The Oklahoma thrombotic thrombocytopenic purpura-haemolytic uraemic syndrome Registry

A model for clinical research, education and patient care

J. N. George; S. K. Vesely; D. R. Terrell; C. C. Deford; J. A. Reese; Z. L. Al-Nouri; L. M. Stewart; K. H. Lu; D. S. Muthurajah

Department of Biostatistics and Epidemiology, College of Public Health, Department of Medicine, College of Medicine, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

Keywords
TTP-HUS, thrombotic thrombocytopenic purpura, cohort studies, rare disorders

Summary
The Oklahoma Thrombotic Thrombocytopenic Purpura-Haemolytic Uraemic Syndrome (TTP-HUS) Registry has a 24 year record of success for collaborative clinical research, education, and patient care. This article tells the story of how the Registry began and it describes the Registry’s structure and function. The Registry provides a model for using a cohort of consecutive patients to investigate a rare disorder. Collaboration between Oklahoma, United States and Bern, Switzerland has been the basis for successful interpretation of Registry data. Registry data have provided new insights into the evaluation and management of TTP. Because recovery from acute episodes of TTP has been assumed to be complete, the increased prevalence of hypertension, diabetes, depression, and death documented by long-term follow-up was unexpected. Registry data have provided opportunities for projects for students and trainees, education of physicians and nurses, and also for patients themselves. During our follow-up, patients have also educated Registry investigators about problems that persist after recovery from an acute episode of TTP. Most important, Registry data have resulted in important improvements for patient care.

Schlüsselwörter
TTP-HUS, thrombositisch-thrombozytopenische Purpura, Kohortenstudien, seltene Erkrankung

Zusammenfassung
Das Oklahoma-Register für thrombositisch-thrombozytopenische Purpura, Kohortenstudien, seltene Erkrankung

Correspondence to:
James N. George, M.D.
The University of Oklahoma Health Sciences CenterHematology-Oncology Section, Room CHB-335P.O. Box 26901, Oklahoma City, OK 73126–0901, USATel. 405/271 42 22, Fax 405/271 64 44E-mail: james-george@ouhsc.edu

Oklahoma-Register für thrombositisch-thrombozytopenische Purpura / hämolytisch-urämisches Syndrom

This article tells the story of the Oklahoma Thrombotic Thrombocytopenic Purpura-Haemolytic Uraemic Syndrome (TTP-HUS) Registry. It has six objectives (►Tab. 1):
1. to tell how the Registry began,
2. to tell how the Registry works,
3. to demonstrate the potential value of prospective cohort studies for understanding uncommon disorders,
4. to describe the synergy of the international clinical and laboratory collaboration,
5. to describe how the Registry has become a resource for education at multiple levels: for students and postdoctoral trainees who analyze and publish Registry data, for physicians and nurses who care for patients with TTP and HUS, and for patients who have re-
covered from TTP or HUS. Equally important, Registry investigators have been educated by our patients, whose experiences have provided new insights about their problems following recovery.

6. to describe how patient care has been improved by using Registry experience to change management protocols.

### Oklahoma TTP-HUS Registry History

We begin with the history of the Oklahoma TTP-HUS Registry: why it began, how it began, and how it became a registry. The beginning was in 1990, when Dr. George began to attend the weekly staff meetings of the Oklahoma Blood Institute (OBI). At these meetings, each patient treated with plasma exchange (PEX) was presented and discussed by the OBI staff. These discussions focused on how to appropriately use PEX for patients with TTP. PEX was still a new treatment for TTP; the randomized clinical trial documenting the efficacy of PEX was not published until 1991 (1).

An unexpected observation from these discussions was how many patients had received platelet transfusions before the diagnosis of TTP was considered, without apparent adverse effects. This was striking since it was “well known” by hematologists that platelet transfusions were dangerous for patients with TTP.

From these meetings came two projects for Dr. George and Dr. Mayez El-Harake, a hematology fellow at the University of Oklahoma in 1991.

- The first was to document the absence of harm from platelet transfusions. This proved to be very difficult because of the heterogeneity of patients treated with PEX for TTP; this project was not completed and published until 18 years later (2).
- The second project seemed simpler – to document the community practice of PEX treatment for TTP with the goal of developing a standard protocol for our University practice. To do this project, Mayez identified all patients treated with PEX by the OBI for a diagnosis of TTP. The records were complete back to January 1, 1989.

As he reviewed patients’ records at each of the hospitals in the OBI service region, it became apparent that the diagnosis of HUS was used interchangeably with TTP by community physicians. We had assumed that the term, HUS, was primarily a pediatric term for children with “typical” diarrhea-associated HUS. We learned that the term HUS was also commonly used for adults who had renal failure. Although children with typical diarrhea-associated HUS are usually managed only with supportive care, we also learned that PEX was requested for some children with typical HUS who had severe neurologic abnormalities. Therefore, we adapted our search of OBI records to include all patients for whom PEX was requested for a diagnosis of either TTP or HUS.

Multiple things happened during the next several years that transformed this project into the Oklahoma TTP-HUS Registry. First, Dr. George began to see each patient treated by the OBI for a diagnosis of TTP or HUS. This was requested by the community physicians because these were uncommon disorders and the community hematologists-oncologists primarily focused on oncology. Then Dr. Gary Raskob, an epidemiologist whose office was next to Dr. George’s office, recognized the unique opportunity provided by identifying every patient for whom PEX had been requested at the time of their initial diagnosis of TTP or HUS. Because the OBI was the sole provider of PEX for 55 of the 78 counties in the state of Oklahoma, a region with a population of 2,310,000, and because PEX had become the standard of care for patients with TTP, this meant that the OBI identified all patients in this defined region with a diagnosis of TTP (as well as some patients with a diagnosis of HUS). These qualities defined a cohort of all consecutive patients identified at a uniform point in their disorder, the time of their initial diagnosis. Therefore, this was an “inception cohort.” With recognition of the potential value of these patients’ data, the OBI nurses began to collect serum samples from each patient immediately before beginning the first PEX procedure in 1995.

The concept of a registry began in 1997 when Dr. Raskob’s student, Ms. Sara Vesely, decided to use these patients’ data for her PhD (biostatistics) dissertation. As part of her effort, she developed data collection forms, established reproducible definitions for clinical features and patient outcomes (3), and created a comprehensive database. This was when our project became the Oklahoma TTP-HUS Registry. In 1998 ADAMTS13 deficiency was described as an etiologic factor for TTP (4, 5). We had

- complete clinical data,
- serum samples.

<table>
<thead>
<tr>
<th>Model for</th>
<th>History</th>
<th>How the Registry began</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>How the Registry works</td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>The value of prospective cohort studies for understanding uncommon disorders</td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>The synergy of clinical-laboratory collaboration</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>Involvement of students and trainees at all levels in all projects and publications</td>
<td></td>
</tr>
<tr>
<td>Improving patient care</td>
<td>The ultimate goal</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria for</th>
<th>Inclusion</th>
<th>Telephone call to the Oklahoma Blood Institute requesting plasma exchange treatment for a patient with a diagnosis of TTP or HUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Tab. 1: The Oklahoma TTP-HUS Registry as a model for clinical research, education, patient care and criteria for enrolling patients.
We needed collaboration to measure ADAMTS13 activity. This was achieved when Dr. Vesely and Dr. Bernhard Lämmlle, Director of the Department of Hematology at the University of Bern, Switzerland, first met in 2001 at the XVIIIth Congress of the International Society on Thrombosis and Haemostasis in Paris. The rest of this story is recorded in the many publications of Registry data.

Structure

The defining feature of the Registry is the single inclusion criterion for patients with no exclusion criteria (► Tab. 1). Therefore, all patients in whom the diagnosis of TTP or HUS is considered with sufficient confidence to request PEX treatment are enrolled. Even the rare patients who never have a plasma exchange treatment, because of a change of treatment plan or death before beginning PEX, are enrolled. Because the Registry is a simple observational study with the potential benefit of additional information and with no risks, all patients (or their families) have consented to be enrolled. Many patients enrolled in the Registry may not be considered to have TTP or HUS several days or weeks later, when more information is available.

However, a rule of the Registry is that the diagnosis of TTP or HUS can never be excluded and all patients are followed forever.

Therefore, Registry patients are heterogeneous, creating a distinction from other reported case series of retrospectively selected patients. This heterogeneity creates opportunities to describe the multiple etiologies of thrombotic microangiopathy (TMA) that can mimic TTP or HUS. The only patients with TTP or HUS who are not usually treated with PEX and who are therefore not included in the Registry are children with typical diarrhea-positive HUS who are managed only with supportive care. Therefore, the Registry includes all patients with TTP or HUS treated with PEX within a defined geographic region. There is no selection or referral bias.

The Registry is feasible because all PEX procedures are performed in the Oklahoma City metropolitan area hospitals, with rare, brief exceptions. Although the OBI provides all of the blood products for all hospitals in the Registry region, patients are transferred to Oklahoma City hospitals for PEX. This allows the effective use of apheresis nursing staff and equipment and also makes all patients accessible to Registry investigators. Initially accrual to the Registry increased rapidly (► Fig. 1a), parallel to the experience in Canada following publication of their clinical trial that documented efficacy of PEX (1, 6). As annual enrollment stabilized, the Registry allowed an accurate estimate of the incidence of TTP (7) and revealed the striking demographic disparities among different patient groups (7, 8). As of 31 December 2011, the Registry had enrolled 451 patients, 427 for their first episode of clinically diagnosed TTP or HUS. Seventy (23%) of 301 patients who had their first episode of clinically diagnosed TTP or HUS and who had ADAMTS13 measurements, 1995–2011, had an ADAMTS13 activity < 10%. Twelve patients were enrolled when they had a recurrent episode of TTP and their initial episode had been before 1989 or outside of the Registry region, or for their initial episode if PEX treatment had already begun outside of the Registry region. These patients are analyzed separately because they are not part of the inception cohort. Twelve additional patients were enrolled following diagnosis of TMA by renal biopsy, not by the diagnostic clinical features of TTP. These patients are also analyzed separately because they often did not meet clinical diagnostic criteria for TTP; some did not have thrombocytopenia or microangiopathic haemolytic anaemia; none of the nine patients who had ADAMTS13 measurements had activity < 10%.

Model for uncommon disorders

The feasibility of the Registry has been the key to its durability and success. The protocol includes only simple observational data. It is a community project, enthusiastically supported by the OBI staff and community physicians. Because patients with TTP or HUS (or suspected TTP or HUS) are complex, physicians always welcome Registry involvement (9). In addition to new insights about the heterogeneity of TMA among patients diagnosed with TTP or HUS, perhaps the most original and valuable insights come from long-term follow-up. Long-term follow-up is essential to accurately document the frequency of uncommon events; it is feasible because there are not many Registry patients and because almost all patients become bonded to Registry investigators. Bonding occurs because follow-up is a two-way process; in addition to gathering information from patients, Registry staff provide support by helping patients with medical and administrative issues. Follow-up has been enhanced by regular support group meetings which have been held three times each year since 1996 (► Fig. 1b) (10, 11). These meetings were begun in order to provide information about TTP and HUS to patients and their families, which is essential for their adjustment to these uncommon and unfamiliar disorders. But the meetings immediately became a valuable source of new insights about long-term outcomes; they have functioned as focus groups. For example, patients and their families consistently described that they did not feel that they had completely regained their health following recovery. Many patients, and especially their spouses, described problems with memory, concentration, and endurance – not severe enough to restrict activities or occupations, but noticeable. The patients could not believe or accept that there was no awareness of these problems in the medical literature. These stories lead to our documentation of:

- abnormalities of health-related quality of life (12),
- persistent cognitive abnormalities (13), and
- the increased frequency of major depression (14) (► Tab. 2).

Long-term follow-up of patients who had severe ADAMTS13 deficiency has documented the

- frequency of relapse (15),
- the low risk of relapse with subsequent pregnancies (16), and
- the increased risk for developing systemic lupus erythematosus (17).
Other unexpected observations have occurred with long-term follow-up, including increased prevalence of hypertension, diabetes, and death, but no demonstrable impairment of renal function (18) (▶Tab. 2).

The feasibility of prospective cohort studies for uncommon disorders contrasts to the difficulty of completing randomized clinical trials. Although randomized clinical trials are considered to be the best method for providing definitive answers to clinical questions, accrual of patients with uncommon disorders may not be possible for academic medical centers. For example, the Transfusion Medicine/Haemostasis Clinical Trials Network (TMH/CTN) of the National Heart Lung and Blood Institute was established in 2002 to provide a national (US) network of academic medical centers to perform randomized clinical trials for uncommon haematologic disorders. A randomized clinical trial of rituximab treatment for TTP was one of the projects initially proposed in 2002 (19, 20). Planning the study, including an agreement with Genentech/Roche to provide the rituximab, required seven years. Enrollment began in April, 2009; among all 16 US participating medical centers, only three patients were enrolled in six months (two were from Oklahoma); the trial was then stopped for futility (personal communication, Julie N. Miller, New England
Research, Inc., TMH/CTN coordinating center). The lesson from this experience is to focus on feasibility. Successful randomized clinical trials may require an international effort and corporate support.

**Clinical-laboratory collaboration**

The success of the Registry can also be attributed to the synergy of the 11 year collaboration between Oklahoma and Bern (21). Without the expertise of the Haematology Laboratory of Bern University Hospital, the interpretation of patient data from the Registry would be limited. Without the detailed individual patient data from the Registry, the interpretation of ADAMTS13 data from Bern would be incomplete. This collaboration involves all projects. Importantly, Registry data have determined the clinically important definition of ADAMTS13 deficiency as less than 10% by either of two methods of measurement (15). This is the level that identifies the risk for relapse (15), except for rare patients with apparently unique distinctive characteristics of ADAMTS13 (22). Measurement of ADAMTS13 activity by a fluorogenic assay using FRETS-VWF73 substrate and by quantitative immunoblotting of degraded, plasma-derived VWF substrate may be inconsistent in some patients (15).

The identification of a patient group with ADAMTS13 activity <10% by either of these two methods has then allowed documentation of the incidence, demographic and presenting clinical features of the 70 patients with severe ADAMTS13 deficiency (Tab. 3) (5, 23, 24). Importantly, these data illustrate that the “classic pentad” of presenting clinical features, initially established in 1966 (25), is obsolete. Only three (4%) of 70 patients had the complete “pentad”; in two of these patients, the clinical features were subsequently attributed to sepsis; the third patient had been previously diagnosed with systemic lupus erythematosus.

**Table 2** Long-term outcomes in patients with severe ADAMTS13 deficiency who survived their initial episode of TTP, 1995–2011

<table>
<thead>
<tr>
<th>outcome</th>
<th>description</th>
</tr>
</thead>
</table>
| relapse                     | - Relapses (almost) only occur in patients who have severe ADAMTS13 deficiency (activity <10%) at the time of their initial episode of TTP.  
- Most relapses occur within the first two years after the initial episode, but can occur more than ten years after the initial episode.  
- estimated risk for relapse at 7.5 years is 43%  
- The occurrence of ADAMTS13 activity <10% during remission may not predict relapse and, in the absence of signs of TTP, may not be an appropriate indication for treatment with rituximab. |
| relapse with subsequent pregnancy | - Ten patients who have recovered from TTP associated with severe ADAMTS13 deficiency have had 17 subsequent pregnancies.  
- Relapse occurred in two patients, 8 and 38 days after delivery.  
- Therefore, our estimated risk of recurrent TTP with a subsequent pregnancy is 12%. |
| cognitive function          | - Problems with concentration, memory and fatigue are common.  
- For patients who had recovered from TTP associated with severe ADAMTS13 deficiency, cognitive function tests had significant but minor abnormalities. |
| major depression            | - With long-term follow-up, patients have increased prevalence of major depression compared to Oklahoma and US population data. |
| systemic lupus erythematosus | - 8 (11%) of 70 patients with TTP associated with severe ADAMTS13 deficiency have developed SLE preceding (4), concurrently (2), or following (2) their initial episode. |
| hypertension                | - With long-term follow-up, patients have increased prevalence of hypertension requiring regular medication, compared to the age, gender, race-adjusted US population. |
| diabetes mellitus           | - With long-term follow-up, patients have increased prevalence of diabetes requiring regular medication, compared to age, gender, race-adjusted US population. |
| renal function              | - With long-term follow-up, patients have normal renal function. |
| survival                    | - With long-term follow-up, patients have decreased survival compared to age, gender, race-adjusted US population. |

Data and interpretations are derived from all 57 (81%) survivors of the 70 consecutive patients who presented with ADAMTS13 activity <10%.

**Education**

The Registry has been a remarkable tool for education, both in Oklahoma and Bern. Many students and trainees at all levels, from undergraduate college to post-doctoral trainees in haematology, have participated in projects and publications (Tab. 4). Registry data have provided ideal opportunity for many student projects. Since the initial Registry publication in 1998 (26), many students have had the opportunity to author papers, and many have been the first author (Tab. 4). Student participation has amplified the productivity of Registry research. In the process of their participation, students learn the fundamentals of clinical translational research (21, 27).

But this traditional education is only a small part of the education provided by the Registry. With the care of each patient, Registry experience provides support for the primary physicians and nursing staff. Also important is the education of Registry investigators by the patients themselves, as described.

**Patient care**

Improved patient care is the ultimate objective of everything the Registry does. One recent example is the decreased frequency
Tab. 3 Incidence, demographics, and clinical features of 70 consecutive patients with severe ADAMTS13 deficiency (activity <10%), 1995–2011

<table>
<thead>
<tr>
<th>Incidence and demographic features</th>
<th>1.74</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years, median, range)</td>
<td>40 (9–71)</td>
</tr>
<tr>
<td>gender (% women)</td>
<td>56 (80%)</td>
</tr>
<tr>
<td>race (% black)</td>
<td>24 (34%)</td>
</tr>
<tr>
<td>obesity (% BMI ≥ 30 kg/m²)</td>
<td>37 (53%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical features</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>thrombocytopenia</td>
<td>70 (100%)</td>
</tr>
<tr>
<td>microangiopathic haemolytic anaemia</td>
<td>70 (100%)</td>
</tr>
<tr>
<td>neurologic abnormalities</td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>25 (36%)</td>
</tr>
<tr>
<td>minimal</td>
<td>21 (30%)</td>
</tr>
<tr>
<td>none</td>
<td>24 (34%)</td>
</tr>
<tr>
<td>kidney function abnormalities</td>
<td></td>
</tr>
<tr>
<td>acute renal failure</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>renal insufficiency</td>
<td>29 (41%)</td>
</tr>
<tr>
<td>normal renal function</td>
<td>35 (50%)</td>
</tr>
<tr>
<td>fever</td>
<td>15 (21%)</td>
</tr>
<tr>
<td>complete “pentad” of clinical features</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

From November 13, 1995 through December 31, 2011, 70 (23%) of the 301 patients with an initial episode of clinically diagnosed TTP in whom ADAMTS13 activity was measured had activity <10% by either the FRETS-VWF73 or immune-blotting assay, or both. Incidence was determined from data of 1996–2004 (7). Neurologic and kidney functions abnormalities have been previously defined (3). Two of the patients who had the complete “pentad” of clinical features were subsequently discovered to have systemic infections (hepatitis A with fulminant liver failure, group A streptococcal sepsis); one had a previous diagnosis of SLE. * The relative frequency of *black race is significantly greater than the Oklahoma population (8%, p <0.001) (8), † obesity is significantly greater than the Oklahoma population (22%, p = 0.01) (3).

of complications of PEX treatment. Back at the beginning, during the initial OBI staff meetings, the frequency of major complications of PEX treatment was a common concern. In 1996, the Registry began to prospectively document all complications from every PEX procedure, and not only during the procedure but beginning at the time of insertion of the central venous catheter and continuing after PEX was stopped (28). These data were first published after three years of observations (28) and have been updated at three year intervals (29–32).

The frequency of major complications in Registry patients was much greater than other published data (33–36), apparently because of the inclusion of complications of central venous catheter insertion before PEX was begun and of complications, such as sepsis and venous thrombosis, occurring after PEX was completed – sometimes even after the patient had been discharged from the hospital. During our most recent analysis in 2011 we documented a significant decrease in the frequency of major complications. The decreased frequency occurred only among patients with severe ADAMTS13 deficiency (32) and was attributed to a change of treatment over the previous 15 years (23, 37). With the increased use of corticosteroids and rituximab, the duration of PEX required to achieve a remission had significantly decreased, from 31 to 8 days (32). The decreased number of days of exposure to the central venous catheter had decreased the occurrence of infectious and thrombotic complications (32). This discovery was possible because of the continuous observations of our cohort of patients over many years.

Conclusions

The contributions of the Oklahoma TTP-HUS Registry to greater understanding of TTP, to the education of many students, trainees, physicians, and nurses, and to the improvement of patient care cannot be separated from one another. All outcomes of the Registry are related.

Tribute to Professor Bernhard Lämmle

The Oklahoma TTP-HUS Registry would not have been successful without the enthusiastic and conscientious participation of Professor Bernhard Lämmle. Together with his students and colleagues, Professor Lämmle has influenced every aspect of Registry research by his clinical insights, his scientific expertise, his attention to the smallest details of data interpretation, and his limitless imagination. Due to Professor Lämmle’s efforts, the Oklahoma TTP-HUS Registry has also been a role model for successful international collaboration.

Grant support

This project was supported by the Hematology Research Fund of the University of Oklahoma Health Sciences Center. Dr. Terrell is supported by NIH 3U01HL72283–10S1.

Conflict of interest

The authors have no conflict with this topic or these data. Drs. George and Terrell serve as consultants for Baxter, Inc. for the development of rADAMTS13 as a potential treatment for TTP. Dr. George serves as a consultant for Alexion, Inc. for the development of eculizumab as a treatment for aHUS.

Tab. 4 Publications using data from the Oklahoma TTP-HUS Registry

<table>
<thead>
<tr>
<th>Publications</th>
<th>78</th>
</tr>
</thead>
<tbody>
<tr>
<td>authors</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>76</td>
</tr>
<tr>
<td>students or trainees</td>
<td>38</td>
</tr>
<tr>
<td>who were first author</td>
<td>19</td>
</tr>
</tbody>
</table>

Data beginning with the initial publication using Registry data in 1998 (26) and including manuscripts accepted for publication as of 1 October 2012.
References


