Donor Hemovigilance during Preparatory Plasmapheresis

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Keywords

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Summary

Background: Reports on unexpected donor events (UEs) during preparatory plasmapheresis (PPP) are scarce, and rarely consider technical UEs. **Methods:** Defined local and systemic UEs were graded by severity; technical UEs were not graded. On January 1, 2008, E.B.P.S.-Logistics (EBPS) installed the UE module for plasma management software (PMS). Donor room physicians entered UEs daily into the PMS. Medical directors reviewed entries quarterly. EBPS compiled data on donors, donations and UEs from January 1, 2008 to June 30, 2011. **Results:** 66,822 UEs were observed during 1,107,846 PPPs for a corrected incidence of 6.55% (1.4% local, 0.55% systemic, 4.6% technical UEs). 3.36% of PPPs were accompanied by 1 UE and 1.18% by >1 UE (2–5). 13.7% of donors undergoing PPP for the first time, 9.7% of those having a second PPP and 4.0% of those having a third or more PPPs were associated with UEs. Most common UEs were repeated venipuncture, and broken-off collection due to venous access problems and small hematomas. Severe systemic UEs occurred at a rate of 36 per 100,000 PPPs. **Conclusions:** Technical UEs were common with PPP. UEs accompanied first and second donations significantly more frequently than for subsequent donations.

listed adverse reactions related to BDs and included donor safety standards [5]. Several investigators have discussed safety issues relating to collection of cellular component by cytopheresis [6–9]. Apart from unexpected donor events (UEs) during obsolete manual plasmapheresis [10–12], only

Table 1. Haema criteria for grading severity of unexpected events (UEs)

<i>Grade 1: mild UEs</i>
Brief impairment of health or well-being, no lasting discomfort
Recovery spontaneous or after symptomatic measure only (comfort the donor, release tight belt or collar, Trendelenburg position, distract donor, apply cold pack, give fluids by mouth, remove failed venous access, etc.)
Collection continued or resumed after repeat venipuncture
<i>Grade 2: moderate UEs</i>
Discomfort and symptoms persist beyond removal of cause (needle); ↓ alertness
Recovery protracted (> 30–60 min after circulatory reaction); local inflammation and/or painful ↓ of mobility
Physician orders oral medication (sympathomimetics, Ca ²⁺ tablets, pain reliever) or i.v. infusion of crystalloid fluids
Collection often broken off
<i>Grade 3: severe UEs</i>
Acute and/or severe impairment of donor on site (circulatory collapse, syncope, shock, injury from falling, vomiting, loss of consciousness, generalized convulsions, incontinence, etc.)
Physician administers i.v. medication, infusion of fluids other than crystalloids
Assistance by outside rescue squad or medical team requested; cardiopulmonary resuscitation; ambulance requested for transfer to medical service off site, emergency room or hospital
All systemic UEs occurring after donor left the donor center
Temporary or permanent impairment of donor such as inability to work, disability, compensation
i.v. = intravenous.
*Technical UEs are not graded by severity.

Introduction

Hemovigilance during blood donation (BD) has been receiving increasing attention [1–4]. The European Guide to preparation, use and quality assurance of blood components

Table 2. UEs: Major and sub-categories, codes, definitions and grades of severity

Category by system	Code	Severity	Definition of adverse events (any 1 item sufficient to qualify)
<i>Local UEs at venipuncture site</i>			
Arterial injury	A-1	mild	arterial puncture without sequelae after removal of needle and application of pressure dressing
	A-2	moderate	arterial puncture with moderate sequelae (e.g. hematoma, secondary bleeding) after needle removal and pressure dressing
Hemorrhage (bleeding into perivascular tissue)	A-3	severe	arterial injury requiring surgical intervention and/or resulting in permanent impairment
	H-1	mild	circumscribed hematoma (5–10 cm Ø), no pain, mobility unimpaired; secondary bleeding; includes repeated venipuncture until 31 July 2010*
	H-2	moderate	large hematoma > 10 cm Ø with moderate degree of pain and/or impaired mobility; anti-inflammatory ointment or pain reliever
Nerve injury	H-3	severe	large hematoma extending over upper arm and forearm; severe pain or impaired mobility, temporary or permanent disability; compartment hemorrhage; surgical, medical or physical therapy necessary
	N-1	mild	nerve irritation; paresthesias, severe pain, twitching in nerve region distally from site of venipuncture; all subside after removal of needle
	N-2	moderate	nerve injury with complete recovery within 4 weeks
Vein injury	N-3	severe	nerve injury with temporary (>4 weeks) or permanent disability
	V-1	mild	transient spasms or pain at site of venipuncture and/or radiating proximally; subside after removal of needle
	V-2	moderate	superficial thrombophlebitis: red, swollen, warm, tender, painful palpable cord of vein; subsides <2 weeks after topical treatment
	V-3	severe	deep vein thrombophlebitis or lymphangitis, fever; requiring antimicrobials
<i>Systemic UEs</i>			
Citrate reaction	AC-1	mild	perioral/apical sensations during first red cell-return (tingling, metallic taste)
	AC-2	moderate	paresthesias, tetany, headache, no drop of blood pressure, localized cramps/twitching; improvement after oral administration of Ca ²⁺ tablets
Hypovolemic circulatory reaction	AC-3	severe	generalized convulsions, cardiac and/or respiratory symptoms; requires i.v. application of Ca ²⁺
	CR-1	mild	transient hypotension, tachycardia, lightheadedness, dizziness, nausea, weakness; subside spontaneously or after symptomatic measures only (comforting and distracting the donor, positioning legs up, cold pack to forehead, fluids by mouth, removing needle from hematoma)
	CR-2	moderate	in addition to CR-1, protracted hypotension, impaired consciousness, delayed responsiveness; recovery delayed >30–60 min; improvement after medical treatment (sympathomimetics, i.v. fluids); collection often discontinued and not resumed
Vasovagal reaction	CR-3	severe	severe hypotensive reaction, collapse, syncope, shock, loss of consciousness, vomiting, convulsions, injury from falling, incontinence, i.v. medication; CPR; requiring outside medical assistance (rescue team, hospital transfer); any circulatory reaction after leaving the donor center; temporary or permanent impairment; inability to work; disability, compensation by insurer
	VR-1	mild	vasovagal reaction prior to or shortly after start of donation (e.g. <350 ml collected) and/or due to anxiety, fear, pain, manipulation at venipuncture site, etc.; heart rate usually low; recovery spontaneous or after measures as for CR-1
	VR-2	moderate	in addition to VR-1, protracted hypotension, impaired consciousness, delayed responsiveness; recovery delayed (>30 min); improvement after medical treatment (sympathomimetics, i.v. infusion of crystalloids); collection often impossible or prematurely discontinued
Hypersensitivity reaction	VR-3	severe	vasovagal reaction prior to or shortly after start of donation (<350 ml collected) with shock, unconsciousness, vomiting (as CR-3)
	HR-1	mild	mild immediate type hypersensitivity reaction (e.g. with urticaria, conjunctivitis, rhinitis)
	HR-2	moderate	moderate immediate type allergic reaction (e.g. shortness of breath, bronchospasm)
Other reactions	HR-3	severe	severe immediate type allergic reaction (e.g. anaphylactic shock)
	XH-2	moderate	hypertensive circulatory reaction with headache, dizziness, blood pressure increase by >50 mm Hg
	XC-3	severe	cardiopulmonary complications (e.g. bronchial asthma, cardiac arrhythmia, angina pectoris)
	XR-3	severe	rare severe complications not otherwise specified (e.g. tinnitus; visual disturbances, CVA)
<i>Technical UEs</i>			
Blood counts	T-BC	none	early breaking off collection due to irregular result of CBC (e.g. high hematocrit; platelets or WBCs high or low)
Compliance	T-DC	none	collection broken off due to bladder urgency or scheduling problems or due to deferral reasons initially concealed by donor and/or recognized later on by staff; donor wants collection broken off (no reason given)

Table 2 continued on next page

Table 2. *Continued*

Category by system	Code	Severity	Definition of adverse events (any 1 item sufficient to qualify)
Incomplete RBC return	T-RR	none	incomplete return of RBC reservoir content: RBC loss >1/4 reservoir (>30 ml RBC) (the cause of RBC loss is always another defined UEs leading to breaking off the collection)
Lipemia	T-LP	none	collection broken off due to lipemic plasma
Machine failure	T-MF	none	machine failure, environmental problems (not necessarily associated with incomplete collection)
Set defects	T-SD	none	disposable for A200 defective: centrifuge, tubing leakage; bent needle; plasma flow insufficient; red plasma (RBC overflow)
Operator error	T-OE	none	incorrect programming of A200; incorrect assembly of disposable; handling errors
Repeat venipuncture*	T-RP*	none	repeated venipuncture for failure to establish/maintain adequate blood flow after first venipuncture
Venous access	T-VA	none	collection broken off due to inability to establish/maintain adequate blood flow

Ø = diameter, CVA = cerebrovascular accident, CBC = complete blood count, WBC = white blood cell, RBC = red blood cell.
 * Until July 31, 2010, repeated venipuncture was included with H-1-category. Thereafter, it was considered a technical problem and introduced as new technical category T-RP.

few reports have focused on the safety concerns of preparatory plasmapheresis (PPP) [13–16], and these have often been abstracts [17–19] or case reports [20]; only 1 older report considered PPP-related UEs [21]. Heuft et al. [22] have started a national, web-based system to assess UEs during or after cell separator procedures.

The International Society of Blood Transfusion (ISBT) and the European Hemovigilance Network (EHN) advanced a system for documenting UEs during BD and hemapheresis procedures [23]. It provided 5 codes for hemapheresis-related problems, for citrate reaction, hemolysis, generalized allergic reaction, and air embolus. In our view, this does not cover the scope of UEs that we have observed regularly during PPP, particularly its technical problems. After 3.5 years, we summarize our experience with a computer-assisted UE system for all facets of UEs seen among 1,300 donors served daily.

Material and Methods

E.B.P.S.-Logistics (EBPS) developed and maintained a plasma management software (PMS) based on a SQL (structured query language) database. In 2003, the first version of the PMS-UE-documentation system was established in 6 donor centers [24]. Its objective was to document all local, systemic, and technical problems, side effects, untoward occurrences, and operator errors accompanying a donation process, including those resulting in broken-off collections (BOC). An update on January 1, 2008 included 3 grades of severity for each of 4 local and 5 systemic UE categories. 9 technical UEs were not graded for severity (tables 1, 2). 2 new donor centers were added when they opened in December 2008 and January 2009. During donor registration and processing, donor and donation data were entered into the PMS. Thus, all information about a donor and his former donations was available on-line at every work station.

Definition of a UE

A UE was defined as any occurrence locally at the venipuncture site or systemically adversely affecting the donor's wellbeing shortly before, during or within 24 (48–72) h after donation, as well as any technical problem related to equipment, staff and/or environment and impairing the procedure. The time frame of 24 h after donation was extended for local UEs, which took time to develop or to become evident. The physi-

cian determined causal relationship to donation. The principles for grading severity of local and systemic UEs are shown in table 1. To help distinguish UEs of mild from those of moderate degree, they include subjective criteria rather than limiting grading strictly to measured criteria.

UE Recording

If a UE occurred, donor room staff and/or the physician manually recorded the following on the donation protocol: collection status at UE onset, donor complaints, signs and symptoms, vital signs, physical findings, technical aspects of the UE, therapeutic measures, their effects, time to recovery, and donor status at release by the physician. The physician assigned the appropriate category, code and severity-grade and transferred all UE information to the PMS-UE module.

UE Documentation in the UE Module

By scanning the donor barcode on the donation protocol, the physician could open the PMS-macro with all identifying information. After opening the UE-module by mouse click, 5 more clicks entered an UE. Click 6 allowed a brief description of the UE to be entered. If the UE was of grade 3, a 7th step was required – the physician had to contact the donor for follow-up within 24 h of a systemic grade 3 UE (possibly later in case of a local grade 3 UE).

Multiple UEs during a Single Donation

Multiple UEs during a single donation were recorded in the appropriate categories as separate UEs rather than as singular UE to facilitate computer-assisted evaluation. Multiple UEs within a single donation were cross-referenced by their codes. A ratio (number of all UEs / donations associated with UEs) was used as an indicator of documentation accuracy, reflecting the proportion between single and multiple UEs with a singular donation.

UE Data Review and Trend Analysis

Quarterly, the medical director evaluated and corrected all UEs for clarity, code assignment, completeness, plausibility and cross-referencing. Summaries of 14 quarters between January 1, 2008 and June 30, 2011 served as basis for calculating UE-incidence rates.

Donor Database

For epidemiological analysis, EBPS compiled the data from the 8 centers, including: data on donors, numbers and types of donations, donor status, groups of gender, age and of body weight, their respective UE rates, data on multiple UEs at the same donation, and of donors with UEs at several donations.

We used the Fenwal Autopheresis C A200 apparatus (Fenwal Inc., Lake Zurich, IL, USA). Depending on donor body weight, we collected

Table 3. Preparatory plasmapheresis (PPP) donors and donations with and without UEs

	Scores	M:F
Donations, n	1,107,846	1.08
Donations without UEs, n (% of donations)	1,059,596 (95.6)	1.09
Donations with UEs, n (% of donations)	48,250 (4.3)	0.94
Donations with 1 UE, n (% of donations with UEs)	35,178 (72.9)	1.04
Donations with >1 UEs at same donation, n (% of donations with UEs)	13,072 (27.1)	0.71
All UEs with donations, n	66,822 ^a	0.86
Donors of plasma only, n (% of donors)	2,655 (6.21)	0.47
Donors of blood and plasma, n (% of donors)	40,061 (93.78)	1.03
All donors of plasma or blood, n	42,716	0.99
Donors without UEs, n (% of donors)	20,604 (48.2)	1.02
Donors with UEs, n (% of donors)	22,112 (51.8)	0.95
Donors with 1 UE, n (% of donors with UEs)	8,341 (37.7)	1.02
Donors with >1 UE at same donation, n (% of donors with UEs)	9,054 (40.9)	0.77
Donors with UEs at different donations, n (% of donors with UEs)	10,719 (48.5)	0.97
Mean number of donations/donor in study period (range)	25.93 (1–178)	1.10
Donor age range, years (mean/median)	18–73 (31/27)	

M:F = male to female ratio.

^a Compiled from 14 quarterly UE summaries from each of the 8 Haema Centers using PMS.

Table 4. Donation frequency, UEs and UE incidence

Donations/ donor	Donors, n (%)	Donations, n (%)	Donations with UE, %	UEs with donations, n ^a	Uncorrected ^b UE incidence, n × 10 ⁻⁵	UEs/donations with UEs
1	5,046 (11.8)	5,046 (0.5)	28.9	2,026	40,151	1.39
2	2,838 (6.6)	5,676 (0.5)	19.2	1,553	27,361	1.42
3–5	5,388 (12.6)	21,406 (1.9)	11.1	3,337	15,589	1.40
6–10	5,996 (14.0)	47,028 (4.2)	7.7	5,093	10,830	1.40
11–20	6,997 (16.3)	104,839 (9.5)	5.8	8,361	7,975	1.37
21–30	4,140 (9.7)	104,591 (9.4)	4.9	7,052	6,742	1.35
31–50	4,974 (11.6)	195,710 (17.7)	4.2	10,905	5,572	1.33
51–100	5,274 (12.3)	377,908 (34.1)	3.5	17,345	4,590	1.32
101–150	2,033 (4.8)	240,921 (21.7)	2.9	9,008	3,739	1.30
151–178	30 (0.1)	4,721 (0.4)	4.0	235	4,978	1.23
Total	42,716	1,107,846	4.3	64,915	5,859	1.34

^aData compiled by E.B.P.S.-Logistics from the 8 Haema Centers using PMS for the epidemiologic donor analysis of UEs.

^bNot corrected for introduction of T-RP on August 1, 2010.

Fig. 1. UE incidence by major category and donor status.

Table 5. UE incidence associated with first, second and multiple (≥ 3) donations

	Severity	Code	All PPP n	All PPP incidence ($n \times 10^{-5}$)	First PPP incidence ($n \times 10^{-5}$)	Second PPP incidence ($n \times 10^{-5}$)	≥ 3 PPP incidence ($n \times 10^{-5}$)
Total UEs, n			1,107,846		29,612	25,856	1,052,378
Local UEs							
Arterial injuries	mild	A-1	3	0.3	0	0	0.3
	moderate	A-2	0	0	0	0	0
	severe	A-3	0	0	0	0	0
Hematomas (hemorrhage into perivascular tissues)	mild	H-1 until July 31, 2010	16,433	2,034 ^a	3,945 ^a	4,129 ^a	1,922 ^a
	mild	H-1 after August 1, 2010	3,679	1,227 ^a	3,823 ^a	3,814 ^a	1,112 ^{a,*}
	moderate	H-2	328	30	37	77	28
Nerve injuries	severe	H-3	276	25	27	23	25
	mild	N-1	93	8	30	19	7
	moderate	N-2	23	2	3	0	2
Vein injuries	severe	N-3	1	0.1	0	0	0.1
	mild	V-1	905	82	155	139	78*
	moderate	V-2	35	3	0	4	3
	severe	V-3	9	1	0	0	1
		subtotal	21,785	1,379 ^b	4,075 ^b	4,076 ^b	1,256 ^{b,*}
Systemic UEs							
Citrate reactions	mild	AC-1	265	24	240	104	16*
	moderate	AC-2	21	2	20	19	1*
	severe	AC-3	0	0	0	0	0
Hypovolemic circulatory reactions	mild	CR-1	2,346	212	2,293	1,048*	133*
	moderate	CR-2	2,076	187	2,326	1,102*	105*
	severe	CR-3	357	32	206	151	25*
Vasovagal reactions	mild	VR-1	471	42	645	193*	22*
	moderate	VR-2	457	41	530	174*	24*
	severe	VR-3	42	4	47	12*	2*
Immediate hypersensitivity reactions	mild	HR-1	5	0.4	7	0	0.3
	moderate	HR-2	2	0.2	0	0	0.2
	severe	HR-3	0	0	0	0	0
Other reactions	moderate	XH-2	56	5	20	4	5*
	severe	XC-3	3	0.3	0	0	0.3
	severe	XR-3	0	0	0	0	0
		subtotal	6,101	551	6,335	2,808*	333*
Technical UEs							
Blood counts out of limits		T-BC	689	62	101	39*	62*
Donor compliance		T-DC	1,634	147	412	305*	136*
Incomplete RBC return		T-RR	6,745	609	1,101	1,133	582*
Lipemia		T-LP	5,792	523	993	870	501*
Machine failure		T-MF	399	36	34	35	36
Operator error		T-OE	1,624	147	159	147	146
Disposable defective		T-SD	5,827	526	588	538	524
Repeat venipuncture ^a		T-RP ^b	4,562 ^b	1,522 ^b	4,045 ^b	3,460 ^b	1,422 ^b
Venous access		T-VA	11,664	1,053	3,029	2,467*	962*
		subtotal	38,936	4,625 ^b	10,462 ^b	8,994 ^{b,*}	4,366 ^{b,*}
Total UEs ^b			66,822	6,555 ^b	20,872 ^b	15,878 ^{b,*}	5,960 ^{b,*}

^aPrior to 1 August 2010, repeated venipuncture was part of H-1; it then became T-RP. Subsequently, H-1-incidence dropped by 807×10^{-5} . H-1 incidence is thus corrected.

^bT-RP, H-1 and total UE incidence based on all donations after August 1, 2010: 299,807 PPP (first: 6,774, second: 5,925, ≥ 3 : 287,108).

*Differences significant, $p < 0.05$.

Fig. 2. Incidence of technical UEs by subcategory and donor status.

Fig. 3. Quarterly UE incidence.

660, 760 or 860 ml plasma in order to maintain extracorporeal volume < 15%. At the end of collection, the disposable system was rinsed with 500 ml saline to be infused into the donor, limiting red cell loss to 0.7 ml per PPP. Hemoglobin was measured photometrically in a capillary blood sample by an azide-methemoglobin method using HemoCue Hb 201 DM (HemoCue GmbH, Grossostheim, Germany) [25]. Minimal hemoglobin levels for donor eligibility for males was > 8.4 mmol/l and for females > 7.8 mmol/l.

Statistical Analysis

The statistical analysis was carried out by MedCalc using the comparison of proportions. The test performed a Chi-square test for the comparison of 2 proportions (from independent samples), expressed as a percentage [26]. Where the calculated p value was less than 0.05, the conclusion was that the 2 proportions were significantly different. The chi-square test Yates' correction for continuity was applied and those p values were 2-sided (or 2-tailed).

Results

Table 2 lists UEs by major and sub-categories, codes, definitions of the specific features and grades of severity based on specific signs and symptoms, vital signs, technical aspects, therapeutic measures taken, and time needed for recovery; technical UE definitions are also specified there. Table 3 presents details on donors and their donations with and without UEs. 95.6% of PPP proceeded without any UEs. 48% of donors never experienced a UE, while 25% experienced them repeatedly. While only 1.2% of PPP were associated with more than 1 UE, 27% of UE-associated PPP had several UEs with the same donation.

Table 4 relates donation frequency to yield and UE incidence. Whereas first or second time PPP donors had associated UEs very frequently (29 and 19%, respectively), the

Table 6. Most frequently observed UE combinations in the same plasma donation according to donor status

	PPP with 2 UEs (n = 9,950)			PPP with 3 UEs (n = 2,670)			PPP with 4 UEs (n = 436)		
	n	UE code	%	n	UE code	%	n	UE code	%
First donation	678			189			43		
		H-1, T-VA	30.5		H-1, T-VA, T-RR	45.7		H-1, T-VA, T-RR, T-RP	41.9
		H-1, T-RP	16.1		H-1, T-VA, T-RP	15.9		H-1, CR-2, T-VA, T-RR	13.9
		T-VA, T-RR	10.0		CR-2, T-VA, T-RR	3.7		H-1, CR-1, T-VA, T-RR	9.3
		T-SD, T-RR	7.8		T-VA, T-RR, T-RP	3.2		H-1, VR-2, T-VA, T-RR	9.3
Second donation	475			177			32		
		H-1, T-VA	31.4		H-1, T-VA, T-RR	57.1		H-1, T-VA, T-RR, T-RP	37.5
		H-1, T-RP	16.6		H-1, T-VA, T-RP	7.3		H-1, CR-1, T-VA, T-RR	15.6
		T-VA, T-RR	13.3					H-1, CR-2, T-VA, T-RR	12.5
		T-SD, T-RR	9.3						
Third donation	8,797			2,304			361		
		H-1, T-VA	26.1		H-1, T-VA, T-RR	67.1		H-1, T-VA, T-RR, T-RP	51.8
		T-SD, T-RR	20.7		H-1, T-VA, T-RP	8.5		H-1, CR-1, T-VA, T-RR	8.6
		H-1, T-RP	17.6					H-1, CR-2, T-VA, T-RR	8.3
		T-VA, T-RR	15.4						

Table 7. Incidence and cause of early broken-off plasma collection (BOC)

	n	BOC incidence, n × 10 ⁻⁵
All donor visits with venipuncture during donation	1,107,846	
Complete donations (target volume ± 10 ml)	1,080,653	
Blood sampling only for laboratory control or pre-donation screening	4,443	
All donations with early BOC	26,234	2,368
1st donations with early BOC	1,974	6,666
2nd donations with early BOC	1,260	4,873*
≥3 donations with early BOC	23,000	2,186*
Early BOC due to:		
Local UEs	243	22
Systemic UEs	1,503	136
Technical UEs	24,525	2,214
CBC parameter out of limits	668	60
Donor noncompliance	1,554	140
Lipemic plasma	5,766	520
Machine malfunction	645	58
Operator error	1,059	96
Defective disposables	3,453	312
Venous access problem	11,358	1,025

*Differences between different donor status are significant.

UE incidence gradually decreased to below 3% as donors gained experience. The overall uncorrected UE incidence was 5.9%. The single to multiple UE ratio with a single donation remained fairly constant around 1.4 for the first 10 PPP; with growing donor experience, the ratio dropped to 1.3 UEs per PPP.

Figure 1 compares the incidence of major UE categories and their sub-categories according to donor status as first-, second- or multiple-time (≥3) donor. Local and technical UEs occurred with similar incidence among first- and second-time

donors, while systemic UEs occurred significantly less often among second- compared to first-time donors. Considering local UEs at the venipuncture site (table 5), 95% were small circumscribed hematomas at the venipuncture site; these UEs were common (1.27%), more so with inexperienced donors. We observed 1 instance of severe nerve injury and 9 cases of severe thrombophlebitis or lymphangitis.

Of the systemic UEs (table 5), 93% of citrate reactions were mild. Overall, systemic UEs in first and second PPP were 19-fold and 8-fold higher than in ≥3 PPP. 79% of dona-

Table 8. Determinants of severe (grade 3) hypovolemic (CR-3) and vasovagal (VR-3) reactions

	CR-3		VR-3	Total		
	on site	off site ^a	on site	n	% of grade 3 criteria	% of donors affected
Parameter, n						
Loss of consciousness	109	48	24	181	25.0	45.4
Vomiting	130	12	14	156	21.5	39.1
Syncope	64	62	7	133	18.3	33.3
Severe circulatory insufficiency	0	57	0	57	7.9	14.3
Convulsions	38	2	14	54	7.5	13.5
Rescue team	17	28	0	45	6.2	11.3
Emergency room observation	17	22	2	41	5.6	10.3
Falling down	24	12	1	37	5.1	9.3
Injury from falling	14	6	1	21	2.9	5.3
Prolonged recovery	8	0	2	10	1.4	2.5
Bladder incontinence	3	0	1	4	0.5	1.0
Temporary unfit for work	2	1	0	3	0.4	0.7
Hospital admission	0	2	0	2	0.3	0.5
Total grade 3 criteria, n	407	252	66	725		
Donors involved, n	233	124	42	399		
Donors total, n		357	42			
Male donors, %		20.2	57.1	96		24.1
Donations incomplete, % male		40.3	91.7	51		53.1
First-time donors, % male		19.4	45.8	25		26.1
Female donors (%)		79.8	42.9	303		75.9
Donations incomplete, % females		33.0	83.3	109		36.0
First-time donors, % females		17.2	72.2	62		20.5
^a After donor had left the blood center						

tions with hypovolemic reactions (CRs) were complete: either the donors responded quickly to therapeutic measures, taken so that the procedure could be continued, or the reactions occurred near or after the end of collection. Hypovolemic reactions represented 78% of all systemic reactions. We defined psychogenic vasovagal reactions (VRs) as part of the early donation process or even preceding it; nevertheless, in more than 50%, collection was completed after supportive therapy (VR-1: 100%, VR-2: 26%, and VR-3: 12%). They accompanied first PPP 29-fold more frequently than ≥ 3 donations.

Severe systemic reactions (CR-3, VR-3, moderate hypertensive circulatory reaction (XH-2), severe cardiopulmonary complications (XC-3) and rare severe complications not otherwise specified (XR-3)) had an incidence of 0.04%, again with significant differences according to donor status. XH-2 were very rare. XC-3 UEs occurred in 3 donors: 1 had angina pectoris, 1 with had myocardial infarction, and 1 had sudden supraventricular tachycardia. All 3 donors recovered uneventfully.

Considering technical UEs (fig. 2), 42% concerned problems with establishing or maintaining venous access (repeated venipuncture (failing to establish/maintain blood flow, T-RP) and BOC due to venous access problem (T-VA)), with significant differences according to donor status. These two subcategories were seen in 1.5% of all donations. Defective disposables (T-SD), BOC due to lipemic plasma (T-LP), and in-

complete return of red cells due to another specified cause (T-RR) accounted each for >15% of technical UEs. Machine failure or environmental problems (T-MF), T-SD, and operator error in programming or set assembling (T-OE) did not vary with donor status. BOC due to poor donor compliance (T-DC and T-LP) related more to new donors.

Figure 3 shows quarterly UE incidences of the 3 major categories. Systemic UEs were stable throughout the study period. Local UEs decreased with introduction of the technical category T-RP in the third quarter of 2010, while technical UEs increased correspondingly. Table 6 shows the most frequent UE combinations seen with the same donation by donor status: donations with multiple events related most often to venous access problems and small hematomas, irrespective of donor status. Table 7 shows incidence and causes of BOC by donor status; 97% of all PPP were complete. The highest BOC incidence pertained to the first PPP. More than 90% of BOC were due to technical difficulties, mostly venous access problems. Table 8 shows the distribution of parameters that defined grade 3 systemic reactions with 399 PPP (357 CR-3 and 42 VR-3). Common parameters of severe systemic reactions were loss of consciousness, vomiting, syncope, severe circulatory insufficiency outside of donor center, and convulsions. 24% of donors with grade 3 reactions were male (26% of them first-time donors).

Discussion

Analysis of our first PMS UE-documentation module revealed that UEs were frequently associated with PPP (5.6%) [24]. However, this earlier system did not meet the subsequent requirements of the government authorities for documenting UEs by severity and for reporting the most severe UEs of the donors. The system presented here remedied that deficit [5].

Database

As of December 2, 2008, authorities requested that EBPS combine donor data from all PMS centers into a single database. 1,002 individuals registered in >1 center (1.7% of all donors). Data regarding status of such multiply registered donors as first-time, second- or multiple- (≥ 3) time donors were not corrected for this analysis. Thus, some of these individuals could possibly account for first donations in several centers. As they contributed only 1.4% of all PPP, their effect on the UE-incidence rates was considered negligible.

There were differences in the numbers of local UEs obtained from the UE modules and those obtained from the EBPS, in part due to record unification as described, and in part due to a change in defining a donation only after a minimum of 50 ml was collected, effective from January 1, 2011. The blood centers continued to count all venipunctures performed after clearance of a donor as a donation, even if unsuccessful or none or only a few milliliters were collected. Thus, the EBPS compiled 1,921 (2.9%) PPP-UEs less than UEs compiled by the blood centers. We used blood center data for calculating UE incidence rates. For epidemiological information we had to rely on the data compiled by the EBPS. Retrospective reconciliation of these differences was not possible.

Documentation Process

Physicians required 2 min or less to enter 94% of all UEs (mild or technical) into the database. Moderate and severe UEs required more time because of the comments given. On starting the system, 10% documentation errors were found; in the meantime, the error rate has reached 2–5% of all UEs.

Our catalogue of local and systemic UEs corresponds to that established in the literature for BDs [5, 23]. Of course, issue could be taken with our UE definitions. Newman [27] presented a comprehensive review on donor reactions and injuries occurring as a result of a BD: overall, 11–21% of donors experienced a reaction or injury from BD, including 9–16% bruises or hematomas, 2–5% vasovagal symptoms and <0.5% other injuries or reaction. Generally accepted risk factors for systemic BD UEs were: first donation, young age, low body weight, female gender, fatigue, long waiting period, and crowded facility [27–33]. Up to now, comparable data with respect to PPP were largely unavailable [34]. The 210 UEs reported by Franchini et al. [15] with 19,565 PPP do not compare; they found the following UE rates: 0.6% vasovagal reac-

tions, 0.08% citrate toxicity and 0.4% local injuries. Our findings indicate that UEs are more common. In the literature, we found no accounts of UE rates seen with the second donation. Our data showed that the first and second PPP were commonly associated with high UE incidence. This indicates that the possible effectiveness of special care for inexperienced PPP donors (as provided for first BD) should be evaluated.

Considering local UEs, small circumscribed hematomas may not have great significance for BD, where the donation interval must exceed 8 weeks. By that time, donors have likely forgotten the small nuisance in the bend of the elbow after their last donation. 87% of our local and systemic UEs were graded as mild. Yet, we considered them significant, as they may affect whether the donor returns: 31% of our donors donated only 1–5 times, contributing only 2.9% of all donations. These low frequency donors experienced 11% of all UEs (table 4). Newman et al. [35] elucidated, through post-donation interviews of BD donors, a substantial drop of donor return rates even after mild local and systemic UEs such as small hematomas, sore arm, fatigue, and/or circulatory donor reaction. Others also established a relationship of mild donor reactions after BD to a lesser likelihood of donor return [36–40]. Although frequent PPP donations at short intervals provided good feedback on local and systemic UEs occurring after leaving the center, there is 1 limitation to our analysis: we did not obtain systematical post-donation UE feedback from non-returning donors. With respect to PPP, the significance of mild hematomas must be emphasized: a donor with hematomas presenting within days for his next PPP had a problem – especially if both arms were affected. We would never access a vein through an old hematoma.

Distinction of injuries to nerves from those to veins and perivascular tissues was at times difficult if based strictly on clinical grounds: a direct injury of a nerve may have caused pain similar to the pain evoked by a rapidly developing hematoma with pressure on perinervous tissues. For nerve injury, it was decided that their radiating distally from the site of venipuncture was an essential criterion to distinguish them from injuries to the veins and perivascular tissues; symptoms from the latter were considered to be limited to the site of venipuncture and/or to radiate proximally.

For systemic UEs, signs and symptoms of citrate toxicity were rare with PPP, and at times difficult to distinguish from brief hyperventilation that may accompany vasovagal reactions [9]. Therefore, a separate hyperventilation category was not established.

Vasovagal reactions occurred mostly prior to, or within a few minutes after, the start of donation before a significant reduction of circulating blood volume took place [41]. Hypotensive reaction, sometimes referred to as ‘delayed vasovagal reaction’ [23], is mostly due to hypovolemia, typically occurring in the recovery lounge after a BD. We consider hypovolemia as the main causative factor for a hypovolemic reaction once the donated product volume has exceeded 350 ml. The

saline rinse of the disposable system at the end of PPP limits the volume loss with PPP to 59–77% of donated volume, depending on the volume of plasma donated. Möller et al. [42] presented studies on the changes in different compartments during PPP; immediately after PPP, only 130 ml extravascular volume was lost.

The grading of vomiting as a severe reaction could be disputed. However, as many donors use public transportation for their visit at the donor center, they perceive soiled and malodorous clothing as significant problem.

Grading any Systemic UEs Occurring after a Donor Had Left the Center as Severe

Here, we depended entirely on the donor's information. If he/she reported a systemic UE by phone or on his/her next visit, we considered it as significant and graded it as severe. Our analysis of such events supported this approach.

Uncommon and Rare Severe UEs

Upon review of UEs associated with >300,000 PPP during the years 2003 and 2004, it was considered appropriate to bundle some very rare severe systemic UEs under the category XR-3 [24], i.e. tinnitus, visual disturbances, or cerebrovascular accidents. Today, hemolysis and air embolism are rarely seen with modern blood collection equipment [9]. Severe outcomes [30, 43], arterial puncture [44], citrate toxicity, severe injuries to subcutaneous nerves [45–50], thrombosis of upper extremity veins [51, 52], formation of an arteriovenous fistula [53, 54], pseudoaneurysm [55–57], or compartment syndrome [58] are all extremely rare, as are some other rare events [59]. We did not see any of these rare UEs [60–62].

Technical UEs

Technical UEs are an integral part of PPP, representing 58% of all UEs. There has only been 1 report on technical problems relating to PPP [63].

European regulations now require documentation of failed attempts to include unsuccessful venipuncture [5]. Repeated venipuncture warranted an UE category of its own. Frequently,

a hematoma at the site of a failed first attempt towards venous access necessitated a second venipuncture; initially, both had been documented as a single UE in the perivascular hemorrhage-1 (H-1) category. This did not offer the desired feedback for the phlebotomy team. Therefore, on 1 August 2010, a separate technical category for repeated venipuncture (T-RP) was introduced. For the corrected overall UE incidence, we applied the T-RP- and the H-1-incidence rates observed after that date. The introduction of a T-RP-category was a practical way to comply with the European regulations.

The catalogue of technical UEs is new to donor hemovigilance. Although Klein et al. [64] reviewed complications related to equipment and technique, their report dealt mainly with cytapheeresis procedures. The economic implications of technical UEs are obvious, as they contribute to cost in terms of personnel time, supplies and lost donors [17].

Donations with Multiple UEs

Of UE-associated PPP, 27% have multiple UEs at 1 donation. Common combinations are hematoma, repeated venipuncture, failure to establish/maintain venous access, and BOC with incomplete return of donor red cells. No other references to multiple UEs with the same donation could be found in the literature.

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Disclosure Statement

The authors declare that they have no conflicts of interest relevant to the manuscript submitted.

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