Donor Hemovigilance with Blood Donation

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Summary

Background: Reports on unexpected events (UEs) during blood donation (BD) inadequately consider the role of 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 PMS. Medical directors reviewed entries quarterly. EBPS compiled data on donors, donations, and UEs from January 1, 2008 to June 30, 2011. **Results:** 6,605 UEs were observed during 166,650 BDs from 57,622 donors for a corrected incidence of 4.30% (0.66% local, 1.59% systemic, 2.04% technical UEs). 2.96% of BDs were accompanied by one UE and 0.45% by >1 UE (2–4). 6.3% of donors donating blood for their first time, 3.5% of those giving blood for their second time, and 1.9% of donors giving their third or more BD experienced UEs. Most common UEs were: discontinued collections due to venous access problems, repeated venipuncture, and small hematomas. Severe circulatory UEs occurred at a rate of 16 per 100,000 BDs. **Conclusions:** Technical UEs were common during BD. UEs accompanied first and second donations significantly more often than subsequent donations.

Introduction

Hemovigilance in blood donation (BD) has received increasing attention [1–4]. The European Guide to Preparation, Use and

Quality Assurance of Blood Components listed adverse reactions related to BDs and included donor safety to its standards [5]. Several investigators studied intensively issues of blood donor safety and explored ways to avoid unexpected events (UEs) [6–19]. In 2003, we established in 6 centers an UE documentation system for local, systemic, and technical problems, side effects, untoward occurrences, and operator errors accompanying BDs, including those resulting in discontinued collections [20].

In 2007, the International Society of Blood Transfusion (ISBT) and the European Hemovigilance Network (EHN) advanced a system for documenting and reporting UEs during BD and donation by hemapheresis procedures [21]. In our view, ISBT/EHN did not address in sufficient detail the scope of technical problems that we have observed regularly. After 3.5 years, we summarize our experience with a computer-assisted UE system for all facets of UEs seen among 200 blood 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. On January 1, 2008, we updated our UE documentation system of 2003, to include 3 grades of severity for each of 4 local and 5 systemic UE categories. Seven technical UEs were not graded for severity (tables 1, 2). Two new donor centers were added after they had 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 online at every workstation.

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 physician 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 de-

Table 1. Criteria for grading severity of UEs

Grade 1: mild UEs	a. Brief impairment of health or wellbeing, no lasting discomfort b. 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.) c. Collection continued or resumed after repeat venipuncture
Grade 2: moderate UEs	a. Discomfort and symptoms persist beyond removal of cause (needle); ↓ alertness b. Recovery protracted (>30 to 60 min after circulatory reaction); local inflammation and/or painful ↓ of mobility c. Physician orders oral meds. (sympathomimetics, Ca²⁺-tablets, pain reliever) or i.v. infusion of crystalloid fluids d. Collection often discontinued
Grade 3: severe UEs	a. Acute and/or severe impairment of donor on site (circulatory collapse, syncope, shock, injury from falling, vomiting, loss of consciousness, generalized convulsions, incontinence, etc.) b. Physician administers i.v. medication or infusion of fluids other than crystalloids c. Assistance by outside rescue squad or medical team requested; cardiopulmonary resuscitation; ambulance requested for transfer to medical service off site, emergency room or hospital d. All systemic UEs occurring after donor left the donor center e. Temporary or permanent impairment of donor such as inability to work, disability, compensation
*Technical UEs are not graded by severity. i.v.= Intravenous.	

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

gree, 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 into 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 UEs to be entered. If the UE was of grade 3 UE, 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 one singular UE to facilitate computer-assisted evaluation. Multiple UEs with a singular 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 of 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.

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>A) 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 & pressure dressing
	A-3	severe	arterial injury requiring surgical intervention and/or resulting in permanent impairment
Hemorrhage (bleeding into perivascular tissue)	H-1	mild	circumscribed hematoma (5–10 cm Ø), no pain, mobility unimpaired; secondary bleeding; includes repeated venipuncture until July 31, 2010*
	H-2	moderate	large hematoma >10 cm Ø with moderate degree of pain and/or impaired mobility; anti-inflammatory ointment or pain reliever
	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
Nerve injury	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
	N-3	severe	nerve injury with temporary (>4 weeks) or permanent disability
Vein injury	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>B) Systemic UEs</i>			
Hypovolemic circulatory reaction	CR-1	mild	transient hypotension, tachycardia, lightheadedness, dizziness, nausea, weakness; subside spontaneously or after symptomatic measures only (comforting & 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
	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
Vasovagal reaction	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)

Table 2 continued on next page

Table 2. Continued

Category by system	Code	Severity	Definition of adverse events (any 1 item sufficient to qualify)
<i>C) Technical UEs</i>			
Blood counts	T-BC	none	early discontinued collection due to irregular result of CBC (e.g. high hematocrit; platelets or WBC high or low)
Compliance	T-DC	none	collection discontinued 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 discontinued (no reason given)
Machine failure	T-MF	none	Failure of blood drawing apparatus; scanning device; environmental problems (not necessarily associated with incomplete collection)
Set defects	T-SD	none	Disposable leakage; bent needle
Operator error	T-OE	none	Incorrect programming of blood drawing apparatus; 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 discontinued due to inability to establish maintain adequate blood flow
*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.			

Donor Database

For epidemiologic 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 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 Fresenius Kabi CompoGuard blood collection apparatus with software version 1.3.0. (Fresenius Kabi, Bad Homburg, Germany) to collect a unit of blood (500 ± 10 ml). Hemoglobin was measured photometrically in a capillary blood sample by an azide-methemoglobin method using HemoCue Hb 201 DM (HemoCue GmbH, Grossostheim, Germany) [22]. Minimal hemoglobin levels for donor eligibility for males and for females was >8.4 mmol/l and >7.8 mmol/l, respectively.

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 two proportions (from independent samples), expressed as a percentage [23]. Where the calculated p value was less than 0.05, the conclusion was that the two 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 summarizes our definitions of the different UEs by major and sub-categories, codes, specific features, and grades of severity based on their significant signs and symptoms, vital signs, technical aspects, therapeutic measures taken, and time needed to recovery; technical UE definitions are also specified there. Table 3 presents the number of donors and their donations with and without UEs. 96.6% of BDs proceeded without any UE. 90.0% of donors never experienced a UE, while 7.6% experienced them repeatedly. Multiple UEs with a single donation were uncommon (0.45% of donations). Yet, 13.2% of UE-associated BDs had several UEs with the same donation.

Table 4 relates donation frequency to yield and UE incidence. While first- or second-time donors of BDs commonly had associated UEs (7.7% and 4.8% of donations), the UE incidence gradually decreased below 2% of donations as donors gained experience. The overall uncorrected UE incidence amounted to 3.89%. The single to multiple UE ratio with a singular donation remained fairly constant around 1.15 for the first 10 BDs.

Table 5 lists the incidence of major UE categories and their sub-categories according to donor status as first-time, second-time, or multiple-time donor (≥3 donations). In all major UE categories, multiple donors experienced UEs significantly less often than first- or second-time donors. 58% of UEs were related to venous access problems (H-1: small circumscribed hematomas, T-RP: repeat venipunctures, and T-VA: unsuccessful collections due to inability to establish or maintain adequate venous access), and this did not vary much with the donor status. Figure 1 shows the UE incidence by major category and donor status emphasizing the importance of technical UEs regardless of donor category.

Local UEs

96.1% of the local UEs at the venipuncture site (table 5) were small circumscribed hematomas at the site of venipuncture; they

Table 3. Blood donations and blood donors with and without UEs

	Scores	M : F
Donations	166,650	1.34
Donations without UEs, n (% of donations)	160,974 (96.6%)	1.37
Donations with UEs, n (% of donations)	5,676 (3.4%)	0.82
Donations with 1 UE, n (% of donations with UEs)	4,926 (86.8%)	0.82
Donations with >1 UE at same donation, n (% of donations with UEs)	750 (13.2%)	0.77
All UEs with donations, n	6,605	0.81
Donors of blood only, n (% of donors)	17,561 (30.5%)	0.81
Donors of blood and plasma, n (% of donors)	40,061 (69.5%)	1.03
All donors of plasma or blood, n	57,622	0.97
Donors without UE, n (% of donors)	52,401 (90.9%)	0.89
Donors with UEs, n (% of donors)	5,221 (9.1%)	0.83
Donors with 1 UE, n (% of donors with UEs)	4,186 (80.2%)	0.85
Donors with >1 UE at same donation, n (% of donors with UEs)	735 (14.1%)	0.85
Donors with UEs at different donations, n (% of donors with UEs)	396 (7.6%)	0.68
Mean number of donations / donor in study period (range)	2.89 (1–21)	1.38
Donor age, range, years (mean/median)	18–73 (32/33)	
Data compiled from 14 quarterly UE summaries from each of the 8 centers using PMS.		
M : F = Male to female ratio.		

Table 4. Blood donation frequency, UEs, and UE incidence

Donations/donor	Donors, n (%)	Donations, n (%)	Donations with UE, %	UEs with donations, n*	Uncorrected [†] UE incidence (n × 10 ⁻⁵)	UEs / donations with UEs
1	25,902 (44.9)	25,902 (15.5)	7.7	2,264	8,741	1.13
2	10,779 (18.7)	21,558 (12.9)	4.8	1,182	5,483	1.14
3	6,125 (10.6)	18,375 (11.0)	3.4	719	3,913	1.16
4	3,921 (6.8)	15,684 (9.4)	2.8	508	3,239	1.15
5	2,782 (4.8)	13,910 (8.3)	2.4	378	2,717	1.14
6	2,103 (3.6)	12,618 (7.6)	2.0	291	2,306	1.14
7	1,526 (2.6)	10,682 (6.4)	2.1	264	2,471	1.18
8	1,134 (2.0)	9,072 (5.4)	2.0	212	2,337	1.14
9	842 (1.5)	7,578 (4.5)	1.6	142	1,874	1.17
10–21	2,496 (4.3)	30,995 (18.6)	1.5	518	1,671	1.14
Outside range	12 (<0.1)	276 (0.7)	1.1	3	1,087	1.00
Total	57,622	166,650	3.41	6,481	3,889	1.14
*Data compiled by EBPS from the 8 centers using PMS for the epidemiologic donor analysis of UEs.						
[†] Not corrected for introduction of T-RP on August 1, 2010.						

were uncommon (0.29% of donations). Mild injuries to veins were uncommon (<1.0%), while moderate-size hematomas were rare (<0.1%). Arterial puncture, injuries of all degrees to nerves and veins, and large hematomas were all very rare (< 0.01%). We observed only 1 case of severe thrombophlebitis. The local UE rate of first-time donors was 2.5-times higher (1.14%) compared to that of multiple donors (0.45%).

Systemic UEs

Overall, systemic UEs (table 5) in first- or second-time donors occurred 9 or 4 times more frequently than in multiple donors. 97% of donations with hypovolemic reactions were complete re-

gardless of severity grade (grade 1: 100%, grade 2: 93.3%, grade 3: 94.6%): either the donors responded quickly to therapeutic measures taken so that the procedure could be carried on, or the reactions occurred near or after the end of collection. Hypovolemic reactions represented 89.6% of systemic reactions. We defined psychogenic vasovagal reactions as part of the early donation process, they may even precede donation; nevertheless, in 51.4% of donations with vasovagal reactions, collection was completed after supportive therapy (grade 1: 100%, grade 2: 21.7%, grade 3: 14.8%). They accompanied first-time donations 8 times more often than multiple donations. 68.6% of vasovagal reactions occurred in first-time donors and another 9.4% in second-time donors.

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

Category	Severity	Code	Blood donations (BD)				UEs with multiple (≥ 3) BD (n = 91,483) incidence (n × 10 ⁻⁵)
			UEs with all BD (n = 166,650)		UEs with first BD (n = 46,793)		
			n	incidence (n × 10 ⁻⁵)	incidence (n × 10 ⁻⁵)	incidence (n × 10 ⁻⁵)	incidence (n × 10 ⁻⁵)
Local UEs							
Arterial injuries	mild	A-1	3	2	6	0	0
	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	1,169	997*	1,195*	1,060*	797*
	mild	H-1 after August 1, 2010	311	629*	1,104*	846*	416**
	moderate	H-2	19	11	10	14	11
	severe	H-3	15	9	8	7	10
	mild	N-1	6	4	4	3	3
Nerve injuries	moderate	N-2	2	1	0	0	2
	severe	N-3	0	0	0	0	0
	mild	V-1	11	7	8	7	5
Vein injuries	moderate	V-2	3	2	2	3	1
	severe	V-3	1	1	0	0	1
	Subtotal		1,540	663†	1,142†	881†‡	450†‡
Systemic UEs							
Hypovolemic circulatory reactions	mild	CR-1	1,294	776	1,703	828‡	231‡
	moderate	CR-2	854	512	1,348	426‡	68‡
	severe	CR-3	240	137	293	183‡	46
Vasovagal reactions	mild	VR-1	99	59	163	39‡	8‡
	moderate	VR-2	129	77	153	39‡	46‡
	severe	VR-3	27	16	42	7‡	4‡
Immediate hypersensitivity reactions	mild	HR-1	1	1	0	0	1
	moderate	HR-2	0	0	0	0	0
	severe	HR-3	0	0	0	0	0
Other reactions	moderate	XH-2	7	4	10	3	1‡
	severe	XC-3	0	0	0	0	0
	severe	XR-3	0	0	0	0	0
Subtotal			2,651	1,591	3,705	1,526‡	404‡

Table 5 continued on next page

Table 5. Continued

Category	Severity	Code	Blood donations (BD)				UEs with multiple (≥ 3) BD (n = 91,483) incidence (n × 10 ⁻⁵)
			UEs with all BD (n = 166,650)		UEs with first BD (n = 46,793)		
			n	incidence (n × 10 ⁻⁵)	incidence (n × 10 ⁻⁵)	UEs with second BD (n = 28,370) incidence (n × 10 ⁻⁵)	
Technical UEs							
Blood counts out of limits	none	T-BC	104	62	113	70	31‡
Donor compliance	none	T-DC	11	7	8	7	5
Machine failure	none	T-MF	61	37	30	25	43
Operator error	none	T-OE	125	75	64	46	87
Disposable defective	none	T-SD	10	6	8	3	5
Repeat venipuncture*	none	T-RP†	416†	842	1,149†	997†	704†‡
Venous access	none	T-VA	1,687	1,012	1,530	1,057‡	683‡
Subtotal			2,414	2,041†	2,906†	2,185†‡	1,558‡†
Total UEs†			6,605	4,298†	7,753	4,592†‡	2,412†‡
*Prior to August 1, 2010, repeated venipuncture was part of H-1; then it became T-RP. Subsequently, H-1 incidence dropped by 368 × 10 ⁻⁵ . H-1 incidence is so corrected. †RP and H-1 and total UE incidence based on all donations after August 1, 2010: 49,423 BDs (first: 11,054, second: 6,855, multiple (≥): 31,514). ‡ Differences significant, p < 0.05.							

*Prior to August 1, 2010, repeated venipuncture was part of H-1; then it became T-RP. Subsequently, H-1 incidence dropped by 368×10^{-5} . H-1 incidence is so corrected.

[†]RP and H-1 and total UE incidence based on all donations after August 1, 2010: 49,423 BDs (first: 11,054, second: 6,855, multiple ($\geq$): 31,514).

[‡] Differences significant, $p < 0.05$.

Severe systemic reactions such as severe hypovolemic circulatory reactions, severe vasovagal reactions, moderate hypertensive circulatory reactions, severe cardiopulmonary reactions, and rare severe complications not otherwise specified occurred at a rate of 0.16%, again with significant differences according to donor status. Moderate hypertensive circulatory reactions were very rare. We observed no severe cardiovascular or other rare UEs.

Technical UEs

87.1% of technical UEs (fig. 2) concerned problems with establishing or maintaining venous access (repeat venipuncture, unsuccessful collection due to inability to establish or maintain adequate venous access), with significant differences according to donor status. Donor compliance, machine failure, defective disposable, and operator error did not vary with donor status. Discontinued collections due to venous access problems (table 7) accounted for 67% of technical UEs and involved 1% of all donations.

Figure 3 shows quarterly UE incidences of the three major UE 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 discontinued collections by donor status. 84% of all donations were complete. The highest incidence of discontinued collections pertained to the first donation. More than 90% of discontinued collections were due to technical difficulties, mostly venous access problems.

Table 8 shows the distribution of parameters that define grade 3 systemic reactions seen with 267 blood donations (240 grade 3 hypovolemic circulatory reactions and 27 grade 3 vasovagal reactions). Common parameters of severe systemic reactions were loss of consciousness, syncope, vomiting, falling down, and convulsions. 33% of donors with grade 3 reactions were male (70% of them first-time donors).

Discussion

Analysis of the first PMS-UE documentation module revealed that UEs were commonly of technical nature [20]. The earlier system did not meet the subsequent requirement of documenting UEs by severity and of reporting the most severe donor UEs to government authorities. 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 more than 1 center (1.7% of all donors). Data regarding status of such multiply registered donors as first-, second- or multiple-time (≥ 3) donors were not corrected for this

Fig. 2. Incidence of technical UEs by sub-category and donor status.

Fig. 3. Quarterly UE incidence.

analysis. Thus, a few of these individuals could possibly account for first-time donation in several centers. As they contributed only 0.9% of all donations, their effect on UE incidence rates was considered negligible.

There were small differences in the numbers of local UEs obtained from the UE modules and those obtained from 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, which has been effective since January 1, 2011. The blood center continued to count as donation all venipunctures performed after clearance of a donor even if unsuccessful or none or only a few milliliters were collected. Thus, EBPS compiled 110 (1.7%) BD UEs less than UEs compiled by the blood centers. We used blood center data for calculating UE incidence rates. For epidemiologic

information we had to rely on the data compiled by 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 UEs) 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 reached 2–5% of all UEs.

The Catalogue of Local and Systemic UEs

Our catalogue of local and systemic UEs corresponds to that established in the literature for BDs [5, 21, 24]. Applying EMA criteria for frequency of adverse drug reactions [25] to donor hemovigi-

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

	BDs with 2 UEs (n = 695)			BDs with 3 UEs (n = 55)		
	n	UE codes	%	n	UE codes	%
First donation	302			22		
		H-1, T-VA	53.6		H-1, T-VA, T-RP	36.4
		H-1, T-RP	14.6		H-1, VR-1, T-VA	18.2
					H-1, CR-1, T-RP	9.1
Second donation	139			8		
		H-1, T-VA	62.6		H-1, T-VA, T-RP	25.0
		H-1, T-RP	16.5		H-1, VR-1, T-VA	25.0
					H-1, CR-1, T-RP	12.5
					H-1, CR-1, T-VA	12.5
Multiple (≥3) donations	254			25		
		H-1, T-VA	54.3		H-1, T-VA, T-RP	68.0
		H-1, T-RP	20.1		H-1, CR-2, T-RP	8.0

Table 7. Incidence and cause of early discontinued blood collection

	n	Incidence of discontinued blood collection, n × 10 ⁻⁵
<i>Donations (all donor visits with venipuncture towards donation)</i>	166,650	
<i>Complete donations (target volume ± 10 ml)</i>	140,341	
<i>Blood sampling only for laboratory control or pre-donation screening</i>	24,139	
<i>All blood donations with early discontinued blood collection</i>	2,002	1,201
<i>First donations with discontinued blood collection</i>	918	1,962
<i>Second donations with early discontinued blood collection</i>	341	1,202
<i>≥3 donations with early discontinued blood collection</i>	743	812
<i>Early discontinued blood collection due to</i>		
Local UEs	17	10
Systemic UEs	180	108
Technical UEs	1,810	1,086
CBC parameter out of limits	31	19
Machine malfunction	55	33
Operator error	91	55
Defective disposables	4	2.4
Venous access problem	1,625	975

lance, overall local, systemic and technical UEs as defined here were commonly associated with BD (2.4%). Subgroups of donors donating blood only once or twice as well as first- and second-time donors had UE rates between 4.6 and 7.7%, regardless of gender and/or age. In experienced donors, systemic UEs were uncommonly seen (0.4%). In the literature, we found no account of UE rates seen with second blood donation. Our donor staff is required to attend to any first-time blood donor during the entire donation process.

UE incidence in several recent BD series (American Red Cross [3], the British National Blood Service [2], Brasil [26], and Denmark [4], each reporting on well above 1 million BDs) corresponded, by and large, to the data presented here. Yet, each of these reports selected a different set of parameters, making a comparison difficult.

Newman [9] presented a comprehensive review on donor reactions and injuries from 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 reac-

tions. Generally accepted risk factors for BD-associated systemic UEs were: first donation, young age, low body weight, female gender, fatigue, long waiting period, and crowded facility [10, 12, 15–19].

Of course, one could take issue with our UE definitions. 69.4% of local and systemic UEs were graded as mild. Yet, we considered them significant, as they were likely to affect the donor's willingness to return for further donations: 74.2% of our donors donated only 1–3 times. These low-frequency donors contributed 39.5% of all BDs; yet they experienced 64.3% of all UEs seen with BD (table 4). Newman et al. [11] elucidated through post-donation interviews of blood 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 between mild donor reactions after BD and a lesser likelihood of donor return [6, 7, 13, 27, 28].

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

Parameter for grade 3 reaction	Severe hypovolemic reactions (CR-3)		Severe vasovagal reactions (VR-3)	Total		
	on site	off site*	on site	n	% of grade 3 criteria	% of donors affected
Loss of consciousness	150	17	20	187	35.0	70.0
Syncope	112	19	5	136	25.5	50.9
Vomiting	55	2	5	62	11.6	23.2
Falling down	40	9	0	49	9.2	18.3
Convulsions	31	1	11	43	8.0	16.1
Injury from falling	14	4	0	18	3.4	6.7
Severe circulatory insufficiency	0	11	0	11	2.1	4.1
Rescue team	9	7	1	17	3.2	6.4
Emergency room observation	3	1	0	4	0.7	1.5
Bladder incontinence	2	0	0	2	0.4	0.7
Hospital admission	2	1	0	3	0.6	1.1
Temporary unfit for work	1	1	0	2	0.4	0.7
Total grade 3-criteria, n	419	73	42	534		
Donations involved, n	208	32	27	267		
	Severe hypovolemic reactions (CR-3)		Severe vasovagal reactions (VR-3)	Total		
				n	% of donors affected	
Donors total, n	240		27			
Male donors, %	75		14	89		33.3
Donations incomplete, % male	4		10	14		15.7
First-time donors, % male	57		10	67		75.3
Female donors, %	165		13	178		66.7
Donations incomplete, % female	9		13	22		12.4
First-time donors, % female	108		13	121		68.0

*After donor had left the blood center.

Local UEs

Small circumscribed hematomas may not have great significance for BDs where the donation interval must exceed 8 weeks. 70% of donors also attended our frequent PPP donation program in short intervals, thus providing good feedback on local UEs and on systemic UEs occurring after leaving the center. There is, however, one limitation to our data: We did not obtain systematical post-donation UE feedback from non-returning donors.

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 the perineurium. For nerve injury, it was decided that symptoms radiating distally from the site of venipuncture were 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.

Systemic UEs

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 [17]. Hypotensive reaction

– sometimes referred to as ‘delayed vasovagal reaction’ [21] – are mostly due to hypovolemia, typically occurring in the recovery lounge after a blood donation. We consider hypovolemia as the main causative factor for a hypovolemic reaction. We often observed a heart rate above the pre-donation rate as an expression of compensatory attempts to volume loss. In the early phase of vasovagal reaction, we often observe bradycardia of some degree.

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 as severe any systemic UEs occurring after a donor had left the center: 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 presented in table 8 supported this approach.

Uncommon and rare severe UEs: Upon review of UEs associated with >300,000 donations of plasma by apheresis during the years 2003 and 2004, it was considered appropriate to bundle some very rare severe systemic UEs under the category XR-3 [20], i.e. tinnitus, visual disturbances, or cerebrovascular accidents. Today, he-

molysis and air embolism are rarely seen with modern blood collection equipment [29]. Severe outcomes [15, 30], arterial puncture [31], severe injuries to subcutaneous nerves [32–37], thrombosis of upper extremity veins [38, 39], formation of an arteriovenous fistula [40, 41], pseudoaneurysm [42–44], or compartment syndrome [45] are all extremely rare, as are some other rare events [46]. We did not see any of these rare UEs.

Technical UEs

Technical UEs are an integral part of BDs, representing 36.5% of all UEs. 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 one single UE in the perivascular hemorrhage-1 (H-1) category. This did not offer the desired feedback for the phlebotomy team. Therefore, on August 1, 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 regulation. Of course, one may look upon repeated venipunctures and failing to establish or maintain sufficient blood flow as part of local UEs. However, technical UEs have substantial economic implications as they contribute substantially to cost in terms of personnel time, supplies, and lost donors [24]. These aspects are simply not covered by the designating such UEs as ‘hematoma’, and they are not primarily of concern to the donor. The catalogue of technical UEs is new to donor hemovigilance. Although Klein et al. [47] reviewed complications related to equipment and technique, their report dealt mainly with cytopheresis procedures.

Donations with Multiple UEs

For the sake of transparency and for easy computer-assisted analysis, we preferred giving each UE a narrow definition and rather reported several UEs during a single donation than describing multiple aspects of an event as a single UE. Therefore, we documented >1 UE in 13.2% of UE-associated BDs. Common combinations are hematoma, repeated venipuncture, and discontinued col-

lection after failing to establish sufficient blood flow. No other references to multiple UEs with the same donation could be found in the literature.

We should point to the higher UE incidence observed in both new donations centers compared to the six established centers. This may in part have reflected lack of experience – on the side of staff and donor. On the other hand, we noted excellent UE documentation practices in new centers due to intensive staff training and feedback during the early phase of a new center. Though it was not necessarily the staff’s experience that governed phlebotomy failure rates [48, 49]; interpersonal skills were likely to be more important [50]. Another consideration, of course, is that donors with UEs at their initial donation(s) are less likely to return for more, as was discussed earlier.

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Contributors

U. Diekamp initiated the documentation system, collected the data, and wrote this report.

J. Gneissl developed and services plasma management software (PMS) and compiled the data from the 8 centers using PMS.

U. Diekamp and A. Rabe served as medical directors of the PMS blood centers, reviewed and corrected the documentation of all adverse events.

S.T. Kiessig performed the statistical analysis, reviewed, and corrected the manuscript.

Disclosure Statement

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

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