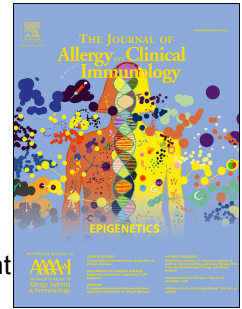


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Characterizing drug-induced capillary leak syndromes using the World Health Organization Vigibase

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CAPSULE SUMMARY

Our study enabled the identification of significant pharmacovigilance signals for 52 drugs associated with CLS. The diagnosis of drug-induced CLS cannot be ruled out based on the absence of the typical findings of idiopathic CLS.

KEY WORDS: Capillary leak syndrome, Clarkson syndrome, Drug adverse effect

To the Editor:

Capillary Leak Syndrome (CLS) is a rare and potentially life-threatening condition (1) that may result in profound hypotension, generalized or segmental edema, hemoconcentration (elevated hematocrit) and hypoalbuminemia in the absence of albuminuria, findings which are virtually pathognomonic for the disease (2). CLS can be idiopathic (3-5) or secondary to autoimmune diseases, malignant hematological diseases, viral infections, snake bites, and treatments such as chemotherapies and therapeutic growth factors (4-7). Whilst drug-induced CLS remains a rare condition, it lately becomes more and more apparent that the drugs associated with CLS are commonly used in practice.

Here, we used VigiBase (<http://www.vigiaccess.org/>), the World Health Organization (WHO) global Individual Case Safety Report (ICSR) database, which contains reports of suspected adverse drug reactions (ADRs) collected by national drug authorities in over 130 countries between 1967 and February 2018, to describe the main drugs associated with secondary CLS, as well as the detailed characteristics of these cases.

This observational retrospective study included all ADRs reported as "capillary leak syndrome" according to the Medical Dictionary for Drug Regulatory Activities (MedDRA) term (Preferred term [PT] level). The drugs considered in the analysis were those notified as suspected treatments.

For each suspected treatment associated with CLS in Vigibase, a case/non-case analysis was performed. This method compares the proportion of specific ADR reported for a single drug with the proportion of the same ADR for all other treatments in Vigibase. In this case-non case study, the specific ADRs studied (CLS) were considered as cases and all other reports were considered as non-cases. For this, we extracted from Vigibase the Information Component (IC), an indicator value for disproportionate reporting that compares observed and expected values to find drug-adverse effect combinations that have been reported more often than one would expect (8). We also report the IC025, which is the lower end of the 95% credibility interval for the Information Component. A positive IC025 value is the threshold used in statistical signal detection in Vigibase (8). For each drug with significant association with CLS, we performed a Medline search using the International non-proprietary names of the drug and the MeSH term for Capillary Leak Syndrome ("Capillary Leak Syndrome"[Mesh]). Immunoglobulins IV, a first line treatment of idiopathic CLS, were considered as a co-reported drug and were therefore excluded from the final drug by drug analysis. Interleukins was a drug reported in Vigibase with no further details available, and was therefore also excluded from the final drug by drug analysis.

A total of 576 CLS ICSRs were identified from 29 countries. Both genders were equally concerned by drug-induced secondary CLS (F/M sex ratio = 0.93) (data available for 94.8% ICSRs), and the median age at onset of CLS was 57 years (IQR: 33-67) (data available for 74.8% ICSRs).

In total, 243 suspected drugs were associated with at least one case of CLS. A significant pharmacovigilance signal ($IC_{025} \geq 0$) was observed for 52 of these drugs (table 2) responsible for 560 ICSRs. Strikingly, 45 (86.5%) of those 52 drugs were antineoplastic and immunomodulating agents (ATC category L, data available upon author contact). The drugs

associated with the highest number of CLS cases and IC025 were Gemcitabine (n=83, 14.8%; IC025: 5.11), Clofarabine (n=52, 9.3%; IC025: 6.10) and Denileukin diftitox (n=48, 8.6%; IC025: 6.13).

Because some cases of CLS were associated with more than one suspected drug, we calculated for each drug the number of cases which were associated to other molecules of a higher IC025 (table 2). We found that Denileukin diftitox, Clofarabine, Aldesleukin, Oprelvekin, Lenograstim, Acitretin and Nivolumab were not associated to any other drugs with a superior IC025, and therefore appear as strong candidates for drug-induced CLS. On the contrary, Busulfan, Treosulfan, Bexarotene, Thiotepa, Pegaspargase, G-CSF, Methotrexate, Dexamethasone, Doxorubicin, Carboplatin and Folinic Acid were always used with other molecules of higher IC025.

The median delay between start of the suspected inductor treatment and CLS occurrence was of 8 days (IQR: 2.25- 31.7) (data available for 33.3% ICSRs) (see table 1).

CLS was reported as a serious adverse event in 496 cases (86.1% of ICSRs). Death (directly linked to CLS or not) occurred in 132 cases (27%) (data available for 84.2% ICSRs) (see table 1).

A total of 3011 concomitant other adverse events were reported in the CLS ICSRs. Among those, the most common were edema with no other specifications (excluding pulmonary edema) (22%), hypotension or shock (19.4%), renal failure (14.8%), pulmonary edema (11.3%) and pleural effusion (9.5%) (see table 1). In the European registry for Clarkson's disease (3), the median hematocrit and blood albumin level were of 58.8% and 2.1g/dL, respectively. Importantly, this virtually pathognomonic laboratory profile (4, 5) was uncommonly reported in the 576 CLS cases from Vigibase: low albumin levels were reported in 21 (3.6%) of cases, increased hematocrit in 6 (1.0%), and the combination of both in only 1 case. Further, pulmonary edema was reported in 65 CLS cases from the Vigibase study, while

it is a very uncommon manifestation at presentation of Clarkson's disease (4-6). Together, this may either reflect further meaningful clinical differences between drug-induced CLS and Clarkson's disease, be related to the extensive use of saline infusions and frequent transfusion of blood-derivative products in the context of oncologic or haematological diseases or result from reporting biases. Nevertheless, based on these findings and our previous review of the literature (6), the diagnosis of drug-induced CLS may not be ruled out based on the absence of the typical clinical and laboratory findings observed in idiopathic CLS (4, 5).

While drug-induced CLS have been reported as individual cases or short series, this analysis is the first comprehensive series to report a detailed analysis of suspected inductor treatment on a larger scale, including the median delay of CLS outcome. Our study identified 32 new drugs associated with CLS, while 20 (38.4%) had been previously reported in association with CLS (6). This analysis enables the identification of a detailed list of suspected drugs along with the fact that more than 80% of these drugs are antineoplastic and immunomodulating agents may prove useful to physicians when confronted to potential CLS cases.

The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. The information does not represent the opinion of the WHO.

Table 1: Individual case safety reports (ICSRs) characteristics

Characteristics	N (%)	Data availability, n (%)
Region reporting, n (%)		576 (100)
Americas	320 (55.6)	
Europe	218 (37.8)	
Oceania	2 (0.3)	
Asia	34 (5.9)	
Africa	2 (0.3)	
Reporters		489 (84.9)
Health professional	451 (92.3)	
Non-Health professional	38 (7.7)	
Gender		546 (94.8)
Male	283 (51.8)	
Female	263 (48.2)	
Age at onset, median (IQR)	57 (33-67)	431 (74.8)
Median delay between suspected inductor treatment and autoimmune AE (in days), median (IQR)	8 (2.25-31.7)	192 (33.3)
Seriousness of AEs	496 (86.1)	576 (100)
Death (directly linked to CLS or not)	132 (27.2)	485 (84.2)
Related adverse events*		576 (100)
Edema [§]	127 (22.0)	
Hypotension or shock	112 (19.4)	
Renal failure ^{§§}	85 (14.8)	

Pulmonary edema	65 (11.3)	
Pleural effusion	55 (9.5)	
Sepsis	47 (8.2)	
Weight increased	32 (5.6)	
Pericardial effusion	22 (3.8)	
Hypoalbuminemia	21 (3.6)	
Rhabdomyolysis or increased CK	14 (2.4)	
Hematocrit increased or hemoconcentration	6 (1.0)	

*According to MEDRA terms; ^sEdema with no other specifications, excluding pulmonary edema; ^{ss}Renal failure: acute kidney injury or renal failure or increased creatinine blood levels.

Table 2. Information component (IC) and the lower endpoint of its 95% credibility interval (IC₀₂₅), comparing CLS adverse drug reaction in individual treatments versus the full VigiBase database.

Substances	Nb of CLS cases*	IC025	IC	Total Nb of AEs	Serious CLS§ n (%)	Fatal CLS n (%)	Number of cases associated with another drug of higher IC025 (%)
ATC CATEGORY L : Antineoplastic and immunomodulating agents (86.5%)							
<i>Antimetabolites: purine analogues (L01BB)</i>							
Clofarabine	52	6.10	6.52	2 086	51 (98)	33 (63)	0
Fludarabine	10	2.61	3.64	9 772	9 (90)	5 (50)	6 (60)
<i>Antimetabolites : pyrimidine analogues (L01BC)</i>							
Gemcitabine	83	5.11	5.44	40 688	72 (87)	14 (17)	1 (1.2)
Cytarabine	33	4.13	4.67	23 466	31 (94)	12 (36)	13 (39.3)
<i>Antimetabolites: folic acide analogues (L01BA)</i>							
Pemetrexed	4	0.42	2.16	14 597	4 (100)	1 (25)	1 (25)
<i>Immunostimulants: interleukins (L03AC)</i>							
IL-2							
Aldesleukin	19	4.42	5.14	1 531	16 (84)	6 (32)	0
IL-11							
Oprelvekin	11	3.50	4.47	509	6 (55)	3 (27)	0
<i>Plant alkaloids and other natural products: taxanes (L01CD)</i>							
Docetaxel	46	3.54	3.99	69 525	40 (87)	5 (11)	6 (13)
Paclitaxel	12	1.13	2.06	71 543	9 (75)	3 (25)	7 (58.3)
<i>Plant alkaloids and other natural products: podophyllotoxin derivatives (L01CB)</i>							
Etoposide	17	2.78	3.55	28 402	17 (100)	10 (59)	1 6 (94.1)
<i>Plant alkaloids and other natural products: vinca alkaloids and analogues (L01CA)</i>							
Vincristine	8	1.33	2.50	28 746	8 (100)	3 (38)	7 (87.5)
<i>Immunostimulants: colony stimulating factors (L03AA)</i>							
Pegfilgrastim ^{§§}	20	3.38	4.08	20 409	20 (100)	4 (20)	4 (20)
Filgrastim ^{§§}	14	3.22	4.08	10 306	12 (86)	5 (36)	4 (28.6)
GM-CSF	6	2.14	3.52	1 920	3 (50)	0 (0)	3 (50)
G-CSF ^{§§}	4	1.31	3.05	1 222	4 (100)	2 (50)	4 (100)
Lenograstim^{§§}	3	0.61	2.66	1 556	3 (100)	0 (0)	0
<i>Immunosuppressants: selective immunosuppressants (L04AA)</i>							
Antithymocyte Ig	12	3.14	4.07	7 043	9 (75)	4 (33)	1 (8.3)
Alemtuzumab	6	1.68	3.05	8 119	6 (100)	3 (50)	1 (16.7)
Mycophenolic acid	5	0.25	1.77	31 707	4 (80)	2 (40)	4 (80)

<i>Immunosuppressants: calcineurine inhibitors (L04AD)</i>							
Ciclosporin	14	2.07	2.92	40 433	13 (93)	3 (21)	9 (64.2)
Tacrolimus	7	0.68	1.94	41 746	7 (100)	4 (57)	5 (71.4)
<i>Immunosuppressants: other immunosuppressants (L04AX)</i>							
Methotrexate	14	1.23	2.08	83 640	14 (100)	4 (29)	14 (100)
<i>Immunosuppressants: interleukin inhibitors (L04AC)</i>							
Basiliximab	3	0.57	2.62	2 016	3 (100)	2 (67)	1 (33.3)
<i>Immunostimulants: interferons (L03AB)</i>							
Interferon alfa-2b	5	0.93	2.46	14 272	2 (40)	2 (40)	3 (60)
<i>Alkylating agents: nitrogen mustard analogues (L01AA)</i>							
Cyclophosphamide	34	2.95	3.48	74 270	34 (100)	14 (41)	24 (70.6)
Melphalan	6	1.71	3.09	7 559	5 (83)	4 (67)	5 (83.3)
Bendamustine	4	0.82	2.56	7 586	4 (100)	2 (50)	3 (75)
<i>Alkylating agents: alkyl sulfonates (L01AB)</i>							
Busulfan	6	1.98	3.35	3 880	6 (100)	1 (17)	6 (100)
Treosulfan	5	1.89	3.42	376	5 (100)	3 (60)	5 (100)
<i>Alkylating agents: ethylene imines (L01AC)</i>							
Thiotepa	5	1.77	3.30	1 688	5 (100)	3 (60)	5 (100)
<i>Cytotoxic antibiotics and related substances: anthracyclines and related substances (L01DB)</i>							
Daunorubicin	10	2.85	3.88	6 122	10 (100)	4 (40)	9 (90)
Doxorubicin	8	0.53	1.69	60 792	8 (100)	3 (38)	8 (100)
<i>Other antineoplastic agents (L01XX)</i>							
Denileukin diftitox	48	6.13	6.57	348	36 (75)	12 (25)	0
Bortezomib	13	2.39	3.28	25 441	13 (100)	4 (31)	6 (46.1)
Pentostatin	6	2.26	3.64	657	6 (100)	1 (17)	3 (50)
Bexarotene	5	1.88	3.40	566	5 (100)	0 (0)	5 (100)
Pegaspargase	5	1.60	3.12	3 756	5 (100)	2 (40)	5 (100)
<i>Other antineoplastic agents: monoclonal antibodies (L01XC)</i>							
Rituximab	19	2.29	3.01	54 743	19 (100)	5 (26)	13 (68.4)
Trastuzumab	11	2.14	3.12	23 502	11 (100)	1 (9)	7 (63.6)
Dinutuximab	4	1.43	3.17	46	4 (100)	0 (0)	2 (50)
Bevacizumab	11	1.33	2.31	51 962	11 (100)	1 (9)	7 (63.6)
Blinatumomab	3	0.60	2.65	1 671	3 (100)	1 (33)	1 (33.3)
Nivolumab	4	0.28	2.01	17 578	4 (100)	2 (50)	0
<i>Other antineoplastic agents: platinum compounds (L01XA)</i>							
Oxaliplatin	10	1.03	2.06	57 505	10 (100)	1 (10)	2 (20)
Carboplatin	7	0.51	1.77	48 738	7 (100)	2 (29)	7 (100)
ATC CATEGORY B : Blood and blood forming organs (1.9%)							
Folinic acid	4	0.37	2.11	15 499	4 (100)	0 (0)	4 (100)
ATC CATEGORY D : Dermatologicals (1.9%)							
Acitretin	3	0.48	2.53	3 062	3 (100)	0 (0)	0
ATC CATEGORY H : Systemic hormonal preparations, excluding sex hormones and insulins (3.8%)							

Dexamethasone	8	0.86	2.03	45 138	8 (100)	0 (0)	8 (100)
Methylprednisolone	5	0.34	1.87	28 773	5 (100)	1 (20)	1 (20)
ATC CATEGORY J : Antiinfectives for systemic use (1.9%)							
Voriconazole	4	0.68	2.42	9 814	4 (100)	1 (25)	1 (25)
ATC CATEGORY V : Various (1.9%)							
Palifermin	3	0.74	2.79	200	3 (100)	2 (67)	2 (66.7)
NON-CLASSIFIABLE BECAUSE OF LACK OF INFORMATION (1.9%)							
Investigational drug [†]	5	0.98	2.51	13 412	5 (100)	2 (40)	2 (40)

*In some cases, several drugs were classified as suspected in relation to a CLS attack. [§]Serious adverse event, as reported in Vigibase. ^{§§}Drugs recorded separately in Vigibase and considered separately for IC & IC025 calculations. [†]Experimental drugs (without details) as coded in Vigibase. In bold: drugs with less than 10% of co-reporting with another drug of higher IC025.

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