Wound Infection Rates After Invasive Procedures in HIV-1 Seropositive *Versus* HIV-1 Seronegative Hemophiliacs

JEFFREY L. BUEHRER, M.D.,* DAVID J. WEBER, M.D., M.P.H.,†§ ANTHONY A. MEYER, M.D., PH.D.,* PAUL R. BECHERER, M.D.,† WILLIAM A. RUTALA, PH.D., M.P.H.,†§ BREJETTA WILSON, R.N.,§ M. LYNN SMILEY, M.D.,† and GILBERT C. WHITE II, M.D.‡

One-hundred and two patients with hemophilia A, hemophilia B, or acquired antibody to factor VIII who had undergone invasive procedures were cross referenced with patients participating in an ongoing prospective natural history study of HIV-1 infection in hemophiliacs. Matching revealed that HIV-1 status was known for 83 patients (83%) who had undergone 169 procedures between July 1979 and April 1988. Invasive procedures were classified as clean in 108 patients (63.9%), clean-contaminated in 45 (26.6%), contaminated in 2 (1.2%), and infected in 14 (8.3%). Wound infection rates by HIV-1 status were as follows (95% confidence intervals): HIV+ 1.4% (0% to 5%), HIV− 0% (0% to 9%), and procedure before testing HIV+ 1.5% (0% to 6%). There were no significant differences between the wound infection rates of HIV-positive and HIV-negative hemophiliacs nor in the wound infection rate among all three subgroups of patients ($p > 0.5$, Fisher's Exact Test). We conclude that surgery in HIV-1–infected patients who have not progressed to AIDS does not entail an increased risk of postoperative wound infections.

PATIENTS INFECTED WITH the human immunodeficiency virus who have developed the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC) appear to have an increased incidence of a variety of bacterial infections.[1,2] Disseminated atypical mycobacterial infection was recognized early in the HIV-1 epidemic as a manifestation of AIDS.[3–5] More recently infection with *M. tuberculosis* has been reported in 5% to 10% of AIDS patients studied in retrospective series.[6–10] Patients with AIDS have also been reported to have increased susceptibility to a variety of other bacterial pathogens including Salmonella, Listeria, *Streptococcus pneumonia, Haemophilus influenzae, Branhamella catarrhalis, Campylobacter jejuni*, Campylobacter-like organisms, and Shigella.[1,2]

Address correspondence to David Jay Weber, M.D., M.P.H., CB 7030 Burnett-Womack 229H, Division of Infectious Diseases, UNC at Chapel Hill, Chapel Hill, NC 27599-7030.

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From the Division of Trauma and Critical Care, Department of Surgery; Divisions of Infectious Diseases† and Hematology,‡ Department of Medicine, University of North Carolina at Chapel Hill; and Department of Hospital Epidemiology, University of North Carolina Hospital,§ Chapel Hill, North Carolina*

HIV-1–infected patients undergo routine surgery as well as diagnostic and therapeutic procedures for complications of their immunodeficiency. Operative risks, including that of nosocomial infections, in HIV-1–infected patients who have not progressed to AIDS are unknown. These persons (Centers for Disease Control [CDC] class II) represent the largest group of the estimated 1.5 million HIV-1–infected persons in the United States.[11,12] There is reasonable concern about indications and risks in operating on clinically asymptomatic HIV-infected patients because many have demonstrable subclinical immune dysfunction on laboratory testing or anergy by skin testing. Such impaired immune function might increase the risk of perioperative infection, including wound infection.

To determine if HIV-1–infected patients, before the development of ARC or AIDS, were at increased risk for the development of postoperative wound infections, we compared the operative risks of HIV-1–infected hemophiliacs with those of non–HIV-1–infected hemophiliacs.

Methods

This study was conducted at the University of North Carolina Hospital, a 600-bed acute-care hospital that serves as the main teaching hospital for the University of North Carolina School of Medicine at Chapel Hill. Nosocomial infection surveillance of all hospital patients is conducted by three full-time infection-control practitioners and directed by two staff members from the Division of Infectious Diseases.

As part of a natural history study, HIV-1 testing has been offered to all hemophiliacs currently under care at the University of North Carolina Comprehensive Hemophilia Diagnostic and Treatment Center (see Smiley et al.[13] for details). HIV-1 status was determined by Western Blot analysis. We confined our study to patients with hemophilia A (deficiency of clotting factor VIII), hemophilia B (deficiency of clotting factor IX), and patients with an inhibitor (acquired antibody to factor VIII). The degree of hemophilia was classified as severe (≤ 1% of the normal clotting factor activity in the blood), moderate (1% to 5% of the normal clotting factor activity in the blood), or mild (more than 5% of the normal clotting factor activity in the blood).

Using a computerized retrieval system in Medical Records, we ascertained all patients with hemophilia A or B who underwent invasive procedures between July 1978 and April 1988. Charts of all hemophilia patients undergoing invasive procedures were reviewed independently by an infection control practitioner and a surgeon, and coded for type of procedure, date of procedure, complications including bleeding or hematoma, and development of wound or nosocomial infection. Medical evaluation after invasive procedure is standard for all hemophiliacs cared for at the Comprehensive Hemophilia Diagnostic and Treatment Center and was available for all subjects. Procedures were defined as clean, clean-contaminated, contaminated, or infected using CDC criteria.[14] Chart reviewers were blinded as to the HIV-1 status of the patient, although at times this information was recorded in the chart.

The HIV-1 status at the time of procedure was retrospectively coded as known or unknown. Patients with a known HIV-1 status included patients with procedures subsequent to a positive HIV-1 test (HIV+) and patients with procedures before a negative HIV-1 test (HIV-). Data also were accumulated on patients with an unclear HIV-1 status who had undergone procedures before a positive HIV-1 test (pre-HIV+).

T4-lymphocyte subset analysis was performed in the Hematology Laboratory, University of North Carolina Hospital. T4 levels were performed on many patients at 6- to 12-month intervals beginning in 1983. For procedures performed before 1983, the T4 level obtained in 1983 was used in our analysis. For procedures performed after 1983, the T4 level obtained most closely in time to the procedure was used, provided that the T4 level was obtained within 6 months of the procedure.

For the purpose of this study the outcome variable of major interest was wound infections. If patients underwent multiple procedures, each procedure's risk of infection was considered an independent event. T4-lymphocyte levels among patient groups (HIV−, pre-HIV+, HIV+ pre-AIDS, HIV+ AIDS) were compared using an analysis of variance on the ranks of the raw data (*i.e.*, equivalent to the Kruskal-Wallis test) because the data was not normally distributed.

Results

Patient Population

As of July 1987, HIV-1 status was known on 276 patients with hemophilia A or B. The likelihood of being HIV positive correlated with severity of hemophilia. For patients with hemophilia A, the number of patients testing HIV positive over the patient population was as follows: severe clotting factor deficiency 126 of 162 patients (77.8%), moderate clotting factor deficiency 2 of 6 patients (33.3%), and mild clotting factor deficiency 4 of 41 patients (9.8%). For patients with hemophilia B, the number of patients testing HIV positive over the patient population was as follows: severe clotting factor deficiency 13 of 30 patients (43.3%), moderate clotting factor deficiency 0 of 3 patients (0%), and mild clotting factor deficiency 1 of 8 patients (12.5%). Seven of twenty-six patients (26.9%) with acquired antibody to factor VIII were HIV-1 positive.

One hundred two hemophilia patients who underwent invasive procedures were ascertained by retrospective review of the medical records. Charts were available for review on 100 patients (98%). Comparison of these patients with our ongoing prospective natural history study revealed that HIV-1 status was known for 83 patients (83%) who had undergone 169 procedures (average of 2 procedures per patient) between July 1979 and April 1988.

HIV-1–positive hemophiliacs in our study had more severe clotting factor deficiency than HIV-1–negative hemophiliacs (Table 1). Patients classified as pre-HIV positive were similar to HIV-positive patients in regard to their type and severity of hemophilia. The time intervals between the invasive procedure and positive HIV-1 test for the pre–HIV-positive group were as follows (cumulative %): less than 1 year, 9 patients (13%); 1 to 2 years, 17 patients (39%); 2 to 3 years, 13 patients (58%); 3 to 4 years, 5 patients (66%); 4 to 5 years, 8 patients (78%); 5 to 6 years, 7 patients (88%); and more than 6 years, 8 patients (100%).

Invasive procedures undergone by patients in our study were classified as clean, 108 patients (63.9%); clean-contaminated, 45 patients (26.6%); contaminated, 2 patients (1.2%); and infected, 14 patients (8.3%) (Table 2). The most common clean procedures were orthopedic reconstructions.

Wound Infection Rates

There were only two cases of postprocedural wound infection in these 169 procedures (Table 3). Wound infection rates by HIV-1 status were as follows (95% con-

TABLE 1. *Type and Severity of Hemophilia By HIV Status*

Hemophilia	HIV−		Pre-HIV+		HIV+	
	Pt*	IP†	Pt	IP	Pt	IP
Severe VIII deficiency	6	7	33	61	38	64
Moderate VIII deficiency	2	2	1	1	0	0
Mild VIII deficiency	5	8	0	0	0	0
Severe IX deficiency	4	5	1	2	2	2
Moderate IX deficiency	1	1	0	0	0	0
Mild IX deficiency	1	2	1	1	1	1
Inhibitor	4	6	2	2	2	4
Total	23	31	38	67	43	71

* Number of patients.

† Number of invasive procedures.

TABLE 2. *Invasive Procedures Performed in Patients Stratified by HIV Status*

Procedure	HIV−	Pre-HIV+	HIV+
Clean			
Orthopedic			
Joint replacement	0	11	3
Radial head excision	0	7	2
Arthroplasty/synovectomy	3	12	3
Other	2	3	7
Biopsy			
Lymph node (excisional)	1	1	2
Liver	3	5	0
Bone marrow	0	1	9
Brain	0	0	1
Breast	1	0	0
Drainage hematoma			
Intracranial	1	1	2
Intra-abdominal	1	0	0
Soft tissue	0	0	1
Hickman/Portacath	1	0	3
Splenectomy	0	0	4
Hernia repair	2	2	3
Vascular (ex., A-V fistula)	0	3	0
Tubal ligation	1	0	0
Thoracotomy	1	0	0
Excision epidermal/brachial cyst	1	1	0
Other	0	2	1
Clean-contaminated			
Tooth extraction (mean, 4.3)	4	10	3
Intra-abdominal	4	0	5
Respiratory	1	2	4
ENT	3	1	6
Other	1	0	1
Contaminated			
Intra-abdominal	0	0	1
Skin graft	0	1	0
Infected			
Soft-tissue abscess	0	0	3
Intra-abdominal abscess	0	0	2
Perirectal abscess	0	1	1
Central nervous system abscess	0	0	1
Bone/joint	0	1	2
Amputation	0	0	1
Removal infected broviac	0	1	0
Removal infected tooth	0	1	0

fidence intervals): HIV positive, 1.4% (0% to 5%); HIV negative, 0% (0% to 9%); and pre-HIV positive, 1.5% (0% to 6%). There were no significant differences between the wound infection rates of HIV-positive and HIV-negative hemophiliacs nor in the wound infection rates comparing any two subgroups of patients ($p > 0.5$, Fisher's Exact Test).

By April 1988, 12 of the 43 HIV-positive patients who had undergone invasive procedures had progressed to AIDS. Two patients developed AIDS in 1985, 2 in 1986, 6 in 1987, and 2 in the first 4 months of 1988. Of the 71 procedures performed in HIV-positive patients, seven were done after the patients were classified as having AIDS. Bleeding complications were noted in four of these seven procedures, but no wound infections complicated the patients's postoperative courses.

Bleeding Complications

Clinically significant bleeding and/or wound hematomas occurred during many of the procedures. Rates of these complications by HIV-1 status were as follows (95% confidence intervals): HIV positive, 14% (7% to 23%); HIV negative, 19% (8% to 35%); and pre-HIV positive, 18% (10% to 28%). There were no significant differences in the rate of clinical bleeding and/or hematoma formation between patients who were HIV positive or HIV negative, nor among any two subgroups of patients ($p > 0.50$, Fisher's Exact Test).

Mortality

Four patients died within 30 days of their procedure. HIV-1 status at the time of death was as follows: HIV negative, HIV positive pre-AIDS 1, HIV positive AIDS 2. Of the two patients with AIDS, one died from a gastrointestinal hemorrhage during a hospitalization in which a left hip prosthesis was removed due to infection with *Staphylococcus aureus* and the other died of *Pneumocys-*

TABLE 3. *Wound Infections and Clinically Significant Bleeding Resulting from Invasive Procedures in Patients Stratified by HIV Status*

	HIV−			Pre-HIV+			HIV+		
Invasive Procedure	IP*	WI†	BL‡	IP	WI	BL	IP	WI	BL
Clean	18	0	4	49	1	10	41	0	5
Clean-contaminated	13	0	2	13	0	1	19	1	4
Contaminated	0	0	0	1	0	0	1	0	0
Infected	0	0	0	4	0	1	10	0	1
Total	31	0	6	67	1	12	71	1	10

* Number of invasive procedures.
† Number of wound infections.
‡ Number of procedures complicated by bleeding.

titis carinii pneumonia during a hospitalization in which a tracheostomy was performed. Causes of death for the remaining two patients were presumed illicit narcotic overdose and an anteroseptal myocardial infarction.

T4-Lymphocyte Subset Analysis

T4-lymphocyte subset analysis was available on many patients (Table 4). T4 levels around the time of surgery in order of decreased mean levels were as follows: HIV negative, 622; pre-HIV positive, 518; HIV positive pre-AIDS, 335; and AIDS, 139. Although these values were all statistically different, the patient's HIV-1–infection status accounted for only about 20% of the variability in the T4-lymphocyte count (*i.e.*, $R^2 = 0.21$).

Discussion

Treatment center-based studies of HIV-1 prevalence in hemophiliacs have revealed that 33% to 92% of subjects with hemophilia A and 14% to 52% of subjects with hemophilia B are infected with HIV.[15] Seropositivity of HIV-1 among hemophiliacs is uniformly distributed throughout the United States, reflecting the national distribution of clotting factor concentrates they received before 1985. Seropositivity is related to the type and severity of coagulation disorder.[12] Overall about 70% of persons with hemophilia A and 35% with hemophilia B are seropositive. Within each type of hemophilia, seropositivity increases with the severity of factor deficiency and, hence, with the amount of clotting factor received.[16] Among the 407 cases of hemophilia-associated AIDS reported to the CDC by September 1987, the distribution of specific opportunistic infections and tumors, with the exception of significantly fewer reports of Kaposi's sarcoma, was similar to homosexual-associated and intravenous drug user-associated AIDS.[15]

Several series have compiled complication rates of surgery in hemophiliacs operated on after 1960. Unfortunately differences among the series in types of surgery performed and relative frequency of type and severity of hemophilia make comparisons among the series difficult. Bleeding complications have been reported to occur in 4% to 23% of procedures, usually in the postoperative period rather than during operation.[17–23] While one study

TABLE 4. *T4 Lymphocyte Subset Analysis of Patients at Time of Procedure*

			HIV+	
T4 Subset Analysis	HIV−	Pre-HIV+	Pre-AIDS	AIDS
Patients (% total patients)	18 (78.3)	31 (81.6)	34 (85.0)	5 (83.3)
Procedures (% total procedures)	22 (71.0)	54 (80.6)	47 (73.4)	6 (85.7)
Procedures by T4 level				
Less than 200	2	8	12	4
200–399	1	14	19	2
400–599	6	15	10	0
More than 600	13	17	6	0
Mean T4 level	622	518	335	139
Standard deviation, mean level	281	315	217	148
Mean T4 rank*	90	72	51	21
Standard deviation, mean rank	32	36	33	21

* All comparisons statistically significant ($p < 0.05$, Tukey's adjustment for multiple comparisons employed): HIV− *vs.* pre-HIV+ $p = 0.045$; HIV− *vs.* HIV+ pre-AIDS $p < 0.001$; HIV− *vs.* AIDS $p < 0.001$; pre-HIV+ *vs.* HIV+ pre-AIDS $p = 0.002$; pre-HIV+ *vs.* AIDS $p = 0.001$; HIV+ pre-AIDS *vs.* AIDS $p = 0.045$).

noted a decrease in the incidence of hemorrhagic complications with the use of vigorous clotting factor concentration,[22] another did not.[18] The incidence of postoperative wound infections in these series has been reported to vary from 0% to 1%.[17,18,23]

Eighty-three hemophiliacs in our series underwent 169 procedures with an overall wound infection rate of 1.2%. Dental extractions were included in our data because multiple teeth were usually removed at each procedure (mean, 4.3), these extractions represented a potential site for wound infection, and dental problems are common in HIV-1–infected persons. There was no significant difference in wound infection rates between the HIV-positive and HIV-negative patients. This overall rate of wound infection is similar to rates reported in the literature after surgery in hemophiliacs.[17,18,23] Furthermore this rate is similar to the reported rate for clean surgery and occurred despite an overall 17% incidence of documented bleeding complications. Our incidence of bleeding complications in hemophiliacs is similar to that reported by others and occurred despite the routine use of prophylactic and therapeutic factor replacement during the period of study.

Patients with AIDS are at increased risk of bacterial infection. Atypical mycobacteria has been diagnosed in 8% to 29% of AIDS patients during the course of their illness[24] and *M. tuberculosis* in 5% to 10%. [6–10] In most cases infection with *M. tuberculosis* preceeds development of AIDS.[6–10] Case reports and uncontrolled series have suggested that patients with AIDS or ARC commonly develop bacterial sepsis[25–29] and bacterial infections involving the respiratory tract,[30–32] gastrointestinal tract,[30,33] and skin.[34] Bacterial pathogens reported associated with AIDS have included Salmonella, Listeria, *Streptococcus pneumoniae, Hemophilus influenzae, Branhamella catarrhalis, Campylobacter jejuni,* Campylobacter-like organisms, and Shigella.[12]

Only limited data are available that indicate whether HIV-1–infected patients who have not progressed to AIDS are at increased risk of bacterial infection. Unusually severe Salmonella infection, often associated with bacteremia and relapse despite appropriate therapy, has been noted before or coincident with the diagnosis of AIDS.[35,36] Bacterial pneumonia has been reported to occur more frequently in HIV-infected intravenous drug abusers compared to noninfected controls.[37] An increase in the incidence of pneumococcal bacteremia has been noted in patients at risk of HIV-1 infection but without clinical AIDS or ARC.[38] Infectious eczemoid dermatitis was shown to be significantly more common in HIV-1–infected patients as compared with HIV-1–negative high-risk persons or controls.[39]

Despite the evidence suggesting that patients with ARC or AIDS are at increased risk of bacterial infection, an increased risk of wound infection after invasive procedures has not been described. This may be because the cellular immune dysfunction caused by HIV-1 is different from the granulocyte and antibody deficiencies most often associated with an increased risk of wound infection. Alternatively adequate numbers of patients with ARC or AIDS undergoing invasive procedures have not been analyzed. Two reported series of lymph node biopsies in patients with ARC or AIDS revealed wound infection rates of 0%[40] and 2.5%.[41] In two series of HIV-1–infected patients undergoing splenectomy for thromocytopenic purpura, wound infections were noted in 1 of 15 patients (6.7%)[42] and in none of 11 patients (0%).[43] Despite the low incidence of wound infections in these series, the postoperative mortality rate for HIV-1–infected patients who have progressed to AIDS may be high. Patients with AIDS requiring emergency intra-abdominal surgery have been reported to have a 6-month survival rate of less than 50%.[44,45] AIDS patients undergoing anorectal surgery have been reported to have a rate of poor healing of 88% and a 16% rate of major complications.[46] The morbidity and mortality of surgery in patients with AIDS deserves further study because approximately 18% to 24% of patients with ARC or AIDS require surgical procedures.[44,47]

The decision to perform an invasive procedure must always be analyzed on the basis of the risk-benefit ratio for the patient and an informed decision by the patient and physician. As with other patients, the decision to perform an invasive procedure on an HIV-1–positive individual should be based, in part, on the risks and benefits of the procedure. Our controlled series demonstrated similar risks for postoperative wound infections between HIV-1–infected and uninfected hemophiliacs. While the number of operations in patients who had progressed to AIDS was small, this group also did not have an increased incidence of postoperative wound infections. Although T4-lymphcyte counts were lower in HIV-1–infected compared with noninfected hemophiliacs, they did not predict an increased susceptibility to wound infections. Although our data was derived from a study of hemophiliacs, we believe it is likely to be applicable to HIV-1–infected persons who have acquired infection *via* intravenous drug abuse or heter- or homosexual transmission. Despite the frequent occurrence of wound bleeding and/or hematomas, events that predispose to wound infections, the rate of wound infections in both our HIV-1–infected and noninfected subgroups was within commonly accepted surgical standards.

Published series of surgical procedures among patients with ARC and AIDS have been relatively small. The postoperative morbidity and mortality rates among these patients, particularly among those with gastrointestinal complications of ARC or AIDS, are substantially higher

than those of the general population. Among asymptomatic HIV-1–positive patients in our series, the operative (30-day) mortality rate was 1.7%, while among HIV-1–positive patients with AIDS it was 29%. Additional studies will be needed to further define the postoperative mortality in patients with AIDS because our data was based only on seven operations in the patient group.

Because there is no increased risk of operation in HIV-1–infected patients who do not have AIDS, screening all patients before surgery would not provide additional useful information in assessing patient risk of a postoperative wound infection. Considering the extent of the HIV-1 epidemic, however, further study of the outcome and complications of invasive procedures in patients with all stages and manifestations of HIV-1 infection is warranted.

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