Development of a Novel Algorithm to Identify Capillary Leak Syndrome (CLS) in US Claims Data

Poster MSR120

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BACKGROUND

- CLS is a systemic inflammatory adverse event (AE) associated with several conditions and medications, including anticancer therapies such as tagraxofusp.
- Tagraxofusp is a first-in-class CD123-targeted therapy with a well-characterized and manageable safety profile, without cumulative myelosuppression, and the only drug approved for the treatment of blastic plasmacytoid dendritic cell neoplasm.[1]
- In tagraxofusp-treated patients, CLS has been reported in 21% of patients; however, it is manageable, mostly grade 1 or 2, and predominantly occurs in the first cycle of treatment.[2,3]
- Information on predictors of CLS can help improve healthcare providers' decision-making for patient selection, monitoring, and supportive care.
- Lack of a specific CLS ICD-10 code and overlap of CLS with other clinical diagnoses (eg, sepsis, hypersensitivity reactions) make identification of CLS in claims data challenging.

OBJECTIVE

- To develop an algorithm for identifying patients who experienced CLS in a US claims database.

METHODS & ALGORITHM DEVELOPMENT

- The algorithm identified potential candidate CLS-causing drugs based on product label, reports in scientific data, or documentation in the FDA AE Reporting System (FAERS) database.
  - Drugs were included if there were >4 cases of CLS reported in FAERS and if they were classified as anticancer medications, growth factors, or immunosuppressants.
- Open insurance claims data from PurpleLab (January 1, 2017, to March 1, 2025) were analyzed using a 12-month lookback review window prior to initiating candidate drug treatment, inclusive of procedure, diagnostic, and medication codes.
- Patients from the claims database were included if, within 2 weeks of initiating candidate drug treatment, they had (**Figure 1**):
  - A diagnosis of diseases of the capillaries (ICD-10: I78.8/9); OR
  - A diagnosis of abnormal albumin levels or received intravenous albumin; OR
  - ≥3 indicators of fluid resuscitation/management, edema, hypotension, infusion-related reactions, cardiac arrest, or cardiopulmonary failure.
- Key exclusion criteria included prior history of idiopathic CLS, diagnosis of sepsis, severe hypersensitivity, or cytokine release syndrome (CRS) within 2 weeks of initiating candidate drug treatment (**Figure 1**).
- Candidate drugs for which CLS is listed in the product label and for which FAERS yielded a high number of CLS case reports were identified as treatments of interest.

Figure 1. Eligibility Criteria

Include any patients who **within 2 weeks of candidate drug[a] treatment**, meet

CLS Inclusion Criteria

Inclusion Criteria #1

1. **Diagnosis of systemic capillary leakage**
   - *Diagnostic codes:* ICD-10: I78.8/9; "Other diseases of the capillaries, unspecified"

OR

Inclusion Criteria #2

2. **Indicators of hypoalbuminemia:** ≥1 of:
   - *Diagnostic codes:* Abnormal albumin
   - *Procedure + NDC codes:* IV albumin

OR

≥ any 3 of criteria #3-#6

3. **Indicators of fluid resuscitation/fluid management:** ≥1 of:
   - *Procedure + NDC codes:* IVIG, IV plasma, or diuretics (furosemide, bumetanide, torsemide, metolazone)
4. **Indicators of edema:** ≥1 of:
   - *Diagnostic codes:* Edema (high-level term), eyelid edema, generalized edema, laryngeal edema, edema, edema peripheral, periorbital edema, peripheral swelling, swelling, swelling face, weight increased
   - *Procedure + NDC codes:* Methylprednisolone, dexamethasone, prednisone, prednisolone, hydrocortisone
5. **Indicators of hypotension:** ≥1 of:
   - *Diagnostic codes:* Hypotension, hypovolemia, hypovolemic shock
   - *Procedure + NDC codes:* Dopamine, ephedrine, norepinephrine, norepinephrine bitartrate, phenylephrine, vasopressin
6. **Other indicators:**
   - *Diagnostic codes:* Infusion-related reactions, cardiac arrest, cardiopulmonary failure
   - *Procedure + NDC codes:* TNF-α antagonists, beta-agonists (terbutaline), phosphodiesterase inhibitors (theophylline)

CLS Exclusion Criteria

1. **Idiopathic CLS:**
   - *Diagnostic codes:* Prior medical history of CLS (ICD-10: I78.8/9)
2. **Sepsis and infection[b]:**
   - *Diagnostic codes:* Infection, sepsis, septic shock
3. **Anaphylaxis/severe hypersensitivity:**
   - *Diagnostic codes:* Anaphylactic shock, unspecified; anaphylactic reaction due to adverse effect of correct drug or medication properly administered; anaphylactic reaction due to food, administration of blood and blood products or vaccination
4. **CRS:**
   - *Diagnostic codes:* CRS (D89.83)
   - *Medications:* Tocilizumab

Exclude any patients who meet **any exclusion criteria**

[a]Candidate drugs: asparaginase, azacitidine, bendamustine, bleomycin, bortezomib, busulfan, capecitabine, carboplatin, carfilzomib, cisplatin, clofarabine, cyclophosphamide, cytarabine, daunorubicin, decitabine, docetaxel, doxorubicin, epirubicin, etoposide, fludarabine, fluorouracil, gemcitabine, idarubicin, ifosfamide, melphalan, mercaptopurine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, pegaspargase, pemetrexed, temozolomide, thiotepa, trabectedin, venetoclax, vincristine sulfate, vinorelbine, aldesleukin, alemtuzumab, atezolizumab, axicabtagene, bevacizumab, blinatumomab, bosutinib, ciltacabtagene, daratumumab, dasatinib, denileukin, dinutuximab, gemtuzumab, ibrutinib, imatinib, inotuzumab, interferon alfa-2b, ipilimumab, lifileucel, lisocabtagene, moxetumomab, nilotinib, nivolumab, pembrolizumab, pentostatin, pertuzumab, pertuzumab/trastuzumab, ponatinib, rituximab, ruxolitinib, sorafenib, tagraxofusp, tisagenlecleucel, trastuzumab, ellapegrastim, filgrastim, filgrastim-aafi, filgrastim-ayow, filgrastim-sndz, oprelvekin, pegfilgrastim, sargramostim, tbo-filgrastim, anti-thymocyte globulin, basiliximab, cyclosporine, tacrolimus.

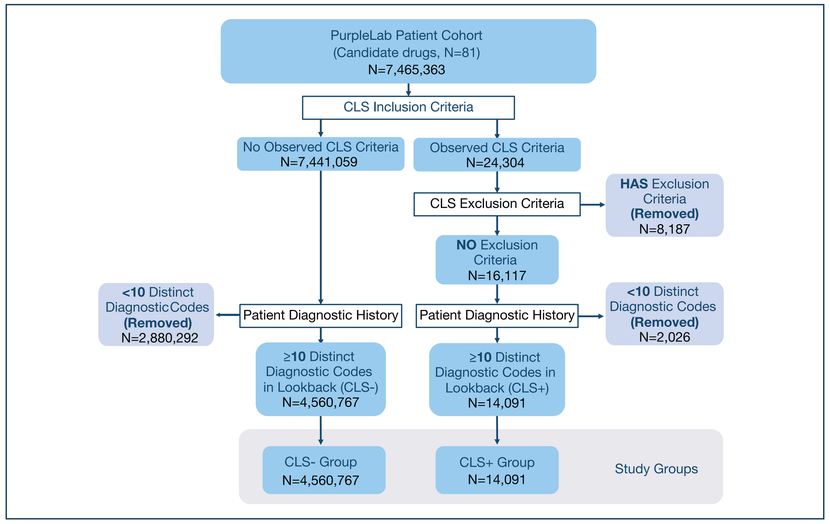
[b]Antibiotic NDC codes have been removed from the exclusion criteria of septic shock due to prophylactic antibiotic use in hematology patients.

RESULTS

CLS Groups Identified Using Selection Algorithm

- Eighty-one CLS-causing drugs were identified in the evaluation of ~7.5 million patients (**Figure 2**).
- After incorporating inclusion and exclusion criteria, CLS was not observed in 4,560,767 patients, and CLS was observed in 14,091 patients.

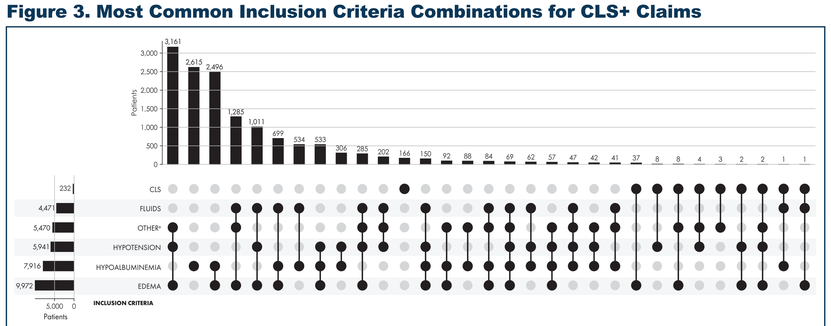
Figure 2. CLS Selection Algorithm



Inclusion and Exclusion Criteria Combinations for CLS+ Claims

- The most common combination of inclusion criteria for CLS+ claims was edema + hypotension + other indicators, followed by hypoalbuminemia alone, then hypoalbuminemia + edema (**Figure 3**).
- Indicators of hypoalbuminemia were found in 56% (7,916/14,091) of the CLS+ group (**Figure 4**).
  - Among the 7,916 patients included due to indicators of hypoalbuminemia, only 10% (n=782) of patients had a diagnosis code for abnormal albumin, whereas 91% (n=7,182) received albumin treatment (**Figure 4**).
- The most common exclusion criteria combinations for CLS+ claims (>5 patients) were sepsis in the overall cohort, followed by idiopathic CLS, CRS, and anaphylaxis/severe hypersensitivity (**Figure 5**).

Figure 3. Most Common Inclusion Criteria Combinations for CLS+ Claims



*Criteria in the "other" category include: Diagnostic codes for infusion-related reactions, cardiac arrest, cardiopulmonary failure, OR NDC codes for TNF-α antagonists, beta-agonists (terbutaline), phosphodiesterase inhibitors (theophylline).

Figure 4. Indicators of Hypoalbuminemia in CLS+ Patients

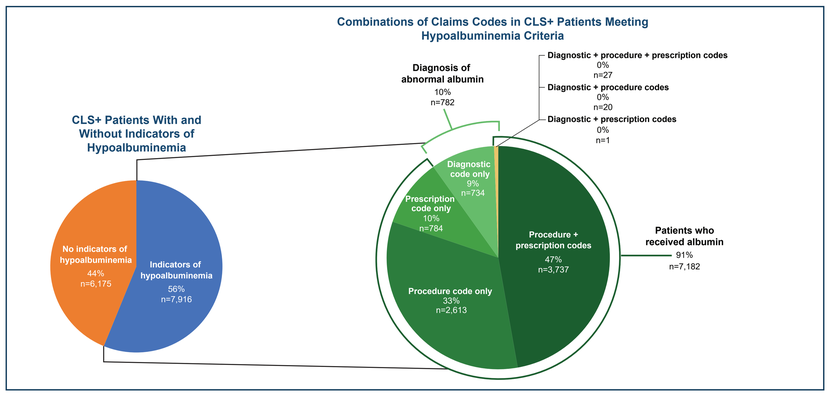
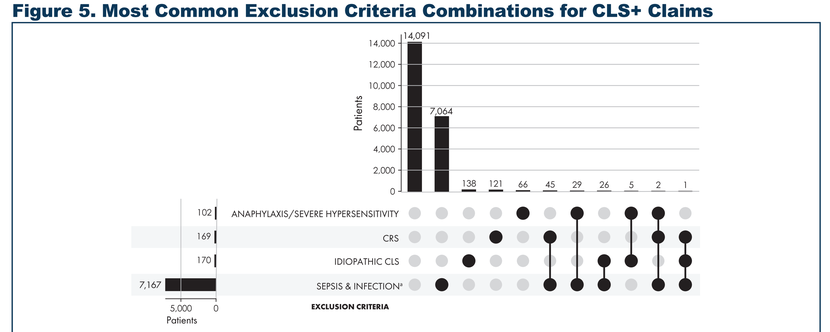


Figure 5. Most Common Exclusion Criteria Combinations for CLS+ Claims



*Antibiotic NDC codes have been removed from the exclusion criteria of septic shock due to prophylactic antibiotic use in hematology patients.

CLS Incidence Identified Using the Algorithm Was Similar to the Known Rates for Other Treatments

- Treatments of interest were identified as aldesleukin, filgrastim, gemcitabine, and tagraxofusp.
- CLS incidence identified using the algorithm was similar to the known rates for these treatments of interest (**Table 1**), providing confidence in the algorithm's ability to detect CLS in claims data.
  - 21% of tagraxofusp patients were identified as experiencing a CLS event, similar to the incidence of investigator-assessed CLS in the tagraxofusp pivotal study.[2]

Table 1. Treatments of Interest

Treatment	CLS-, n(%)	CLS+, n (%)	Reported CLS Incidence
Aldesleukin (n=327)	297 (90.8)	30 (9.2)	5.3%-100%[4]
Filgrastim (n=560,174)	557,609 (99.5)	2,565 (0.5)	<1%[5]
Gemcitabine (n=191,586)	190,240 (99.3)	1,346 (0.7)	<1%[5,a]
Tagraxofusp (n=70)	55 (78.6)	15 (21.4)	21%[2]

[a]Exact incidence unknown. Data limited to case reports.

LIMITATIONS

- This analysis used open insurance claims data from PurpleLab over an ~8 year period, inclusive of procedure, diagnostic, and medication codes.
- Administrative claims are generated for billing rather than research purposes and may be subject to inaccurate, delayed, or incomplete coding of services, fragmentation, and incomplete or biased capture of social determinants of health, which could affect completeness of the data.
- PurpleLab's data cover a majority but not all of the US population, which may risk underrepresentation of groups (eg, uninsured) and selection bias (eg, rural communities).

CONCLUSIONS

- We generated a novel claims-based algorithm for CLS incidence with rates similar to known CLS-causing drugs, including aldesleukin, filgrastim, gemcitabine, and tagraxofusp.
- The algorithm identified CLS incidence as similar to that observed with drugs that cause CLS, supporting the validity of the developed algorithm.
  - Using this US claims-based algorithm, 21% of tagraxofusp patients were identified as experiencing a CLS event, similar to the incidence of investigator-assessed CLS in the tagraxofusp pivotal study.[2]
- This claims-based algorithm will be validated in future evaluations to identify predictors of CLS in tagraxofusp-treated patients.

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ABBREVIATIONS:

AE, adverse event; CLS, capillary leak syndrome; CRS, cytokine release syndrome; FAERS, FDA Adverse Event Reporting System; FDA, US Food and Drug Administration; ICD, International Classification of Diseases; IV, intravenous; IVIG, intravenous immunoglobulin; NDC, National Drug Code; TNF, tumor necrosis factor; US, United States.

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