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Hemolysis Case Algorithm
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List of Acronyms

AHTR	Acute hemolytic transfusion reaction
BEST	Biologics Effectiveness and Safety Sentinel Initiative
CBER	Center for Biologics Evaluation and Research
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
DAT	Direct antiglobulin test
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GEMs	General Equivalence Mappings
HCPCS	Healthcare Common Procedure Coding System
HTR	Hemolytic transfusion reaction
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IVIG	Intravenous immunoglobulins
LDH	Lactic acid dehydrogenase
LOINC	Logical Observation Identifiers Names and Codes
MeSH	Medical Subject Headings
MS	Mini-Sentinel
NDC	National Drug Code
NPV	Negative predictive value
PICO	Population, Intervention, Comparator, Outcome
PPV	Positive predictive value
RBC	Red blood cell
SQ	Subcutaneous

Defining Acquired Hemolysis Using Administrative Claims Data: A Case Algorithm

Patrick Saunders-Hastings,[1] Timothy Burrell,[2] Jenny Srichaikul,[1] Graça Dores,[3] Kinnera Chada,[3] Hui-Lee Wong[3], Azadeh Shoaibi[4]

[1] Gevity Consulting Inc., Ottawa, Ontario, Canada
[2] IBM Watson Health, Bloomington, Indiana, United States of America
[3] Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, United States of America

A Summary

The U.S. Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Sentinel Initiative conducted a literature review (from 2000 to January, 2019) to identify validated methods for ascertaining cases of acquired hemolysis in large administrative health care databases. No algorithms that reported measures of validity (positive predictive value [PPV], negative predictive value [NPV], sensitivity or specificity) were found, although a robust algorithm was previously developed for a FDA study by Winiecki and colleagues.[1] This algorithm was used as the basis for the algorithm presented below.

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were extracted from a study that identified cases of hemolysis after exposure to intravenous immunoglobulins (IVIG) in the FDA Adverse Event Reporting System (FAERS) and Mini-Sentinel (MS) system.[1] This algorithm was developed on the basis of expert judgement, as there are no hemolysis codes specific to IVIG or other blood-derived products. The diagnostic accuracy and validation performance of this algorithm is unknown.

The results of this literature review were used as the basis for developing a draft of an administrative claims-based outcome definition for acquired hemolysis occurring in association with the administration of blood-derived products. Codes were mapped from ICD-9-CM to International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) via forward backward mapping, using General Equivalence Mappings (GEMs) for reference.[i] Input from clinical subject matter experts informed the development and refinement of the algorithm. As an initial step in defining this outcome, the feasibility of applying the algorithm was tested in IBM® MarketScan® Research Databases, using the Treatment Pathways 4.0 analytic platform. Statistics describing the frequency of hemolysis codes included within (and excluded from) the algorithm were generated and the results are reported below.

B Background

Among other responsibilities, FDA is mandated to protect the public health by ensuring the safety and efficacy of drugs, biologics and medical devices.[ii] In support of this mandate, the FDA Center for Biologics Evaluation and Research (CBER) has a mission to conduct policy and regulatory reviews of biologics and related products, including blood products, vaccines, allergenics, tissues, and cellular and

[i] Additional information about GEMs and the methodology for forward and backward mapping can be found at American Society of Clinical Oncology. General Equivalence Mappings (GEMS). https://www.asco.org/practice-guidelines/billing-coding-reporting/icd-10/general-equivalence-mappings-gems. Researchers used the following website to map ICD-9-CM codes to ICD-10-CM: https://www.icd10data.com.
[ii] U.S. Food and Drug Administration. What We Do. March 28, 2018. https://www.fda.gov/aboutfda/whatwedo/

gene therapies. CBER assesses the risks and benefits of new biologic products, as well as previously approved products that have been proposed for new indications. The CBER process emphasizes the pursuit of the maximum public benefit while minimizing risks to the public for each biologic product. The BEST Sentinel Initiative is a program initiated by CBER whose objective is to assess the safety and effectiveness of biologic products using large datasets of administrative claims and clinical data.

The objective of this review was to assess the state of knowledge regarding validated methods of using administrative claims data to identify cases of acquired (i.e., non-hereditary) hemolysis occurring in association with blood-derived products. These methods could draw on a variety of coding standards, including ICD, Healthcare Common Procedure Coding System (HCPCS), Current Procedural Terminology (CPT), National Drug Code (NDC), and Logical Observation Identifiers Names and Codes (LOINC).

Hemolysis refers to the (usually premature) destruction of red blood cells (RBCs). Situations in which RBCs are being destroyed faster than they are being created (or replaced) can result in hemolytic anemia.[2] Severe hemolytic anemia can result in serious medical conditions, such as arrhythmias, cardiomyopathy, and heart failure.[3] There is also a well-known association between hemolytic anemia and thrombosis,[4,5] which may be observed with either intravascular (occurring in the blood vessels) or extravascular (usually occurring in the spleen or liver) hemolysis. Although the mechanisms through which hemolytic anemia may cause thrombosis are not well-understood, postulated factors include the effects of free plasma heme or hemoglobin, depletion of nitric oxide, splenectomy, antiphospholipid antibodies in some patients with autoimmune hemolysis, and prothrombotic changes in the surface of affected RBCs.[6-9] Reported risk factors for hemolysis and hemolytic anemia include IVIG recipients with non-O blood types, exposure to high doses of IVIG, and particular inflammatory or autoimmune disorders such as Kawasaki disease and immune thrombocytopenia.[1,13,18,20]

A comprehensive literature review of methods for identifying potential cases of acquired hemolysis using administrative claims data was conducted, leveraging findings from U.S. and international studies to inform the development of a code-based outcome definition (hereafter referred to as an “algorithm”). The draft algorithm was then subject to review by clinical subject matter experts and testing in a large administrative claims dataset (MarketScan Research Databases) using the cloud-based Treatment Pathways analytic platform. **Sections C** and **D** summarize the literature review methodology and findings, respectively; **Section E** provides clinical case definitions for hemolysis, which could be of value in further assessing the performance of the proposed algorithms via chart review validation studies; **Sections F** and **G** present the algorithm and its associated assumptions and decisions, respectively; **Section H** presents the results of the initial characterization of the algorithm in a claims database; and **Section I** provides discussion and concluding thoughts.

C Methodology

The BEST Initiative developed a literature review search strategy based upon a Population, Intervention, Comparator, Outcome (PICO) framework formulated in consultation with stakeholders from FDA CBER. The PICO framework for this review can be summarized as follows:

- **Population:** *any population group (human)*
- **Intervention:** *any intervention*
- **Comparator:** *any comparator, placebo*
- **Outcome:** *hemolysis, acute hemolysis, hyperhemolysis, hemolytic anemia*
- **Setting**: *individuals treated or under care in a clinical setting (including hospital, clinic or other inpatient setting, or outpatient setting)*

Briefly, the review process involved conducting systematic searches of existing publications available in the FDA Sentinel databases[iii] (no articles were retrieved from either database). These searches were followed by a structured review of the academic literature, using PubMed, Medline, and Google Scholar to identify relevant resources. The PubMed search strategy is summarized below:

- Search 1 used keywords (hemolysis [MeSH term]) AND (intravenous immunoglobulin): retrieved 55 articles
- Search 2 used keywords (hemolysis [MeSH term]) AND (diagnos*): retrieved 5838 articles so the search was refined by adding "AND database": retrieved 39 articles
- Search 3 used keywords (hemolysis) AND (diagnostic accuracy study): retrieved 109 articles.

The search strategy was complemented by a review of clinical guidelines and a targeted search of potentially relevant organizations (such as the U.S. Armed Forces Health Surveillance Branch, Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, and Health Canada's *Canada Vigilance Program*) and data repositories (such as the NDC repository).[iv] A snowballing technique was also applied, wherein the bibliographies of relevant studies were scanned for additional resources. The literature search was completed between January 11 and 22, 2019.

All ensuing abstracts of relevant publications were screened, and 22 articles were reviewed in-full. A Microsoft® Excel spreadsheet was developed to extract relevant data. The data elements collected are provided in **Figure 1**. A relevance ranking was assigned based on the judgement of the reviewer and the available information on study location ("Group/Country"), the algorithm specifications ("Algorithm/Criteria"), and the measures of validity and diagnostic accuracy (such as PPV and NPV).

Title	Author	Year	Group/Country	Summary	Relevance	Disease Definition	Algorithm/Criteria	Validity	Comments

Figure 1. Data elements recorded in the extraction spreadsheet.

D Results

Following title and abstract screening, full-text review, and data extraction, three publications were identified as being of particular relevance for identifying a method to ascertain cases of hemolysis occurring after exposure to a blood-derived product using administrative claims datasets.

Winiecki and colleagues queried the FAERS and MS system in an effort to identify cases of hemolysis following IVIG.[1] The following ICD-9-CM codes were included in the code list for hemolysis events:

- 283.10: nonautoimmune hemolytic anemia, unspecified
- 283.19: other nonautoimmune hemolytic anemias
- 283.9: acquired hemolytic anemia, unspecified
- 999.6: ABO incompatibility reaction due to transfusion of blood or blood product
- 999.83: hemolytic transfusion reaction, incompatibility unspecified
- 999.84: acute hemolytic transfusion reaction, incompatibility unspecified
- 999.85: delayed hemolytic transfusion reaction, incompatibility unspecified

[iii] U.S. Food and Drug Administration. Science & Research (Biologics). March 28, 2019. https://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/default.htm
Sentinel. Publications and Presentations. https://www.sentinelinitiative.org/communications/publications

[iv] U.S. Food and Drug Administration. National Drug Code Directory. November 9, 2017. https://www.fda.gov/drugs/informationondrugs/ucm142438.htm

A total of 236 potential cases were identified in FAERS, of which 109 (46.2%) met the clinical case definition criteria. The authors reported a post-IVIG hemolysis incidence rate of 1 per 1,000 treatment episodes and found that 55.3% of events occurred within two days of IVIG exposure (75.3% of events occurred within four days). Hemolysis cases were distributed across all age categories and occurred equally among males and females.

Another U.S. study used the HealthCore Integrated Research Database to assess the risk of same-day hemolytic events following exposure to intravenous (IV) or subcutaneous (SQ) immunoglobulins among a population of 55 million commercially insured individuals across 14 states.[13] Authors applied no age restrictions and did not base eligibility on minimum continuous insurance enrollment (although 72% of the study population had at least one year of continuous enrollment). Authors defined hemolytic reactions using ICD-9-CM codes for "acquired hemolytic anemias, ABO incompatibility reactions, Rh incompatibility reactions, non-ABO incompatibility reactions, unspecified incompatibility transfusion reactions, incompatibility-unspecified hemolytic transfusion reactions (HTRs), incompatibility-unspecified acute HTRs, and incompatibility-unspecified delayed HTRs."[13] Although specific ICD-9-CM codes are not provided, the most closely corresponding codes are the following:

- 283.xx: acquired hemolytic anemias
- 999.6x: ABO incompatibility reaction due to transfusion of blood or blood products
- 999.7x: Rh incompatibility reaction not elsewhere classified
- 999.8x: other and unspecified transfusion reaction not elsewhere classified

The authors reported that, among 20,440 exposures to IV/SQ immunoglobulin products between 2008 and 2014, 211 cases of same-day hemolytic reactions were detected (10.3 cases per 1,000 exposures).[13] Rates were highest in those under 15 years or over 65 years of age and were higher for men than for women.

A study from Taiwan sought to characterize the distribution of inpatient hospitalizations due to acquired hemolytic anemia.[9] Authors used ICD-9-CM codes 283.xx and excluded codes for heritable conditions (ICD-9-CM codes 282.xx). Among their study population of 23 million insured individuals, 3,903 cases of acquired hemolytic anemia were retrieved between 2002 and 2008. Of these cases, 47.2% (1,842/3,903) were due to unspecified acquired hemolytic anemia (ICD-9-CM 283.9), 31.9% (1,246/3,903) were due to autoimmune hemolytic anemias (ICD-9-CM 283.0), 13.1% (513/1,3903) were due to nonautoimmune hemolytic anemias (ICD-9-CM 283.10; 283.19), 4.9% (192/3,903) were due to hemolysis from external causes (ICD-9-CM 283.2), and 2.8% (110/3,903) were due to hemolytic uremic syndrome (ICD-9-CM 283.11).

E Hemolysis Clinical Case Definition

The study by Winiecki and colleagues[1] used the clinical case definition originally provided by Canadian Blood Services and tested in Canadian contexts to define hemolysis.[18] Should a validation study of the hemolysis algorithm be executed, this definition could be used to inform chart review and adjudication. However, the definition outlined below uses a small hemoglobin reduction threshold for defining hemolysis, and future studies may wish to consider different thresholds.

- **Definite**: Drop in hemoglobin of ≥1g/dL[v]
    - **AND** positive direct antiglobulin test (+DAT)
    - **AND** ≥2 minor criteria: increased reticulocyte count, increased lactate dehydrogenase level [LDH], low haptoglobin, increased unconjugated bilirubin or jaundice, hemoglobinuria or red/dark urine, hemoglobinemia or spherocytosis, hepatosplenomegaly, pallor, tachycardia, shortness of breath, or fatigue

[v] In their assessment of the hemolysis cases identified in FAERS, Winiecki and colleagues (2015) reported an average hemoglobin decrease of 4.8 g/dL (range 1.6–9.9 g/dL).

- **Probable**: Drop in hemoglobin **AND** +DAT **BUT** <2 minor criteria
  - **OR** Drop in hemoglobin **OR** +DAT **AND** ≥2 minor criteria
- **Possible:** Drop in hemoglobin **OR** clinical diagnosis of anemia
  - **AND** +DAT **OR** clinical diagnosis of hemolysis

The clinical case definitions for acute and delayed HTR provided by the National Healthcare Safety Network were also noted.[21] These are summarized in **Table 1**.

Table 1. National Healthcare Safety Network clinical case definitions for acute HTR and delayed HTR.

Acute HTR	Delayed HTR
Definite	**Definite**
Occurs during, or within 24 hours of cessation of transfusion with new onset of **ANY** of the following signs/symptoms: • Back/flank pain • Chills/rigors • Disseminated intravascular coagulation • Epistaxis • Fever • Hematuria (gross visual hemolysis) • Hypotension • Oliguria/anuria • Pain and/or oozing at IV site • Renal failure **AND ≥2** of the following: • Decreased fibrinogen • Decreased haptoglobin • Elevated bilirubin • Elevated lactic acid dehydrogenase • Hemoglobinemia • Hemoglobinuria • Plasma discoloration c/w hemolysis • Spherocytes on blood film **AND** Serologic testing is negative, and physical cause (e.g., thermal, osmotic, mechanical, chemical) is confirmed.	Positive direct antiglobulin test (DAT) for antibodies developed between 24 hours and 28 days after cessation of transfusion **AND EITHER** Positive elution test with alloantibody present on the transfused red blood cells **OR** Newly identified red blood cell Alloantibody in recipient serum **AND EITHER** Inadequate rise of posttransfusion hemoglobin level or rapid fall in hemoglobin back to pretransfusion levels **OR** Otherwise unexplained appearance of spherocytes
Probable	**Probable**
Meets signs and symptoms criteria for acute hemolysis (above) **AND** Physical cause is suspected, and serologic testing is negative.	Newly identified red blood cell alloantibody demonstrated between 24 hours and 28 days after cessation of transfusion **BUT** Incomplete laboratory evidence to meet definitive case definition criteria. **NOTE:** Patient may be asymptomatic or have symptoms that are similar to but milder than AHTR; symptoms are not required to meet case definition criteria.
Possible (Optional)	**Possible (Optional)**

Acute HTR	Delayed HTR
AHTR is suspected within 24 hours of cessation of transfusion, but symptoms, test results, and/or information are not sufficient to meet the criteria defined above. Other, more specific adverse definitions do not apply.	Delayed haemolytic transfusion reactions is suspected, but reported symptoms, test results, and/or available information are not sufficient to meet the criteria defined above. Other, more specific adverse reaction definitions do not apply.

Abbreviations: AHTR, acute hemolytic transfusion reaction; DAT, direct antiglobulin test.

Source: Adapted from U.S. Centers for Disease Control and Prevention, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases. *National Healthcare Safety Network: Biovigilance Component Hemovigilance Module Surveillance Protocol.* v2.4. April 2018. http://www.cdc.gov/nhsn/PDFs/Biovigilance/BV-HV-protocol-current.pdf. Case criteria for immune-related hemolysis were excluded.

F Hemolysis Code Algorithm

The results of the literature review were leveraged to identify examples of high-quality, administrative claims-based case definitions of acquired hemolysis associated with biologic products, prioritizing, where possible, those that had been developed for use in the U.S.

Using the Centers for Medicare and Medicaid Services (CMS) GEMs, the ICD-9-CM algorithm presented by Winiecki and colleagues was mapped from ICD-9-CM to ICD-10-CM via forward backward mapping.[22-25] Draft algorithms were then subject to review by clinical subject matter experts from IBM, FDA CBER and Acumen. The ensuing code algorithm is presented in **Table 2**. This algorithm may be subject to refinements as a result of specific research questions that arise in the future. Annual counts of patients with specific diagnosis codes are provided in **Appendix A**.

A specific case definition for acquired hemolysis associated with exposure to blood-derived products has not been universally adopted.[1,26] As a result, the algorithm proposed below does not explicitly consider causality (i.e., likelihood that exposure caused the hemolysis) and may therefore overestimate the observed association in the absence of additional specification. The inclusion of nonspecific codes, which may represent conditions not intended for inclusion in the algorithm, could also result in overestimation, though at this stage the intent was to optimize algorithm sensitivity; researchers may wish to specify the algorithm further depending on their particular research question. Conversely, miscoding of hemolysis type could also result in an underestimation of cases associated with exposure to a blood-derived product. However, the algorithm is consistent with previously published approaches and with case definitions applied to identify hemolytic events associated with IVIG.[1,18,20]

The proposed algorithm may be summarized as follows:

1. **INCLUDE: ANY** (“either–or” logic) of the codes listed below, regardless of health care setting or coding position (only one code required).
2. **EXCLUDE**: Codes for hereditary hemolysis, anemia and jaundice.

Table 2. Hemolysis algorithm.

Code	Description	Code Category	Code Type
283.0	Autoimmune hemolytic anemia	DX	09
283.10	Nonautoimmune hemolytic anemia, unspecified	DX	09
283.19	Other nonautoimmune hemolytic anemias	DX	09
283.9	Acquired hemolytic anemia, unspecified	DX	09
999.60	ABO incompatibility reaction, unspecified	DX	09
999.61	ABO incompatibility with hemolytic transfusion reaction not specified as acute or delayed	DX	09
999.62	ABO incompatibility with acute hemolytic transfusion reaction	DX	09
999.63	ABO incompatibility with delayed hemolytic transfusion reaction	DX	09
999.69	Other ABO incompatibility reaction	DX	09
999.76	Non-ABO incompatibility with hemolytic transfusion reaction not specified as acute or delayed	DX	09
999.77	Non-ABO incompatibility with acute hemolytic transfusion reaction	DX	09
999.78	Non-ABO incompatibility with delayed hemolytic transfusion reaction	DX	09
999.83	Hemolytic transfusion reaction, incompatibility unspecified	DX	09
999.84	Acute hemolytic transfusion reaction, incompatibility unspecified	DX	09
999.85	Delayed hemolytic transfusion reaction, incompatibility unspecified	DX	09
D59.0	Drug-induced autoimmune hemolytic anemia	DX	10
D59.1	Other autoimmune hemolytic anemias	DX	10
D59.2	Drug-induced nonautoimmune hemolytic anemia	DX	10
D59.4	Other nonautoimmune hemolytic anemias	DX	10
D59.8	Other acquired hemolytic anemias (nonspecific)	DX	10
D59.9	Acquired hemolytic anemia, unspecified	DX	10
T80.30XA	ABO incompatibility reaction due to transfusion of blood or blood products, unspecified, initial encounter	DX	10
T80.310A	ABO incompatibility with acute hemolytic transfusion reaction, initial encounter	DX	10
T80.311A	ABO incompatibility with delayed hemolytic transfusion reaction, initial encounter	DX	10
T80.319A	ABO incompatibility with hemolytic transfusion reaction, unspecified, initial encounter	DX	10
T80.39XA	Other ABO incompatibility reaction due to transfusion of blood or blood products, initial encounter	DX	10
T80.910A	Acute hemolytic transfusion reaction, unspecified incompatibility, initial encounter	DX	10
T80.911A	Delayed hemolytic transfusion reaction, unspecified incompatibility, initial encounter	DX	10
T80.919A	Hemolytic transfusion reaction, unspecified incompatibility, unspecified as acute or delayed, initial encounter	DX	10
T80.A10A	Non-ABO incompatibility with acute hemolytic transfusion reaction, initial encounter	DX	10
T80.A11A	Non-ABO incompatibility with delayed hemolytic transfusion reaction, initial encounter	DX	10
T80.A19A	Non-ABO incompatibility with hemolytic transfusion reaction, unspecified, initial encounter	DX	10

Abbreviation: DX, diagnosis.

The aim of this review was to develop an algorithm to identify cases of acquired hemolysis that could reasonably be associated with exposure to blood-derived products. As a result, codes for hereditary hemolysis and hemolytic events associated with external causes were excluded; these codes are listed in **Table 3** along with a justification for their exclusion. The intent of this table is to provide an explanation for the omission of some closely related codes. Annual counts of the patients with specific codes proposed for exclusion are provided in **Appendix B**.

Table 3. Excluded codes relevant to hemolysis.

Code	Description	Code Category	Code Type	Justification
282.xx[a]	Hereditary hemolytic anemia	DX	09	Hereditary (not acquired)
283.11	Hemolytic-uremic syndrome	DX	09	Linked to environmental exposures or hereditary disorder
283.2	Hemoglobulinuria due to hemolysis from external causes	DX	09	Generally reflects hemolysis associated with cold or sleep disorder
285.9	Anemia, unspecified	DX	09	Nonspecific term, majority of entities likely to be unrelated to hemolytic terms of interest
782.4	Jaundice, unspecified	DX	09	Nonspecific term, majority of entities likely to be unrelated to hemolytic terms of interest
D58.x[a]	Hereditary hemolytic anemia	DX	10	Hereditary (not acquired)
D59.3	Hemolytic-uremic syndrome	DX	10	Linked to environmental exposures or congenital disorder
D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]	DX	10	Generally reflects hemolysis associated with sleep disorder
D59.6	Hemoglobulinuria due to hemolysis from external causes	DX	10	Generally used for hemolysis associated with cold
D64.9	Anemia, unspecified	DX	10	Idiopathic/unspecified – too nonspecific
R17	Unspecified jaundice	DX	10	Distinct from acute hemolytic anemia
P55	Hemolytic disease of newborn	DX	10	Distinct etiology unrelated to hemolytic terms of interest

Abbreviations: CBER, Center for Biologics Evaluation and Research; DX, diagnosis; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.
[a] All codes for hereditary hemolytic anemia (i.e., ICD-9-CM 282.xx; ICD-10-CM D58.x) were excluded from the algorithm. However, at CBER's request, only the codes for "unspecified" hereditary hemolytic anemia were included in the code-specific queries reported in **Appendix B**.

G Assumptions and Decisions

The algorithm presented above was reviewed internally and with CBER stakeholders and partners. Decisions and assumptions relevant to the algorithm are listed below. Some of the decisions made may be modified depending on the study research question.

- On the basis of expert judgement, the decision was made to exclude procedural (CPT, HCPCS) codes to diagnose hemolysis, because procedural codes are not specific to acquired hemolysis.
- Similarly, it was decided that prescription (NDC) codes for hemolysis treatment were also unlikely to improve algorithm performance, as NDC codes are not specific to therapy of acquired hemolysis.

The hemolysis algorithm was therefore restricted to ICD coding standard.

- The BEST Initiative sought to develop an algorithm that was specific to acute hemolysis, aiming to exclude chronic hemolysis since it would be difficult to assess the temporality of the exposure and the specified outcome (i.e., outcome may have preceded the exposure). Because the intended use of the algorithm is for surveillance of biologic product safety, including these chronic diagnoses would confound any potential association between the exposure to the blood-derived product and the hemolytic outcome. However, some codes (ICD-9-CM 283.10, 283.19, 283.9; ICD-10-CM D59.4, D59.9) do not distinguish between acute and chronic hemolysis and may need to be considered for exclusion in sensitivity analyses.
    - In addition, consideration could be given to including a "washout period" in the future (to be defined depending on the study question), wherein individuals would be excluded from the study for an acute event if they had received a diagnosis code for hemolysis *prior* to the exposure of interest.
- Clinical subject matter experts discussed whether codes for autoimmune hemolysis (ICD-9-CM 282.9; ICD-10-CM 59.0, D59.1) should be included in the algorithm. Recognizing that Winiecki and colleagues did not include these codes and that there is the potential for confounding by indication associated with the inclusion of autoimmune hemolysis cases, researchers ultimately decided to include these codes. This is because the algorithm incorporates codes for both intrinsic and extrinsic RBC destruction, and autoimmune hemolytic anemia is included in the category of extrinsic RBC destruction. Further, it is likely that cases of autoimmune hemolysis would be included through nonspecific codes that do not distinguish between autoimmune or nonautoimmune hemolysis (ICD-9-CM 293.9, 999.84, 999.85; ICD-10-CM D59.8, D59.9).
- Queries based solely on primary position codes could improperly exclude acquired hemolysis cases. Therefore, in implementing the proposed algorithm (i.e., at the statistical planning stage), users will likely want to include hemolysis codes irrespective of whether the diagnosis code is in a primary, secondary or unspecified position.
- Where specified in ICD-10-CM coding, only "initial" encounters were included (i.e., follow-up visits were not included). This was done in an effort to identify only the "incident" case of hemolysis, rather than assess subsequent visits following the event.
- Users may be interested in exploring delayed acquired hemolysis outcomes or acute hemolysis.
    - Relevant risk windows of interest should be decided at the study planning stage, though an appropriate maximum time period between blood-derived product exposure and the development of hemolysis that would be considered relevant remains to be determined.
        - A 30-day 'risk window' was proposed as an inclusive approach to case identification. However, Sridhar and colleagues required that HTRs occur on the same day as the exposure, in order to limit confounding that could be introduced by extending the risk window (study authors noted that only 18/211 reactions occurred on the day after the exposure).[13] The proper risk window will depend on the specific research question.
- Studies may wish to distinguish between one-time and recurrent or chronic use of blood-derived products (in the case of recurrent exposure, risk windows may instead be determined by the frequency of exposure). This distinction has not been included in the hemolysis algorithm below, but codes for both acute and delayed transfusion reactions have been included.
- Levine and colleagues excluded from their hemolysis algorithm patients who received concomitant treatment with steroids, those with a prior history of renal failure/anemia, and those on nephrotoxic drugs or medications that could cause blood dyscrasias.[27]
    - It was decided that the application of Levin's exclusion criteria could improperly exclude cases (e.g., anemia is not sufficiently specific), so these criteria were not applied.
- To avoid bias, Winiecki and colleagues excluded cases with an alternative cause of hemolysis or evidence of hemolysis prior to IVIG receipt.[1]
    - This potential bias could also be addressed via the application of a washout period, discussed above.
    - Where, possible, however, tt will be important, to extract information on the indication for treatment (e.g., whether the treatment was for hemolysis or for a condition associated

with an increased risk of hemolysis) to prevent confounding by indication. This is not directly available in administrative claims data — and this information was not accounted for in the current hemolysis algorithm — but can be included in future statistical analysis plans for projects that include EHR data.

H Algorithm Characterization

To summarize the epidemiology of hemolysis among an insured population in the United States (including commercial insurance and Medicare), the BEST Initiative used the IBM MarketScan Research Databases (Commercial and Medicare Supplemental), accessed via the Treatment Pathways[vi] platform, to query and analyze the ICD codes for acquired hemolysis in the IBM MarketScan database (**Table 2**). The Treatment Pathways platform supports customizable analyses of data stored on IBM Watson Health servers. The BEST Initiative used the 100% Treatment Pathways sample of data from January 1, 2011 through December 31, 2017.

In order to gather the broadest range of hemolysis cases to support a descriptive analysis of proposed hemolysis codes the analyses presented herein did not require exposure to a particular biologic product and did not apply a washout period; while it is recommended that the proposed algorithm undergo a validation study prior to use, future analytical studies should tailor the algorithm specifications according to the study question of interest.

Age- and gender-specific data on MarketScan Research Database enrollment and counts of individuals receiving a code for a hemolytic event of interest were extracted from the database. In addition to the code-specific queries described in **Section F** (and summarized in **Appendices A and B**), authors executed queries that aggregated all ICD-9-CM codes, all ICD-10-CM codes, and all codes (ICD-9-CM and ICD-10-CM) for each outcome of interest.

The figures presented below have been drawn from a large patient dataset during the study period of January 1, 2014 – December 31, 2017. For all analyses, authors only queried ICD-9-CM for January 1, 2014–September 30, 2015 and only queried ICD-10-CM codes for October 1, 2015–December 31, 2017, reflecting the date when the United States transitioned from ICD-9-CM to ICD-10-CM (October 1, 2015).

Individuals had to be continuously enrolled in any enrollment category to be included in the analysis for a particular year. For example, patients had to be continuously enrolled from January 1 to December 31, 2014 in order to be included in the "2014" dataset. From 2014–2017, there were 41,172,696 unique individuals that were enrolled for at least one calendar year. Age was calculated at the end of each calendar year (i.e., age in 2014 was calculated as of December 31, 2014). Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under one year old), this population group has been left out of the charts depicting the proportions of individuals with a hemolysis code by age.

It is important to note that the data presented below are based on counts of individual patients that had a pertinent hemolysis diagnosis code, rather than total counts of hemolysis cases. As such, counts relate to the first hemolysis event coded for an individual during a given surveillance period (e.g. January 1, 2014–December 31, 2014), and individuals could only be counted once per surveillance period.

Table 4 provides a summary of aggregate counts for ICD-9-CM and ICD-10-CM codes, suggesting that approximately 0.22–0.24 individuals per 1,000 individuals included in MarketScan Research Databases received a code associated with acquired hemolysis each year. Among a cohort of 41,172,696 patients that combined those continuously enrolled for at least one calendar year between January 1, 2014 and

[vi] IBM MarketScan Research. Insight for Better Healthcare. https://marketscan.truvenhealth.com/marketscanportal/Portal.aspx

December 31, 2017, 18,814 individuals (0.05% of the cohort) had at least one ICD-9-CM or ICD-10-CM diagnosis code for hemolysis.

Table 4. Counts of patients with hemolysis by code set and year.

Code/ Description	Year			
	2014	2015[a]	2016	2017
ICD-9-CM	6,441	4,073		
ICD-10-CM		2,375	5,169	4,356
ICD-9-CM OR ICD-10-CM	6,441	5,329	5,169	4,356
MarketScan Research Databases Enrollment	28,407,959	22,117,235	21,616,367	19,802,253
Proportion of Patients with Hemolysis per 1,000 Enrolled Population	0.23	0.24	0.24	0.22

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

[a] In 2015, queries combining ICD-9-CM and ICD-10-CM codes returned lower patient counts than when codes were queried individually. This is because of cases in which both ICD-9-CM and ICD-10-CM codes were reported for the same individual, in the January–September and October–December timeframe, respectively.

The BEST Initiative sought to assess whether the 2015 transition to ICD-10-CM and any associated changes in coding practices resulted in notable shifts in the overall frequency of hemolysis reporting. **Figure 2** illustrates the proportion of the enrolled population with a diagnosis related to hemolysis and suggests that the transition did not result in a substantial change to the proportion of individuals receiving a hemolysis diagnosis.

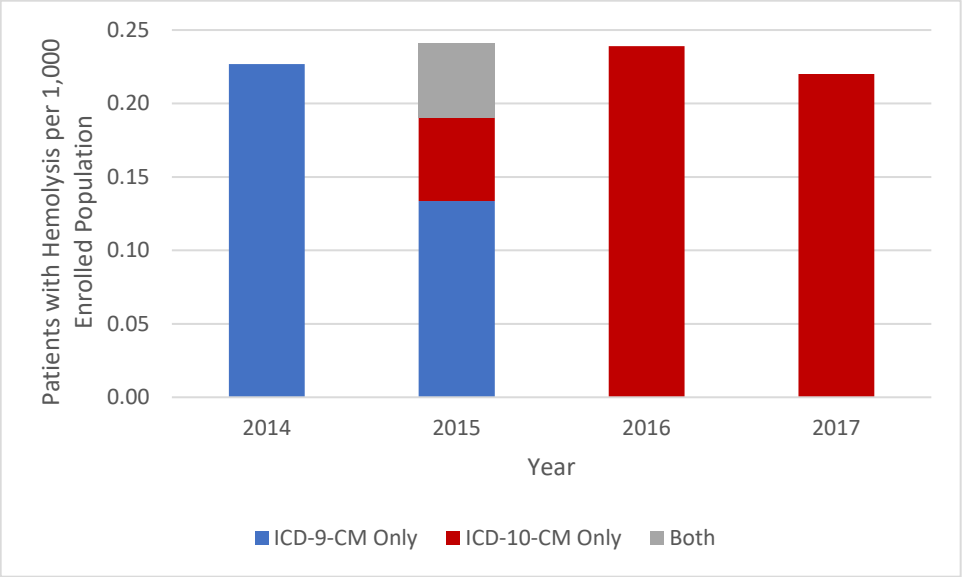

Figure 2. Proportion of patients with hemolysis code per 1,000 enrolled, by year (2014–2017).

Note: In 2015, a patient could receive both an ICD-9-CM and an ICD-10-CM diagnosis, in the January–September and October–December timeframe, respectively.

Figure 3 presents counts of patients with a relevant ICD-9-CM hemolysis code listed in **Table 2** and stratified by age category. Counts were calculated using a combined cohort of 33,216,843 individuals who were continuously enrolled in a participating insurance plan for at least one calendar year in 2014–2015. There were 9,840 individuals with at least one ICD-9-CM code for hemolysis between January 1, 2014 and September 30, 2015, with an average age (calculated at the first event) of 51 years.

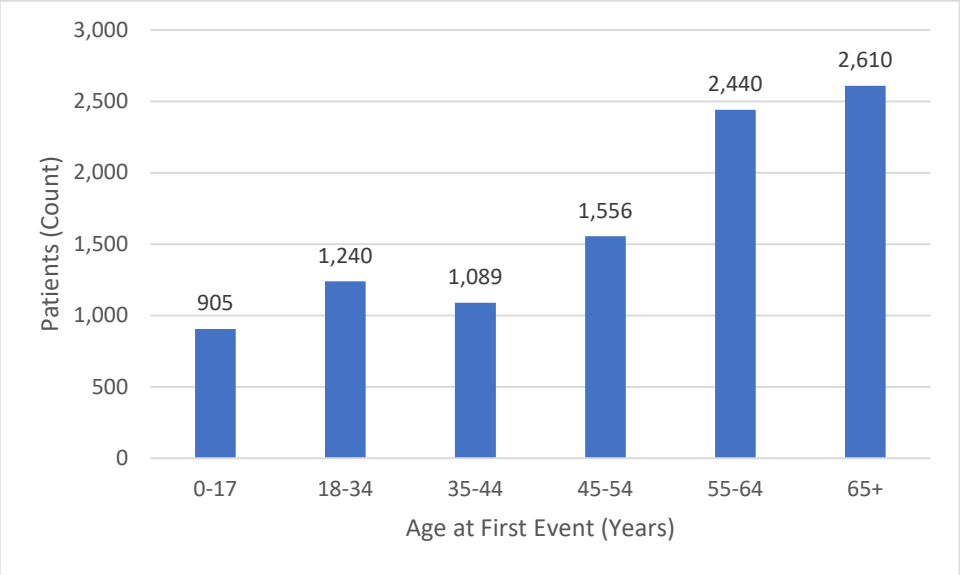

Figure 3. Patients with at least one diagnosis code for hemolysis defined by ICD-9-CM codes, January 1, 2014–September 30, 2015, stratified by age.

Figure 4 presents counts of patients with a pertinent ICD-10-CM hemolysis code listed in **Table 2** and stratified by age category. Counts were based on a cohort of 30,319,401 individuals who were enrolled in a participating insurance plan for at least one calendar year between 2015 and 2017. Among 10,676 individuals with at least one ICD-10-CM code for hemolysis between October 1, 2015 and December 31, 2017, the average age at first event was 52 years.

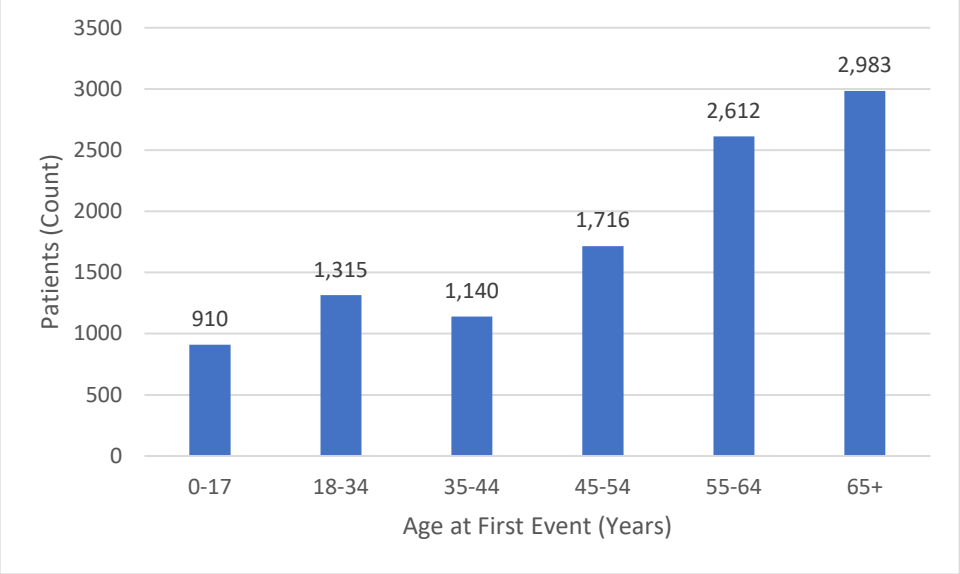

Figure 4. Patients with at least one diagnosis code for hemolysis defined by ICD-10-CM codes, October 1, 2015–December 31, 2017, stratified by age.

Figure 5 presents counts of patients with either an ICD-9-CM or ICD-10-CM hemolysis code among a cohort of 41,172,696 individuals who were continuously enrolled for at least one calendar year between 2014 and 2017. Among 18,814 individuals who received at least one diagnosis code for hemolysis

between January 1, 2014 and December 31, 2017, the average age at first diagnosis was 50 years and absolute patient counts were highest in the 65+ age category.

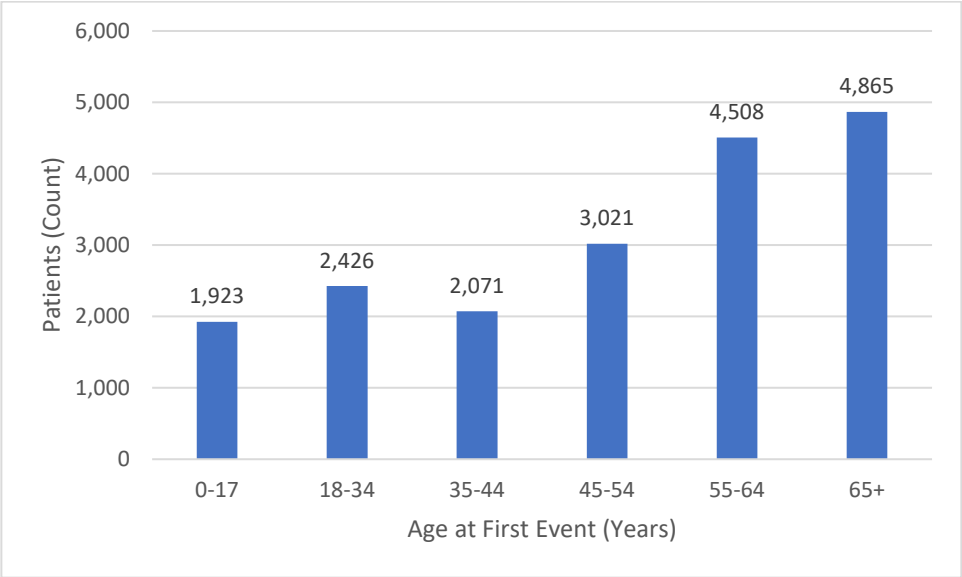

Figure 5. Patients with at least one diagnosis code for hemolysis defined by ICD-9-CM or ICD-10-CM codes, January 1, 2014–December 31, 2017, stratified by age.

The BEST Initiative also gathered age- and gender-specific counts of individuals with a code for hemolysis, as well as the size of the enrolled population by age (between 1 and 100 years) and gender, using these figures to calculate age- and gender-specific proportions of individuals with a diagnosis code for hemolysis. Patients 85 years or older were grouped together in order to minimize the effect of unstable estimates due to the smaller enrolled population sizes available in this age range. The 41-million-patient cohort was used for this analysis and individuals were not required to be enrolled for the full four-year period to be included in this analysis. **Figure 6** depicts the proportion of the population with at least one ICD-9-CM or ICD-10-CM code for hemolysis (per 1,000 population with continuous enrollment in MarketScan Research Databases) between January 1, 2014 and December 31, 2017, by age and gender. Results suggest that the proportion of patients with a hemolysis code remains fairly low throughout the lifecourse before increasing in later life and is higher among elderly men.

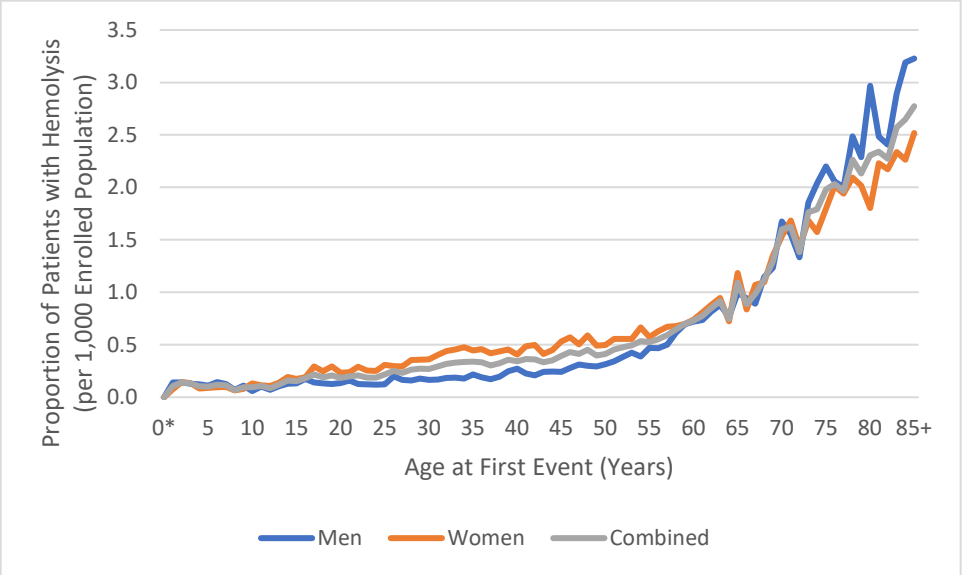

Figure 6. Proportion of patients with at least one diagnosis code for hemolysis (ICD-9-CM or ICD-10-CM) per 1,000 enrolled population, by gender (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under 1 year old experiencing hemolysis has been excluded from the chart and marked as zero.

The BEST Initiative also sought to assess whether there was notable variation in the proportion of patients with acquired hemolysis by calendar year of diagnosis. **Figure 7** presents the annual proportions of patients with hemolysis for ages 1–85+ years old and suggests that observed rates did not vary substantially from year-to-year. It should be noted that the proportions presented in **Figure 7** are substantially lower than those in **Figure 6**, where hemolysis encounters were queried for the entire 2014–2017 period instead of for a single year.

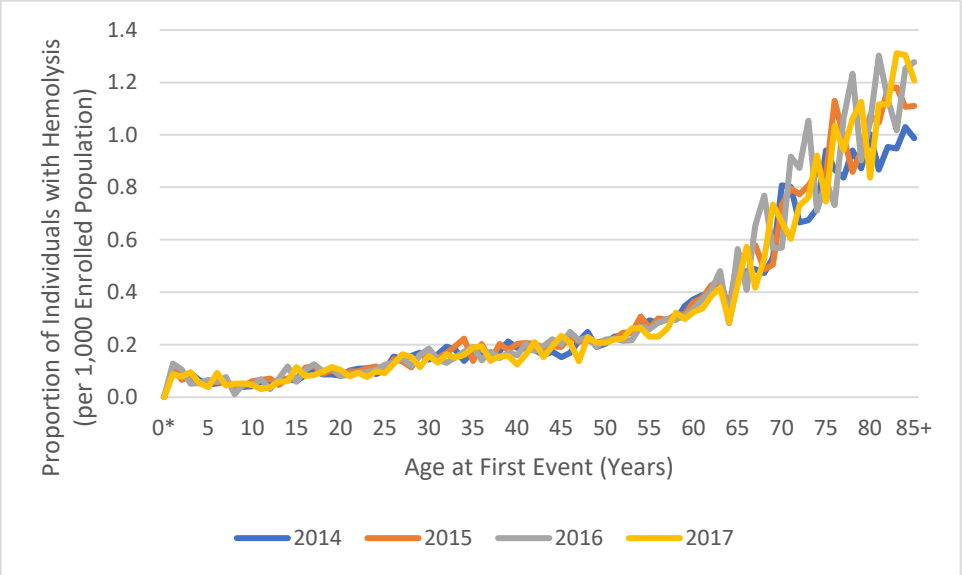

Figure 7. Proportion of patients (1–85+) with at least one diagnosis for hemolysis (ICD-9-CM or ICD-10-CM) per 1,000 enrolled population, by year (January 1, 2014–December 31, 2017).

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e. those under 1 year old), the proportion of those under one year old experiencing hemolysis has been excluded from the chart and marked as zero.

Analyses were also conducted to test whether a temporal association in the occurrence or reporting of hemolysis according to the time of the year. To test this, enrollment and hemolysis encounter data for January 1–June 30 and July 1–December 31 were queried for each year. As presented in **Table 5** and **Figure 8**, there did not appear to be a substantial difference in the proportion of patients experiencing hemolysis during the first and second halves of the calendar year.

Table 5. Counts and proportions of patients experiencing hemolysis,[a] defined by ICD-9-CM or ICD-10-CM codes, stratified by time of year (2014–2017).

Description	Calendar Year			
	2014	2015	2016	2017
January–June patient count	4,453	3,510	3,622	3,023
July–December patient count	4,568	3,806	3,190	3,002
January–June enrollment	31,110,014	24,094,695	23,531,649	21,656,153
July–December enrollment	30,867,380	23,759,879	23,759,879	21,105,240
January–June proportion (per 1,000 enrolled)	**0.14**	**0.15**	**0.15**	**0.14**
July–December proportion (per 1,000 enrolled)	**0.15**	**0.16**	**0.13**	**0.14**

[a] A patient can be counted in both time periods when queries are run separately, whereas they would be counted only once when the query spans the full year. Therefore, the sum of the proportions presented here will exceed those presented for full calendar years.

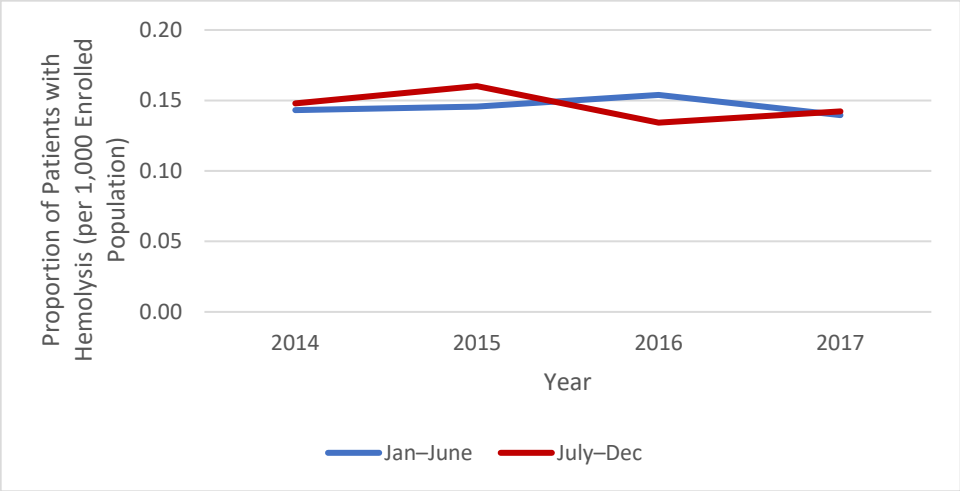

Figure 8. Proportion of patients with at least one diagnosis for hemolysis (ICD-9-CM or ICD-10-CM), stratified by time of year (2014–2017).

I Discussion and Conclusion

The objective of this review was to identify and describe validated methods of identifying cases of acquired hemolysis associated with exposure to blood-derived products using administrative claims data. A structured review found one published study of particular relevance, wherein Winiecki and colleagues applied an ICD-9-CM algorithm to identify cases of post-IVIG hemolysis in FAERS and the MS system.[1] Using this as the basis for a revised algorithm, the BEST Initiative refined the algorithm via consultation with clinical subject matter experts and used GEMs to map the ICD-9-CM algorithm to ICD-10-CM.

Counts of patients with specific diagnosis codes associated with acquired hemolysis were queried (**Appendix A**). The results suggest that the majority of the aggregate counts are represented by codes that do not distinguish between acute and chronic hemolysis: ICD-9-CM codes 283.0 (autoimmune hemolytic anemia) and 283.9 (acquired hemolytic anemia, unspecified) and ICD-10-CM codes D59.1 (other autoimmune hemolytic anemias) and D59.9 (acquired hemolytic anemia, unspecified). This is an important limitation of the algorithm and it is recommended that a washout period be applied to exclude potential chronic cases. The impact of specific code exclusions was tested in **Appendix B**; unspecified anemia and jaundice accounted for the vast majority of exclusions.

Application of the proposed algorithm (**Section H**) suggested that approximately 0.22–0.24 individuals per 1,000 population receive a diagnosis code for acquired hemolysis each year, and that the average age at first diagnosis with hemolysis is approximately 50 years. The proportion of patients with a code for hemolysis remains low through much of the lifecourse, and is distributed fairly evenly between genders, before increasing in later life, with the highest proportions observed among elderly men. These findings are generally consistent with past research on the epidemiology of hemolysis associated with IVIG.[1]

Using the Medical Dictionary for Regulatory Activities standard query (no validation performance measures reported), Taylor and colleagues found that the average age of patients experiencing hemolysis in Canada was 41.7 years and the average hemoglobin decrease was 4.14 g/dL.[18] Through a similar query (also without validation performance measures reported), Berg and colleagues found that hemolysis in Canada occurred across age categories (median 51 years) with no notable gender difference.[20] The average hemoglobin decrease was 4.6 g/dL (range 1–10 g/dL). Where blood type was available, 72% of cases (n=110/152) were associated with Type A (represent 26–40% of the population), 18% were associated with Type AB (represent 2–7% of the population), 7% were associated with Type B

(represent 10–25% of the population), and 3% were associated with Type O (represent 40–57% of the population).

A limitation of this review was the absence of a clear and universal approach to diagnosing acquired hemolysis in administrative databases or determining casual association with biologic therapy (e.g., IVIG exposure). The BEST Initiative found no studies that reported measures of validity for hemolysis algorithms. Regarding data analysis, analyses conducted in MarketScan Research Databases should be viewed as exploratory and additional studies would be required to validate the results and observations stemming from these queries. Lastly, the BEST Initiative included diagnostic codes for 'unspecified' hemolysis in an effort to be as inclusive as possible, although including these codes could lead to the inclusion of chronic hemolysis cases. This is in line with previous approaches that prioritized sensitivity over specificity in the development of hemolysis algorithms or case definitions.[1,18] Conversely, codes were excluded that could potentially represent cases of hemolysis but were viewed as insufficiently specific, such as ICD-9-CM 999.75 (non-ABO incompatibility reaction, unspecified) and 999.80 (transfusion reaction, unspecified). Although these codes were excluded to limit the improper inclusion of non-hemolytic cases, it suggests that not *all* HTRs will be captured by the algorithm proposed.

J Acknowledgements

Development of the hemolysis algorithm and review report benefitted from significant engagement with the FDA CBER team and their partners. We thank them for their contributions and feedback. Additional feedback on the proposed algorithm and draft report was provided by IBM Watson Health, Acumen, and Epi Excellence LLC. MarketScan is a registered trademark of IBM Corporation in the United States, other countries or both.

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Appendix A. Counts of Patients with Specific Codes Proposed for the Algorithm

As an initial test of the proposed algorithm, authors ran code-specific queries on a large patient dataset to assess the number of patients with each diagnosis code proposed for inclusion. This was done to identify what specific codes were likely to account for the majority of the results being returned. Researchers used the MarketScan Research Databases (Commercial and Medicare Supplemental), accessed via the Treatment Pathways analytic platform, to query the past four years of available data (January 1, 2014–December 31, 2017). In 2014, there were 28,407,959 patients enrolled for the entire year; 22,117,235 in 2015; 21,616,367 in 2016; 19,802,253 in 2017; 41,172,696 for at least one calendar year in 2014–2017. Results are presented in **Table A1**.

The transition from ICD-9-CM to ICD-10-CM occurred October 1, 2015; no ICD-9-CM codes were queried after this date and no ICD-10-CM codes were queried before this date. The coding standard-specific subtotal rows were calculated by querying the all codes for a particular coding standard together; the "Total (Count)" column was calculated by querying the individual code in a cohort of patients who were enrolled for at least one calendar year between 2014 and 2017.

Subtotal rows and Total columns may be smaller than the sum of individual cells, because patients with multiple codes in a single year and with more than one of the same diagnosis codes in different years will only be counted once in these rows and columns. As a result, the sum of all "% of Total" cells in a single column may exceed 100%. However, the "Total" column could also be larger than the sum of individual years, as a result of situations where an individual is only enrolled for part of the year that they experience a hemolytic event but is then continuously enrolled for a separate year. For example, an individual could be continuously enrolled for a few days, weeks, or months in 2016 and experience a hemolytic event, then be continuously enrolled for all of 2017. This event would not be captured in the column for the 2015 (as the individual would be excluded from that cohort) but would be captured in the "Total" column.

It appears that ICD-9-CM codes 283.0 (autoimmune hemolytic anemia) and 283.9 (acquired, hemolytic anemia, unspecified), as well as ICD-10-CM codes D59.1 (other autoimmune hemolytic anemias) and D59.9 (acquired hemolytic anemia, unspecified) are the most frequently reported codes.

Table A1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in the hemolysis algorithm (2014–2017).

Code	Code Description	Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
ICD-9-CM											
283.0	Autoimmune hemolytic anemia	2,911	45.2	1,858	34.9					4,161	22.1
283.10	Nonautoimmune hemolytic anemia, unspecified	325	5.0	183	3.4					514	2.7
283.19	Other nonautoimmune hemolytic anemias	420	6.5	276	5.2					748	4.0
283.9	Acquired hemolytic anemia, unspecified	3,386	52.6	2,174	40.8					5,430	28.9
999.60	ABO incompatibility reaction, unspecified	241	3.7	138	2.6					674	3.6
999.61	ABO incompatibility with hemolytic transfusion reaction not specified as acute or delayed	26	0.4	9	0.2					50	0.3
999.62	ABO incompatibility with acute hemolytic transfusion reaction	7	0.1	1	0.0					9	0.0
999.63	ABO incompatibility with delayed hemolytic transfusion reaction	2	0.0	1	0.0					4	0.0
999.69	Other ABO incompatibility reaction	44	0.7	28	0.5					95	0.5
999.76	Non-ABO incompatibility with hemolytic transfusion reaction not specified as acute or delayed	1	0.0	2	0.0					4	0.0
999.77	Non-ABO incompatibility with acute hemolytic transfusion reaction	4	0.1	2	0.0					5	0.0
999.78	Non-ABO incompatibility with delayed hemolytic transfusion reaction	4	0.1	2	0.0					6	0.0
999.83	Hemolytic transfusion reaction, incompatibility unspecified	33	0.5	17	0.3					56	0.3
999.84	Acute hemolytic transfusion reaction, incompatibility unspecified	9	0.1	4	0.1					16	0.1
999.85	Delayed hemolytic transfusion reaction, incompatibility unspecified	11	0.2	9	0.2					21	0.1
ICD-9-CM Subtotal		**6,441**	**100.0**	**4,073**	**76.4**					**10,172**	**54.1**
ICD-10-CM											
D59.0	Drug-induced autoimmune hemolytic anemia			129	2.4	362	7.0	267	6.1	739	3.9
D59.1	Other autoimmune hemolytic anemias			1,097	20.6	2,262	43.8	2,024	46.5	4,322	23.0
D59.2	Drug-induced nonautoimmune hemolytic anemia			47	0.9	106	2.1	114	2.6	288	1.5
D59.4	Other nonautoimmune hemolytic anemias			226	4.2	610	11.8	473	10.9	1,326	7.0
D59.8	Other acquired hemolytic anemias (nonspecific)			118	2.2	338	6.5	328	7.5	785	4.2

Code	Code Description	Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
D59.9	Acquired hemolytic anemia, unspecified			1,010	19.0	2,189	42.3	1,717	39.4	4,738	25.2
T80.30XA	ABO incompatibility reaction due to transfusion of blood or blood products, unspecified, initial encounter			28	0.5	49	0.9	44	1.0	239	1.3
T80.310A	ABO incompatibility with acute hemolytic transfusion reaction, initial encounter			1	0.0	8	0.2	2	0.0	22	0.1
T80.311A	ABO incompatibility with delayed hemolytic transfusion reaction, initial encounter			0	0.0	2	0.0	0	0.0	4	0.0
T80.319A	ABO incompatibility with hemolytic transfusion reaction, unspecified, initial encounter			2	0.0	6	0.1	6	0.1	18	0.1
T80.39XA	Other ABO incompatibility reaction due to transfusion of blood or blood products, initial encounter			8	0.2	24	0.5	12	0.3	53	0.3
T80.910A	Acute hemolytic transfusion reaction, unspecified incompatibility, initial encounter			9	0.2	25	0.5	30	0.7	70	0.4
T80.911A	Delayed hemolytic transfusion reaction, unspecified incompatibility, initial encounter			0	0.0	10	0.2	9	0.2	24	0.1
T80.919A	Hemolytic transfusion reaction, unspecified incompatibility, unspecified as acute or delayed, initial encounter			8	0.2	16	0.3	8	0.2	43	0.2
T80.A10A	Non-ABO incompatibility with acute hemolytic transfusion reaction, initial encounter			0	0.0	0	0.0	0	0.0	2	0.0
T80.A11A	Non-ABO incompatibility with delayed hemolytic transfusion reaction, initial encounter			0	0.0	3	0.1	0	0.0	4	0.0
T80.A19A	Non-ABO incompatibility with hemolytic transfusion reaction, unspecified, initial encounter			0	0.0	3	0.1	2	0.0	5	0.0
ICD-10-CM Subtotal				**2,375**	**44.6**	**5,169**	**100.0**	**4,356**	**100.0**	**10,750**	**57.1**
Total		**6,441**	**100.0**	**5,329**	**100.0**	**5,169**	**100.0**	**4,356**	**100.0**	**18,814**	**100.0**

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

Note: Codes highlighted in yellow represent those that accounted for at least 10% of the overall count among the 2014–2017 cohort.

Appendix B. Counts of Patients with Specific Codes Excluded from the Algorithm

Authors also ran code-specific queries on a large patient dataset to assess the number of patients with each diagnosis code proposed for exclusion. This has been done in order to gain an understanding of how many patients will be excluded as a result of each code being omitted from the algorithm; however, it should be noted that patients with excluded codes may be included in the analysis if they *also* have a code from one of the algorithms detailed in **Table 1**. Researchers used the MarketScan Research Databases (Commercial and Medicare Supplemental), accessed via the Treatment Pathways platform, to generate descriptive statistics in the MarketScan data for January 1, 2014–December 31, 2017. In 2014, there were 28,407,959 patients enrolled for the entire year; 22,117,235 in 2015; 21,616,367 in 2016; 19,802,253 in 2017; 41,172,696 for at least one calendar year in 2014–2017. Results are presented in **Table B1**.

The transition from ICD-9-CM to ICD-10-CM occurred October 1, 2015; no ICD-9-CM codes were queried after this date and no ICD-10-CM codes were queried prior to this date. The coding standard-specific subtotal rows were calculated by querying the all codes for a particular coding standard together; the "Total (Count)" column was calculated by querying the individual code in a cohort of patients who were enrolled for at least one calendar year between 2014 and 2017.

Subtotal rows and Total columns may be smaller than the sum of individual cells, because patients with multiple codes in a single year and with more than one of the same diagnosis codes in different years will only be counted once in these rows and columns. As a result, the sum of all "% of Total" cells in a single column may exceed 100%. However, the "Total" column could also be larger than the sum of individual years, as a result of situations where an individual is only enrolled for part of the year that they experience a hemolytic event but is then continuously enrolled for a separate year. For example, an individual could be continuously enrolled for a few days, weeks, or months in 2016 and experience a hemolytic event, then be continuously enrolled for all of 2017. This event would not be captured in the column for the 2015 (as the individual would be excluded from that cohort) but would be captured in the "Total" column.

The codes for unspecified anemia (ICD-9-CM 285.9; ICD-10-CM D64.9) are by far the most frequently reported codes.

Table B1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes excluded from the hemolysis algorithm (2014–2017).

Code	Code Description	Year								Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)		
ICD-9-CM											
282.9	Hereditary hemolytic anemia, unspecified	1,509	0.2	912	0.1					2,507	0.1
283.11	Hemolytic-uremic syndrome	516	0.1	326	0.0					761	0.0
283.2	Hemoglobulinuria due to hemolysis from external causes	877	0.1	605	0.1					1,433	0.1
285.9	Anemia, unspecified	837,143	97.1	529,712	78.3					1,284,565	55.8
782.4	Jaundice, unspecified	28,802	3.3	17,431	2.6					65,738	2.9
ICD-9-CM Subtotal		**862,354**	**100.0**	**545,465**	**80.6**					**1,341,862**	**58.3**
ICD-10-CM											
D58.9	Hereditary hemolytic anemia, unspecified			591	0.1	1,801	0.3	1,274	0.2	3,666	0.2
D59.0	Drug-induced autoimmune hemolytic anemia			129	0.0	362	0.1	267	0.0	739	0.0
D59.1	Other autoimmune hemolytic anemias			1,097	0.2	2,262	0.4	2,024	0.4	4,322	0.2
D59.3	Hemolytic-uremic syndrome			217	0.0	475	0.1	468	0.1	958	0.0
D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]			145	0.0	282	0.0	247	0.0	482	0.0
D59.6	Hemoglobulinuria due to hemolysis from external causes			101	0.0	272	0.0	223	0.0	605	0.0
D64.9	Anemia, unspecified			212,147	31.4	617,532	97.1	552,624	96.8	1,240,815	53.9
R17	Unspecified jaundice			5,370	0.8	19,752	3.1	19,155	3.4	56,867	2.5
P55	Hemolytic disease of newborn (non-billable)			142	0.0	920	0.1	889	0.2	6,563	0.3
ICD-10-CM Subtotal				**217,543**	**32.2**	**636,146**	**100.0**	**570,659**	**100.0**	**1,294,491**	**56.2**
Total		**862,354**	**100.0**	**676,389**	**100.0**	**636,146**	**100.0**	**570,659**	**100.0**	**2,302,435**	**100.0**

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

Note: Codes highlighted in yellow represent those that accounted for at least 10% of the overall count among the 2014–2017 cohort.