (*see* below).

Infusate

A great deal of evidence indicates that the nature of the infusate administered through a peripheral intravenous catheter powerfully influences the occurrence of infusion phlebitis (1-5): Glucose-containing admixtures, which are quite acidic, and hypertonic glucose, amino

acids, and lipid emulsion, which are used in parenteral nutrition, are all far more phlebitogenic than is normal saline (24, 36, 37). Moreover, additives, such as potassium chloride (28, 29), and various intravenously administered drugs, such as vancomycin, amphotericin B, most betalactam antibiotics (21, 24, 25, 32), benzodiazepines, barbiturates, phenytoin, vasoactive pressor amines, and many cancer chemotherapeutic agents, can produce severe venous inflammation. Some of these drugs, such as norepinephrine, phenytoin, or adriamycin, can produce frank necrosis if the drug extravasates outside the vein (38).

Stable peripheral venous access can prevent the considerable pain and the risk for tissue necrosis that are associated with extravasation of infusate. Stable access is achieved far more reliably with plastic catheters than with steel needles, as shown in several randomized trials (21, 33, 34). Fortunately, the risk for device-related infection that is associated with the small Teflon and PEU-Vialon catheters now available is so low (11, 21-24) (Table 3), recommending the routine use of steel needles rather than of plastic catheters for peripheral intravenous therapy, especially if phlebitogenic or cytotoxic infusate is to be administered, no longer seems to be justifiable.

Our study reaffirms the findings of other studies showing that the administration of intravenous antibiotics through a peripheral intravenous catheter substantially increases the risk for phlebitis (relative risk, 2.0) (Table 4) (34, 38-40). Studies suggest that the increased risk for phlebitis that is associated with the administration of intravenous antibiotics can be reduced by removing the microparticulates that are associated with compounding these drugs with 0.22-μ or 0.44-μ in-line filters (39, 41). Not all randomized trials, however, have shown a substantial reduction in phlebitis with the use of in-line filters (42). Moreover, filters are expensive, must be replaced at periodic intervals, and their use adds substantially to the costs of phlebitis from microparticulates. The costs and benefits of using in-line filters routinely have yet to be determined (43, 44).

Randomized controlled trials have shown that adding hydrocortisone (45, 46), heparin (45, 47), or both (37, 45, 46) to infusate or topically applying a corticosteroid (48) or transdermal glyceryl trinitrate (31, 40) at the insertion site can reduce the risk for infusate-related phlebitis. The routine use of these drugs to prevent infusion-related phlebitis cannot be recommended, however, without the conduction of large-scale randomized trials that show clear benefit without serious adverse effects, such as spurious results of coagulation tests or an increased risk for bleeding, heparin-related thrombocytopenia, hemolysis, osteoporosis, adrenocortical suppression, or catheter-related infection.

Catheter Material

In our comparative trial, catheters made of PEU-Vialon were substantially less phlebitogenic than were catheters made of FEP-Teflon: The reduction in risk was nearly 30% overall; in severe phlebitis, the reduction was nearly 50%. The benefit of PEU-Vialon was greatest with increasing periods of catheter placement (Figure 2). These findings are very similar to those of other investigators who, in smaller comparative trials, found 36% to 49% reductions in the incidence of infusion-related phlebitis with the use of PEU-Vialon catheters compared with the use of control Teflon catheters (25-27).

Our data suggest a cost-effective strategy for the use of intravenous catheters to minimize the risk for phlebitis. Replacing the peripheral catheter every 24 hours

Table 6. *Risk Factors for Infusion Phlebitis in Peripheral Intravenous Therapy**

- Catheter material
  - Polypropylene > Teflon (33)
  - Silicone elastomer > polyurethane (35)
  - **Teflon > polyetherurethane** (25-27)
  - Teflon > steel needles (21, 28, 33, 34)
- Catheter size
  - Large bore > small bore (31)
  - 12-inch > 2-inch Teflon (33)
- **Insertion in emergency room > inpatient units** (28)
- No disinfection of skin with antiseptic before catheter insertion > disinfection of skin with chlorhexidine-alcohol before catheter insertion (50)
- Experience or skill of person inserting catheter
  - House officers, nurses > hospital intravenous team (23, 51)
  - House officers, nurses > decentralized unit intravenous therapy nurse-educator (28)
- **Increasing duration of catheter placement** (21, 22, 25, 28, 29, 32, 33)
- Subsequent catheters beyond the first (22)
- **Infusate**
  - Low pH (for example, dextrose-containing) solutions (36, 37)
  - Potassium chloride (28, 29)
  - Hypertonic glucose, amino acids, lipids (for parenteral nutrition) (24)
  - **Antibiotics** (especially betalactams, vancomycin, metronidazole) (21, 24, 25, 32)
  - High flow rate of intravenous fluid (> 90 mL/h) (32)
- Daily intravenous dressing changes > intravenous dressing changes every 48 h (49)
- Host factors
  - "Poor-quality" peripheral veins (25)
  - **Insertion in the upper arm or the wrist > insertion in the hand** (29)
  - Age
    - Children: older > younger (24)
    - Adults: younger > older (33)
  - **Women > men** (21, 22)
  - White > black (30)
  - Underlying medical disease (21, 22)
  - **Individual biologic vulnerability**
- **Catheter-related infection** (28, 29, 33)

* Identified in prospective studies by multivariate discriminant analysis or in randomized controlled trials. The > symbol denotes a significantly greater risk for phlebitis; factors found to be significant predictors of risk in this study are denoted in boldface type. Factors shown not to increase risk in well-controlled, prospective randomized trials include catheters made of polyethylene compared with siliconized elastomer (52) or catheters made of Teflon compared with siliconized elastomer (34, 53); the type of antiseptic solution used for cutaneous disinfection (54, 55); the use of topical antimicrobial ointment or spray on catheter insertion sites (56-59); the type of dressing (for example, gauze compared with transparent polyurethane dressing) (11, 30, 49); dressing change every 48 hours compared with not at all (11); the administration of infusate by gravity flow compared with by pump (60); the administration of antibiotics by slow infusion compared with by "intravenous push" over 2 minutes (61); the maintenance of heparin-locks with saline compared with by heparinized saline (62, 63); and the frequency of routine change of the intravenous delivery system (9, 64-66).

Table 7. *Kaplan-Meier Risk Estimates for Phlebitis with a 4-Day Peripheral Intravenous Catheterization and Two Consecutive 2-Day Catheterizations*

Catheter Material and Replacement Strategy	Cumulative Risk	
	Phlebitis	Severe Phlebitis
FEP-Teflon		
Every 2 days × 2	0.52*	0.33*
Every 4 days	0.63†	0.42†
PEU-Vialon		
Every 2 days × 2	0.46*	0.20*
Every 4 days	0.51†	0.29†

* 1-(1-probability of $\text{phlebitis}_{2\ \text{days}})^2$, using the Kaplan-Meier estimates for the probability of having phlebitis on day 2.
† The Kaplan-Meier probability of having phlebitis on day 4.

would clearly result in the lowest overall risk and, if feasible, is recommended for high-risk patients (who have shown vulnerability to phlebitis) or during the administration of highly phlebitogenic admixtures. Our analysis of the cumulative risk associated with routinely replacing the catheter every 2 days, as compared with every 4 days, however, suggests that for most patients requiring prolonged peripheral venous access, PEU-Vialon catheters replaced every 3 or 4 days would produce a lower incidence of phlebitis than would FEP-Teflon catheters replaced every 2 days (Table 7).

Catheter-related Infection

Although some studies have not identified an association between phlebitis and catheter-related infection (30, 49), other studies have shown a statistical association (12, 28, 29, 33, 50). In our study, local catheter-related infection (≥ 15 CFUs) was associated with a two- to sixfold increased risk for severe phlebitis by proportional hazards modeling (Table 5). Clearly, only a small proportion of patients with infusion-related peripheral vein phlebitis have catheter-related infection, and only approximately one half of patients with peripheral intravenous catheter-related septicemia show phlebitis (1); however, the presence of phlebitis connotes a substantially increased risk ($P < 0.05$) for infection and indicates the need for the immediate removal of the catheter to reduce the severity of phlebitis and to prevent local catheter-related infection from progressing to septicemia (10).

Other Factors

Like Tully and associates (21) and Tager and colleagues (22), we found that women were more likely than men to develop infusion phlebitis (relative risk, 1.88) (Table 4). Our data further suggested that beyond general predisposition, individuals may vary in biologic vulnerability to developing phlebitis. Most nurses and physicians have encountered patients who appear to be unduly susceptible to developing infusion-related phlebitis, even with rotation of the insertion site every 24 hours. Our proportional hazards models showed that patients developing phlebitis with a first catheter were more likely to develop severe phlebitis with a second catheter, all other factors being equal (relative risk, 1.54) (Table 5). The pathobiologic basis for such vulnerability is unknown, but would seem to be an important subject for investigation. Our data also suggested that placement of a peripheral intravenous catheter in the hand or the wrist, rather than in the forearm, reduced the risk for severe infusion-related phlebitis (Table 5).

Catheters that were placed in the emergency room or operating room, where establishing access quickly is often necessary, were more likely to produce severe phlebitis than were catheters that were placed on an inpatient unit (relative risk, 1.39; $P = 0.06$) (Table 5). Conversely, catheters placed by experienced nurses in an intensive care unit rather than by personnel on a general medical or surgical ward were less likely to cause severe phlebitis (relative risk, 0.59; $P = 0.08$). These two hospital-location variables together were associated with risk ($P = 0.013$) (Table 5). The experience of the person inserting an intravenous catheter clearly influences the risk for phlebitis: The availability of an intravenous therapy team of highly experienced nurses or technicians to insert intravenous catheters and to assure close surveillance of infusions resulted in a twofold lower rate of infusion-related phlebitis and an even greater reduction in catheter-related sepsis in comparative trials (23, 28, 51).

In our study, catheters inserted during the winter months were less likely to produce phlebitis than were catheters inserted during the spring months (relative risk, 0.78; $P < 0.05$) (Table 5). We have no satisfactory biologic explanation for the observation.

Future studies are needed to understand better the biologic factors involved in the pathogenesis of phlebitis, to ascertain the economic cost of infusion phlebitis, and to devise better strategies of infusion management to further minimize associated complications and the economic cost of intravenous therapy.

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