Complications of plasma exchange in patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic uremic syndrome

III. An additional study of 57 consecutive patients, 2002-2005

Because the frequency of plasma exchange (PE) treatment for thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) has increased, complications caused by PE are an increasingly important consideration in management decisions. Because the diagnosis of TTP-HUS is often uncertain, the balance between the potential benefits and risks of PE is a critical issue in deciding appropriate treatment. Our previous two reports on 149 consecutive patients treated with PE for clinically suspected TTP-HUS from 1996 to 2002 have documented major complications in 42 (28%) patients, including three deaths attributed to PE treatment. This report describes our continuing experience during the subsequent 3 years, 2002 to 2005, and confirms the substantial risks associated with PE treatment for TTP-HUS.

From June 25, 2002, to June 25, 2005, a total of 60 consecutive patients were referred to Oklahoma Blood Institute (OBI) for PE treatment of their first episode of clinically suspected TTP-HUS. The OBI is the sole provider for PE procedures in central and western Oklahoma; therefore, all patients for whom PE was ordered for a clinical suspicion of TTP-HUS are included in this case series. Three patients were excluded because they died before a central venous catheter for PE was inserted. Twelve (21%) of the 57 patients included in this analysis subsequently had an alternative diagnosis that explained their acute disorder. Patients were treated in 11 different hospitals; therefore, a variety of catheter types (principally Quinton, Mahukar, and Arrow) were used. Analysis of complications related to catheter type was not done. Catheters in these hospitals are increasingly placed by interventional radiology physicians, although some catheters in this case series were placed by surgeons or intensive-care physicians. PE was routinely performed with cryoprecipitate-poor plasma with ACD-A anticoagulant with an AC ratio of 12:1; no heparin was used except to pack the catheter between procedures, and calcium was not routinely infused. Details of our definitions for major complications have been described previously. Examples of major complications were systemic infection, prevention of the PE procedure because of catheter obstruction, requirement for an invasive procedure such as replacement of the central venous catheter, requirement for or prolongation of hospitalization or transfer to an intensive-care unit, and requirement for systemic medications other than diphenhydramine, hydrocortisone, and CaCl2.

Fifteen of 57 patients (26%) had 19 major complications, similar to our previously reported complication rate; 2 patients died (Table 1). One patient died as a result of sepsis from Staphylococcus epidermidis 15 days after insertion of a left internal jugular catheter. One patient died from acute hemorrhage immediately after percutaneous insertion of a right subclavian central venous catheter. In both patients, the diagnosis of TTP-HUS was supported by the demonstration of a severe deficiency of ADAMTS13 activity (<3%) and the presence of a strong ADAMTS13 inhibitor (assays performed by Drs J. Kremer Hovinga and B. Lämmle, Berne, Switzerland). Both women were obese (Table 1), typical for TTP and obesity may have contributed to catheter-related complications. The death from hemorrhage in Patient 2 occurred in spite of a platelet (PLT) count of 67 × 109 per L; Staphy-

### TABLE 1. Deaths caused by PE treatment for patients with TTP-HUS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Year</th>
<th>Age (years), race, sex</th>
<th>Body mass index (kg/m²)</th>
<th>Cause of death</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2002</td>
<td>41, black, female</td>
<td>37.7</td>
<td>S. epidermidis sepsis, diagnosed 12 days after insertion of left internal jugular catheter by interventional radiology. Died 3 days later. Hemorrhage (1800 mL evacuated by chest tube) and death immediately after insertion of right subclavian catheter by surgery in the operating room, 15 days after diagnosis.</td>
<td>ADAMTS13 &lt; 3%, strong inhibitor. Positive urine drug screen for cocaine on admission. Cardiac arrest 3 hr after admission. Required continuous intubation and ventilation after resuscitation. Unresponsive to PE and steroids. ADAMTS13 &lt; 3%, strong inhibitor. Response to PE and steroids. Initial catheter removed on Day 13 because of S. aureus sepsis. Vancomycin and piperacillin-tazobactam started. Exacerbation 1 day later with PLT count of 39 × 10⁹/L. PLT transfusion given immediately before catheter placement. PLT count increased to 67 × 10⁹/L.</td>
</tr>
<tr>
<td>2</td>
<td>2003</td>
<td>25, white, female</td>
<td>34.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
S. aureus sepsis documented by blood culture 2 days before her death with continued fever on the day of her death may have contributed to her death.

Other major complications (Table 2) included 4 patients with catheter thrombosis that prevented PE and/or required placement of a new central venous catheter; 1 of these 4 patients had catheter-related jugular vein thrombosis requiring systemic anticoagulation. Ten patients, including both patients who died, developed systemic infections: 9 had positive blood cultures (S. epidermidis, 5; S. aureus, 3; α-streptococcus, 1); 1 patient with negative blood cultures was treated with parenteral antibiotics for presumed bacterial sepsis. Major plasma-related complications included hypotension requiring dopamine in 3 patients and acute hypoxia in 1 patient that required intubation with mechanical ventilation.

Twelve (21%) patients developed minor complications, including 6 patients who also had major complications. The majority of the minor complications were urticaria (10 patients); other minor complications included dyspnea responding to nasal cannula oxygen and hypotension responding to intravenous fluids.

These data confirm and extend our previous reports. In summary, over 9 years we have observed 73 major complications related to PE in 57 of 206 (28%) consecutive patients treated for clinically suspected TTP-HUS. Five of 206 (2.4%) patients have died. The rate of major complications has been consistent across the 9 years of these studies. Awareness of the risks of PE is essential for the evaluation and management of patients who may have TTP-HUS.

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Differential transmission of human immunodeficiency virus (HIV) via blood components from an HIV-infected donor

Not all blood transfusions from a human immunodeficiency virus (HIV)-infected donor result in an HIV infection in the recipient.\(^1\)\(^-\)\(^3\) In fact, one component from an HIV-infected donor may transmit HIV, whereas another component from the same collection may not.\(^2\) We report the absence of evidence of HIV infection after the transfusion of a unit of red blood cells (RBCs) from a donor whose platelets (PLTs) from the same blood collection transmitted HIV to another recipient.

In October 2002, whole blood was collected from a 52-year-old man who had successfully donated 53 times previously at the South African National Blood Service. The donor denied HIV-related risk behaviors at the time of this donation. Serum collected at the time of donation tested negative for the presence of the HIV-1 and -2 antibody (Prism HIV O Plus, Abbott, Wiesbaden, Germany) and p24 antigen (Innotest HIV antigen monoclonal antibody test, Innogenetics, Ghent, Belgium). On his return in January 2003, his serum sample tested positive for the presence of the HIV antibody by the same testing systems and procedures. A look-back investigation revealed that three components (RBCs, PLTs, and fresh-frozen plasma [FFP]) were produced from the October 2002 collection (Baxter, top-bottom, buffy coat-depleted). None of the components were leukoreduced. Once again, the donor denied HIV risk behaviors or signs or symptoms of HIV infection.

The RBC component was transfused (12 days after collection) to a 20-year-old patient (Recipient A). The PLT component was pooled and transfused (5 days after collection) to a 12-year-old patient (Recipient B). Pooled PLT components are prepared by adding the buffy coat obtained from five whole-blood collections with the plasma from one of the collections. The FFP had been forwarded to a fractionation center, but was retrieved for further testing.

In January 2003, Recipient B tested positive for the presence of HIV-1 antibodies (third-generation plus HIV enzyme immunoassay, Abbott, Abbott Park, IL) and p24 antigen (Prism HIV O Plus, Abbott). Recipient B had no other HIV risk factors, except prior blood transfusions. No previous HIV test result is available for Recipient B. Phylogenetic analysis of the donor’s and Recipient B’s gp160 sequences demonstrated that the samples clustered with HIV-1 Subtype B with a bootstrap value of 100 percent (National Institute for Communicable Diseases, National Health Laboratory Service, South Africa). Further phylogenetic analysis to include more HIV-1 Subtype B reference sequences supports the hypothesis of HIV transmission from the donor to Recipient B. The env nucleotide distance of the virus between the donor and Recipient B was very low (0.63%), with 17 nucleotide differences between the two samples.

The plasma component was retested by the standard screening test for routine donations, and the results were negative. The plasma sample tested positive, however, by nucleic acid amplification testing for HIV-1 RNA (COBAS AmpliScreen HIV-1 test, v1.5, Roche Diagnostics, Branchburg, NJ). This assay has a sensitivity of between 16.7 and 25 copies per mL, with a sensitivity rate of 50 percent.\(^4\) The viral load was estimated to be 12 copies per mL (COBAS Amplicor HIV-1 Monitor test, v1.5, Roche Diagnostics). The detection limit of this assay is 50 copies per mL with a 95 percent positivity rate\(^4\) with ultrasensitive specimen preparation.

Owing to her rural residence, Recipient A was not contacted for retesting until March 2003. At that time, the hospital physician requested only an HIV antibody test (Abbott HIV-1 and -2 gO, Abbott), which was negative. Recipient A was contacted again in July 2003, and the HIV antibody test remained negative. Polymerase chain reaction (PCR) testing for viral RNA (by the same method used for Recipient B) and Western blot (HIV Blot 2.2, Genelab Technologies, Singapore) was performed on a serum sample from Recipient A. Both these tests were negative. DNA-PCR was not performed on Recipient A.

To exclude the possibility that the implicated unit was erroneously transfused to another patient, blood bank and hospital records were reviewed. As far as reasonably possible, we ascertained that the implicated unit was transfused to Recipient A and not to another patient. We also considered the possibility of low susceptibility to HIV infection. The viral phenotype identified in the donor is known to produce infection in people exposed to it. Recipient A was genotyped as wild-type CCR5 excluding CCR5Δ32. In vitro studies were also performed to establish whether Recipient A’s peripheral blood mononuclear cells could be infected with HIV-1. Eight different HIV-1 Subtype C strains were demonstrated to be capable of infecting the cells of Recipient A in vitro. Because testing was performed before the specific subtype of the donor was identified, Subtype B was not used.
We believe that this case represents differential transmission of HIV via blood components from a donor in the serologic HIV window period. Recipient A did not seroconvert whereas Recipient B contracted HIV. Factors that may contribute to the differential transmission of HIV are the viral load of the blood component,\(^2,3\) different pre-transfusion storage times,\(^2\) and/or the number of lymphocytes in the components.\(^1\) Although our case confirms that differential transmission of HIV via blood components from an HIV-infected donor may occur, it does not explain why it may happen.

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