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Article original

Unacknowledged adverse transfusion reactions: Are they a mine to dig?

Analyse des EIR non listés ou non précisés : une mine à creuser ?

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Abstract

Objectives. – Haemovigilance has long tried to characterize and understand transfusion reactions in order to prevent them. Unacknowledged ones are now a minority but they question us. Are they the result of incomplete clinical setting and/or insufficient medical reasoning, or can they contain real new entities we have not yet understood?
Material and methods. – Ten volunteer experts reviewed 30 recent unacknowledged cases. Their diagnostic propositions were compared with data issued from a five-year repository we have analysed in terms of statistical links between clinical signs and diagnoses.
Results. – Experts' opinions are only quite unanimous in 60% of the cases, and the proposed diagnosis remains unacknowledged in 53%. Repository comparison shows that signs like pain or digestive symptoms are far more frequent in unknown reactions. However, it is more the absence of some other signs which drives to that conclusion, in a default diagnosis mechanism.
Conclusion. – Errors in transfusion reactions medical analysis are rare. Unacknowledged cases are more often linked to poor or unspecific clinical setting. But a particular attention must be paid with infrequent diagnoses which are far less characterised, like metabolic complications. Pain high occurrence in unknown cases also commands us to go further in the characterisation of acute pain transfusion reaction diagnosis, which is suggested by some authors.

Keywords: Transfusion reaction; Clinical reasoning; Case peer-evaluation

Résumé

But/objectif. – Depuis longtemps, l'hémovigilance cherche à caractériser et comprendre les complications de la transfusion sanguine pour mieux les prévenir. Les réactions non caractérisées sont maintenant une minorité, mais continuent de poser problème. Résultent-elles d'un tableau clinique fruste ou d'un mauvais raisonnement clinique, ou bien correspondent-elles à de nouvelles entités diagnostiques que nous n'avons pas encore comprises ?
Matériels et méthodes. – Dix experts volontaires ont accepté de revoir 30 cas conclus en diagnostic non précisé ou non listé. Leurs propositions ont été analysées en regard d'un référentiel sémiologique présentant les liens statistiques entre les signes cliniques observés et les diagnostics retenus dans les déclarations faites pendant une période de cinq ans.
Résultats. – Les propositions des experts convergent dans 60 % des cas, et le diagnostic proposé reste inconnu dans 53 %. L'analyse sémiologique du référentiel montre une présence nettement plus élevée de certains signes comme les douleurs ou les signes digestifs dans les diagnostics inconnus. Pour autant, c'est plus l'absence de certains autres signes qui aboutit à ce type de conclusion, dans un mécanisme de diagnostic par exclusion.

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Conclusion. – Les erreurs dans le diagnostic des réactions transfusionnelles sont rares. Les cas non caractérisés sont surtout liés à des tableaux cliniques pauvres et peu spécifiques. Mais on se doit d'y être attentif car des diagnostics plus rares, comme par exemple les accidents métaboliques, sont également bien moins décrits dans leur diversité possible. De même, la fréquence élevée des douleurs dans ces cas inconnus impose de creuser l'hypothèse d'un diagnostic spécifique de douleur aiguë post-transfusionnelle, suggéré par certains auteurs.

Mots clés : Réaction transfusionnelle ; Raisonnement clinique ; Expertise de cas

1. Background and objectives

The primary goal of French haemovigilance was and still remains to analyse adverse transfusion reactions in order to prevent them [1]. After more than 20 years, a considerable amount of data piled up but, as Williamson said, "do we know how best to use it" [2]? Hopefully, there are proofs of haemovigilance key contributions in transfusion security [3].

In French legislation [4], a healthcare professional aware of an adverse transfusion reaction must report it to the haemovigilance network regardless of its nature or gravity. This report will drive a declaration done by a local haemovigilance officer [5] using a national dedicated software called "e-FIT" [6,7].

The declaration form imposes to assign a diagnosis to the reaction. Since 2010, the diagnosis evidence has to be quoted and an alternative diagnosis can be suggested if this evidence is low. These diagnoses are found in a thesaurus, containing 27 items as of October, 2016. The most prominent ones are described in available factsheets [8,9].

Among those diagnoses, two are dedicated to unacknowledged situations:

- unspecified diagnosis when haemovigilance officers are not able to assign any diagnosis;
- unlisted diagnosis when the assigned diagnosis is not in the thesaurus.

These diagnoses represented respectively 1.4% and 1.3% of the reactions reported in 2015 in France with transfusion imputability at least possible [10].

Such diagnoses are also present in other haemovigilance organisations as "other" or "unknown" [11–14], with sometimes higher frequencies. In an international comparison [15], "other reactions" range from 1.5 to 33.7 for 100,000 transfused red blood cells concentrates. Comparison is not easy because organisations and their diagnoses definitions are different. For example, febrile non-haemolytic transfusion reactions were not in the French thesaurus before 2004 and "unknown" frequency reached nearly 50% at that time [4]. The main problem with these unknown cases is that they do not participate to haemovigilance data analysis while acknowledged diagnoses [16] are more and more studied and understood. In a recently published review [17], they were not even mentioned.

We decided to investigate those reactions to see if they can disclose some interesting aspects and we choose a cooperative approach. A previous similar study [18] had pointed out the ability to identify missing diagnoses. Another one [19] was aimed to identify diagnosis errors among cases with acknowledged diagnoses. More recently, American haemovigilance uses this method to validate its reporting software with a set of fictive cases including unknown ones [20].

2. Material and methods

We selected 30 recent cases of unacknowledged transfusion reactions in our regional database in the e-FIT software. We choose to treat without distinction "unspecified" and "unlisted" diagnoses because it seems their use was not always advisedly done.

Cases were anonymised and presented to the haemovigilance officers of our blood transfusion centre. Ten of them (63%) participated by proposing a diagnosis for each case, sometimes with a comment. Responses were transposed into thesaurus diag-

Table 1
Semeiotic analytical grid.

Sign	Items found in the declaration form
Pulm	At least one item ticked among cough, dyspnoea, bronchospasm, TACO signs
Allg	At least one item ticked among pruritus, urticarial, erythema, angioedema
DIGDig	At least one item ticked among nausea, vomiting, diarrhoea
Pain	Item pain ticked
Other	Item other clinical signs ticked
Shock	Item shock ticked
Shiv	Item shivers ticked
Hyperth	Difference between initial and reaction temperatures $\geq +1\,^{\circ}C$ Reaction temperature alone is known and $\geq 38.5\,^{\circ}C$
Hypoth	Difference between initial and reaction temperatures $\geq -1\,^{\circ}C$ Reaction temperature alone is known and $\leq 36\,^{\circ}C$
Hyperap	Difference between initial and reaction systolic arterial pressure $\geq +20\%$ Reaction systolic arterial pressure alone is known and ≥ 160 mm Hg
Hypoap	Difference between initial and reaction systolic arterial pressure $\geq -20\%$ Reaction systolic arterial pressure alone is known and ≤ 70 mm Hg
Hypercf	Difference between initial and reaction cardiac frequency $\geq +20\%$ Reaction cardiac frequency alone is known and ≥ 120/min
Hypocf	Difference between initial and reaction cardiac frequency $\geq -20\%$ Reaction cardiac frequency alone is known and ≤ 50/min
None	None of above clinical signs

noses, including the "unacknowledged" one when diagnosis remains unknown or out of the thesaurus. We created a specific option "irrelevant" when the haemovigilance officer found the case did not have to be reported.

During this first evaluation phase, we hypothesized that our results analysis will need a repository crossing signs observed during reactions and diagnoses. We chose that such a repository must be "cases-based". We thus built our semeiotic repository with all our 2,074 reported cases during the years 2011–2015, using standardized definitions (Table 1).

Quantitative parameters as body temperature, systolic blood pressure, and heart rate were enrolled when at least a measure during the reaction was recorded. Clinical signs were considered when a specified difference was observed with regard to pre-transfusion value, or when this measure reached specified thresholds. Those thresholds were chosen arbitrarily and not issued from a specific study of the parameters variations during transfusion [21].

3. Results

Table 2 presents diagnoses proposed by the reviewers. A high dispersion exists, with only 3 cases with one to two diagnoses, 24 with three to four ones, and even 3 with five diagnoses. Unacknowledged reactions are obviously complex cases associated with divergence in clinical reasoning. A relative unanimity, defined as the same diagnosis chosen by at least six experts, is found in 60% of the cases.

There is a majority of cases which remain unacknowledged, with 16 of the 30 cases (53%) where this diagnosis remains in the first position.

Semeiotic analysis of the cases is presented in Table 3 and our repository in Table 4. Even if most of our 30 cases are included in the 49 unacknowledged reactions of our database, we have verified that clinical signs of studied cases are not different from those of the repository ones.

From the repository semeiotic analysis (Table 4), two useful tools can be worked out: diagnoses distribution for every sign (Table 5), and signs frequency for every diagnosis (Table 6). For a better readability of these two tables, values are marked in bold type when above 20%, in italics when above 5%, and with a "*" type when below 5%.

Table 5 points out that only rare signs are pathognomonic: allergic signs with allergy diagnosis and absence of clinical signs with allo-immunization. Some other signs are associated with only one dominant diagnosis (digestive signs, pains, shivers, hypertension, tachycardia), most often with a frequency below 50%. Some other signs turn towards two diagnoses (pulmonary signs, other clinical signs, shock, fever, hypotension, bradycardia), confusing differential diagnosis. Still more confusing is hypothermia with no dominant diagnosis, but we must be careful with the sign poor occurrence in the repository.

Table 6 displays diagnosis clinical pictures variety. Some of them are poor like seizure, haemosiderosis, posttransfusion purpura, metabolic abnormality, or viral infection. Other diagnoses are richer, with great variations in the signs frequencies. Here also, we must be careful that a low number of diagnosis cases in the repository could explain paucity of clinical pictures.

Let us come to the point of the specific semeiotic analysis of unacknowledged diagnoses. Table 7 compares signs frequencies of the repository, between "known" and "unknown" diagnoses. Some signs are less found, even absent, in the unknowns, including pathognomonic ones. But other signs are more frequent and the difference may be very significant (pains, digestive signs, other clinical signs).

Same comparisons between the 49 "unknown" and the 2025 "known" diagnoses of the repository can be done on transfusion reactions gravity and imputability (data not shown):

- severe reactions are more frequent than minor ones in unacknowledged diagnoses (18.4% versus 8.8%, $P<0.05$, OR = 2.3) and difference grows if we compare life-threatening and fatal reactions to other ones ($P<0.001$, OR = 6.3);
- doubtful or excluded imputability is more common in unacknowledged diagnoses (34.7% versus 12.7%, $P<0.001$; OR = 3.6), with a near absence of probable or certain imputability.

Table 8 takes back 26 of the 30 study cases where there is a unique first diagnosis. Cases 6, 9, and 11 are excluded because at least two diagnoses have most votes, and case 21 is excluded by nearly all reviewers (no clinical sign, but also no biological one). "Known" diagnoses cases are associated with most of expected major signs of Table 7 (frequency > 20%), but this association is lacking with unacknowledged cases.

4. Discussion

Analysis of 30 unacknowledged transfusion reactions headed by some trained specialists led to a reclassification in known diagnoses in 47% of cases. This value was 43% in a similar study [18] when three diagnoses missing at the times were given consideration. Since then, a couple of them are now in the thesaurus. Likewise, heterogeneity between experts was noted, and our study shows 40% of cases with at least two diagnoses more or less equally chosen. Such heterogeneity seems to be frequent in that kind of work [22].

Our work originality was to try to understand which aspects of a transfusion reaction lead to an unknown diagnosis. As these ones are globally more severe, one can eliminate use of unknown diagnosis as an easy way to treat minor reactions quicker. On the other hand, imputability, which is more frequently excluded, should not play any role because it is usually evaluated after having chosen the diagnosis.

Our basic premise was that setting a diagnosis on a transfusion reaction uses the same medical thinking that in most patient care, first based on observed signs. The fact that we found unusual frequencies of some signs in our 30 cases led us to have a retrospective look and build our semeiotic repository, which confirmed the fact (Table 7).

It is widely admitted that medical reasoning relies on a mental process mixing [23,24]:

Table 2
Proposed diagnoses in the 30 cases.

Cases	Unknown	Irrelevant	Bacterial infection	TACO	Other dyspnoea	Trali	Allergy	Nhftr	HLA incompatibility	Other haemolysis	Metabolic complication	Hypotension	Ineffective transfusion
1	2	1		4	3								
2							10						
3	6	2									2		
4	3		5					2					
5	2		7						1				
6			3	3			3			1			
7	4	2					2					1	1
8	5	1		4									
9	2	2	2				2	2					
10	1		6					2	1				
11	3			3	2		2						
12	2	1						4		3			
13	7	1					1			1			
14								9	1				
15	4		3				3						
16	2	1						7					
17			2					7	1				
18	2							7	1				
19	6	1					1					2	
20	7					1					2		
21	1	5	1					3					
22	4	2					1			3			
23	6		1		2	1							
24	6	2	1									1	
25	5	2	1	1			1						
26	6	2	1			1							
27	6	2				1	1						
28				9		1							
29			3					6		1			
30	7	1	1								1		

Table 3
Semeiotic analysis of the 30 cases.

Cases	Pulm	Allg	Dig	Pain	Other	Shock	Shiv	Hyperth	Hypoth	Hyperap	Hypoap	Hypercf	Hypocf	None
1	Yes			Yes										
2		Yes	Yes		Yes		Yes							
3				Yes										
4							Yes							
5				Yes			Yes	Yes		Yes				
6	Yes		Yes		Yes	Yes	Yes			Yes		Yes		
7					Yes									
8	Yes			Yes	Yes									
9			Yes											
10							Yes	Yes				Yes		
11	Yes													
12								Yes						
13				Yes										
14				Yes			Yes	Yes						
15			Yes	Yes										
16							Yes							
17							Yes	Yes						
18							Yes							
19				Yes	Yes									
20												Yes		
21														Yes
22					Yes									
23				Yes										
24					Yes	Yes								
25			Yes											
26												Yes		
27				Yes										
28	Yes									Yes				
29							Yes	Yes		Yes		Yes		
30												Yes		

Table 4
Semeiotic analysis of the repository.

Diagnosis	*n*	Pulm	Allg	Dig	Pain	Other	Shock	Shiv	Hyperth	Hypoth	Hyperap	Hypoap	Hypercf	Hypocf	None
Allergy	343	55	294	15	17	60	17	53	19	3	20	33	26	6	1
Bacterial infection	201	20	1	18	5	23	3	113	155	3	27	14	30	1	2
Seizure	3	1				3									
TACO	87	84	2	4	8	28	9	7	11	2	34	5	28	1	
Other haemolysis	5				2	1		2	3						
Haemosiderosis	24														24
Other infection	9			1		2	1	5	7		2		2	1	1
Purpura	1					1									
NHFTR	625	35	5	44	35	49	6	321	483	2	85	17	82	5	43
Immune incompatibility	23	3		1	4	3		17	17		4		4	1	1
Metabolic complication	1									1				1	
Viral infection	2														2
TRALI	9	8		1	2	6	1	1	3		5		3	1	
RBC allo-immunization	628	3	5	5	7	4	2	18	21	1	5	5	3	1	592
Unspecified	31	3		7	8	8	1	13	7	2	3		5		1
Ineffective transfusion	7		1			1		5	3						1
Hypertension	29	1	1	7	1	4		10	4	1	23		11		4
Hypotension	25	2		1	2	9	3	2		4		21	7	2	1
Other dyspnoea	3	3		1	1	1		2		1	1		1		
Unlisted	18	2		4	6	7	2	4	2		2		5	1	1
Total	2074	220	309	109	98	210	45	573	735	20	211	95	207	21	674

Table 7
Sign frequencies in "known" and "unknown" diagnoses of the repository.

Sign	"Known" diagnosis ($n=2025$)		"Unknown" diagnosis ($n=49$)		Comparison	
	Cases with sign	Frequency (%)	Cases with sign	Frequency (%)	χ^2	OR
Higher frequency in unknown diagnosis						
Pain	84	4	14	29	$p<0.001$	9.24
Dig	98	5	11	22	$p<0.001$	5.69
Other	195	10	15	31	$p<0.001$	4.14
Hypercf	197	10	10	20	$p<0.05$	2.38
Shock	42	2	3	6	nc	
Hypoth	18	1	2	4	nc	
Lower frequency in unknown diagnosis						
Hyperth	726	36	9	18	$p<0.05$	0.4
None	672	33	2	4	nc	
Allg	309	15	0	0	nc	
Hypoap	95	5	0	0	nc	
Similar frequency between unknown and known diagnoses						
Pulm	215	11	5	10	ns	0.96
Shiv	556	27	17	35	ns	1.4
Hyperap	206	10	5	10	ns	1
Hypocf	20	1	1	2	ns	

ns: not significant; nc: not countable (number < 5).

Table 8
Comparison between experts' choices and repository.

Diagnosis	Cases	n votes	Major signs, ($f \geq 20\%$)		Complementary signs ($F \geq 5\%$)		Minor signs ($F < 5\%$)	
			n in repository	n in case	n in repository	n in case	n in repository	n in case
Allergy	2	10	1	1	9	2	4	1
TACO	28	9	4	2	5	0	4	0
	1	4		1		1		0
Bacterial infection	5	7	2	2	6	1	6	1
	10	6		2		1		0
	4	5		1		0		0
NHFTR	14	9	2	2	7	1	5	0
	17	7		2		0		0
	16	7		1		0		0
	18	7		1		0		0
	29	6		2		2		0
	12	5		1		0		0
Unknown	13	7	5	1	4	0	3	0
	20	7		1		0		0
	30	7		1		0		0
	19	6		2		0		0
	24	6		1		1		0
	3	6		1		0		0
	23	6		1		0		0
	26	6		1		0		0
	27	6		1		0		0
	8	5		2		1		0
	25	5		1		0		0
	15	4		2		0		0
	7	4		1		0		0
	22	4		1		0		0

- analytical strategies, which are conscious and controlled, like in the hypothetico-deductive reasoning;
- non-analytical strategies, which are unconscious and automatic, like a spontaneous recognition in front of a combination of signs.

The latter strategies surely play a minor role in transfusion because of the scarcity of transfusion reactions faced by most medical staff. Analytical strategies rely on knowledge activation and observation of dominant and/or severe signs plays a large part. In three of our cases which were given the same diagnosis

by nine or ten experts, clinical setting was certainly poor but included at least a major sign. These cases remind of an early medical reasoning exit, due to a lack of experience, time, or interest.

Analytical strategies can be divided into two mechanisms. The first one is the hypothetico-deductive reasoning where first observed data lead to diagnostic hypothesis, causing new data search to verify hypothesis. The second one is the forward chaining where there is no initial hypothesis, due to an unusual case or lack of experience, but the use of physiopathological knowledge to elaborate diagnostic hypothesis which would be compared with observations. In both mechanisms, previous knowledge is central, hence the importance of teaching and spreading haemovigilance knowledge.

Insufficient knowledge could not only lead directly to an unknown diagnostic, but also to a poor clinical setting case description because the lack of hypothesis causes a lack of additional data search. The fact that the haemovigilance officer who declares the reaction did not witness it can also explain his inability to obtain a posteriori pertinent data and to express any diagnosis.

It is thus logical that experts who accumulate more experience and knowledge are able to go further in clinical reasoning. It should be noted that the use of statistical tools like our semeiotic repository is another way to compensate insufficient knowledge. That kind of Bayesian approach is another strategy in clinical reasoning, now doing well because of an increasing computer usage [25], which can be useful in haemovigilance.

There are some limitations in this study and the first one is the completeness of the signs which have been considered. Reaction declaration form includes some free text parts that we have not analysed, even when they can mention some signs which are not ticked in the dedicated box. Present checkboxes offer "yes", "no", and "do not know" responses but we do not make any difference between the last two options. Lastly, we do not take into account other information like biological signs or sequence of events which may play a great part in differential diagnosis. Quality of the data collection form used is essential and there are studies which confirm the benefits of computerisation on this point [26–29].

We have chosen to use our semeiotic repository as it stands, even if it may contain some errors. For example, it mentions some clinical signs in 36 cases of isolated allo-immunisation (Table 4), which is formally a delayed reaction without any one. The repository value also depends on signs or diagnoses numbers. A diagnosis poor occurrence contributes to a reduced clinical setting variability, and a sign poor occurrence may be the result of its absence in the data collection form or a lack of observation. Consequently, results are more reliable with frequent signs and diagnoses.

Another study limitation lies in the diagnoses thesaurus itself. Previous study [18] had found that there were missing diagnoses which can explain some unknown ones. The best example is hypotension transfusion-related, which was not in the thesaurus at the time [30]. Since then, it was upgraded and a factsheet was spread, and there is nearly no more suspected case in today unknown reactions. In this regard, the diagnosis of dyspnoea without any acute lung injury [31] was also introduced in the thesaurus, but it struggles to find a place, partly because there is no dedicated factsheet.

But missing diagnoses are still there. Acute pain transfusion reaction [32] was cited in former study [18] and remains a predominant current affair if we take into account the pain occurrence in unacknowledged reactions. In a similar way, metabolic complications is a "known" diagnosis, in the thesaurus, but barely used (one occurrence in five years) while "unknown" cases have a high frequency of heart rhythm disorders. Here again, factsheet absence may be an explanation.

Last but not least in any haemovigilance work, you always have to take care of under-reporting. In a pragmatic way, to diagnose a transfusion reaction is only useful if it improves its care or if it decreases its recurrence. Many reactions do not match these conditions, driving an under-reporting mainly for minor ones [33,34]. In haemovigilance organisations having chosen a mandatory exhaustive declaration like France, there are always discussions about migration towards another model taking only in account major cases [35]. Unacknowledged reactions may be associated with a higher degree of under-reporting [36]. Some "political" aspects should also not be overlooked when a high reaction occurrence is wrongly associated with a bad ranking of the care centre [37].

5. Conclusion

This work creates a group dynamics between some professionals who were not inclined to refer to some colleagues facing an unacknowledged transfusion reaction. They take an avid interest in the 30 cases review. Results and the semeiotic repository were greatly appreciated in a following reunion, changing way of seeing things in some of them. The group decides to interact prospectively with each new case of unknown diagnosis.

It also emphasizes the need to include unused diagnoses in some cases analysis. A specific work about acute pain transfusion reaction should be undertaken later, in order to qualify this diagnostic and to include it in the French thesaurus.

Our factsheets are diagnosis-oriented. This work opens an additional approach, with factsheets established by signs [38]. Such documents should probably include statistic measurements to better assist medical reasoning. To continue with this argument, expert system functionality in the national declaration software would surely be very useful and interesting and would answer to our first question about what to do with so much haemovigilance data.

The level of unacknowledged transfusion reactions could be affected in the future by a recent French decision to allow patients themselves to report their adverse events using a web portal [39]. Lastly, there is an obvious interest in an international collaboration to compare and standardize haemovigilance practice, as recently proposed by some authors [40].

Disclosure of interest

The authors declare that they have no competing interest.

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