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Supplemental Digital Content 1. Additional Methods.

In our electronic ordering system soluble interleukin-2 receptor (sIL2R, also referred to as “soluble CD25” in the literature)\(^1\) appeared as “Interleukin-2 receptor, EIA” and this was confused with the interleukin-2 (IL2) test named “Interleukin-2, circulating.” Natural killer cell (NK) functional tests required a send-out paper order requisition. However, providers evaluating patients for HLH were not aware of this workflow and mistakenly assumed the electronic order “Natural Killer Cells” was the functional test referred to in the HLH-2004 diagnostic criteria. Of note, this NK flow cytometry order only quantified the number of NK cells, and not ordered by clinicians investigating NK diseases. Education was selected as the intervention because mistaken testing was driven by clinician knowledge gap, and education could take effect quickly while other systems-based interventions were developed. The quality improvement intervention consisted of: 1) review of HLH testing, 2) presentation of testing errors to hematology clinicians at the Division meetings, 3) development of an evidence-based HLH consult note with test ordering instructions, 4) dedicated consultation on suspected HLH cases (SAM), and 5) promotion of the HScore to risk stratify HLH consults. Supporters of the intervention were hematology consult service attending clinicians (authors) and fellows. Planned systems corrections were education, development of an HLH-specific order set, and a decision support tool. Final systems interventions included education and erroneous test removal from the electronic test catalog.

Possible HLH patients were identified from administrative and testing databases by: International Classification of Diseases (ICD) 9\(^{th}\) revision code 288.4, ICD-10 code D76.1X, natural killer flow cytometry, IL2, or sIL2R testing. The charts were reviewed and clinical information was recorded.

An order for IL2 or quantitative NK flow cytometry, instead of sIL2R or NK functional assays, was defined as an error, and was corroborated by clinical documentation for each patient. Test number, date, and type was recorded for each patient from laboratory records in a standardized form. Delays in ordering from erroneous testing were thus determined. Ordering of sIL2R was encouraged in HLH evaluation because of our clinical experience of utility, confirmed by a recent report.\(^2\) Ordering of NK functional tests were not encouraged in the intervention due to expert opinion about limited utility in adults.\(^3\) Test costs were obtained from Quest Diagnostics. All evaluations, procedures, and ordered tests were at the discretion of the treating clinicians. None of the intervention participants had conflicts of interest in the intervention. Patient privacy was protected in agreement with standard hospital policies.

The intervention was coupled with a planned retrospective review to determine 1) the effectiveness of the intervention across the institution and 2) to provide data to guide future HLH evaluations. During our
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intervention, we noted several anecdotal major hemorrhagic events and amended the retrospective review to include hemorrhagic outcomes.

The HLH-2004 criteria are: fever; splenomegaly; cytopenias affecting 2 lineages (hemoglobin <9 g/dL, platelet count <100 x 10^9/L, absolute neutrophil count <1 x 10^9/L; hypertriglyceridemia (≥265 mg/dL) or hypofibrinogenemia (≤150 mg/dL); hemophagocytosis on biopsy of bone marrow, spleen or lymph node; elevated ferritin (≥500 ng/mL); impaired NK cell function; and elevated interleukin-2 receptor (≥2400 U/mL). Of note, only the original pediatric diagnostic guidelines reported a fever inclusion value (≥38.5°C), and these criteria require no evidence of malignancy; this malignancy exclusion is not used in other studies of adult HLH, where malignancy is a common HLH trigger. The HLH-2004 criteria, many retrospective studies, and the only prospective trial in adult HLH do not report diagnostic thresholds for splenomegaly, fever, or NK function. For this study, splenomegaly was defined as spleen anterior-posterior length greater than 2 standard deviations above age-matched gender-specific normal range on cross sectional imaging. Fever was defined as documented temperature ≥38.5°C as in a prior study. Impaired NK cell function was determined with either ⁵¹Cr-release assay, perforin flow cytometry, or CD107a flow cytometry conducted at Cincinnati Children’s Hospital (CCH). HLH genetic testing was done at CCH. The HScore (http://saintantoine.aphp.fr/score/) was computed for patients using laboratory data from the first week of hospitalization at our institution. Reported laboratory values for triglycerides, fibrinogen, hemoglobin, ferritin, platelets, and absolute neutrophil counts are given for the first week of hospitalization or before chemotherapy initiation, which ever occurred first.

HLH was defined as infection-triggered if the patient had documented laboratory or pathological evidence of a viral, bacterial, or fungal infection temporally related to disease onset. Epstein-Barr virus (EBV) triggered HLH was defined as HLH occurring in the presence of an EBV plasma viral load ≥10,000 copies/mL, with no evidence of malignancy on pathological evaluation to agree with a prior classification. Patients with HLH from malignancy lacked an infectious trigger and either 1) had active cancer, 2) were treated for cancer in the past 6 months, or 3) were found to have cancer within 12 months after the HLH index presentation. Patients with EBV viremia and hematologic malignancy were classified as malignancy triggered in agreement with a prior study. Autoimmune disease triggered HLH was defined as antecedent or subsequently diagnosed autoimmune disease within 6 months of HLH index hospitalization. Surgery-triggered HLH occurred in the acute post-operative period without an alternative etiology. Idiopathic HLH was a diagnosis of exclusion defined as HLH without an identifiable trigger at the time of patient death or after 12 months of evaluation as above. Autoimmune hemolytic anemia was
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not allowed as a standalone autoimmune etiology due to clinical overlap with HLH because 53% of patients had undetectable haptoglobin (Table 1) suggesting intravascular hemolysis, and 26.8% (11/41) of patients had positive Coombs testing. We used undetectable haptoglobin as the threshold for hemolysis because acute illness and liver disease can interfere with haptoglobin levels. Triggers determined from clinical context after exclusion of other possibilities were classified as “clinical with exclusion.”

International Society on Thrombosis and Hemostasis (ISTH) definitions were used for major bleeding and disseminated intravascular coagulation (DIC), with a DIC score ≥5 signifying DIC. Acute kidney injury was defined by creatinine level and/or need for renal replacement therapy at the discretion of the treating attending nephrologist. Positron emission tomography–computed tomography (PET-CT) scan utility was determined by reviewing attending radiologist scan interpretations and subsequent biopsy results. Staging PET-CT scans for known active malignancy at the time of the scan were excluded. Patients were dichotomously stratified based on marrow, splenic, hepatic, and lymph node patterns of fluorodeoxyglucose (FDG) uptake: 1) normal or diffuse hyperactive uptake, 2) focal uptake abnormalities.

Supplemental Statistical methods:
Assuming a priori that 2 HLH evaluations per month would occur with a 50% intervention effect size, 0.95 confidence level and 0.05 confidence interval, our target intervention sample size was 15 patients. Sensitivity analysis was conducted with varied thresholds for patient age (30 vs 50 years), fibrinogen (150 vs 200mg/dL), and ferritin (10,000 vs 50,000 ng/mL). Patients lost to follow up were censored after last known follow up. Missing data points were omitted from analysis as indicated.

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Supplemental Digital Content 2. Figure that demonstrates project rationale and context, quality improvement timeline, and analysis flow diagram. A) Two concurrent HLH patients with erroneous testing prompted our quality improvement (QI) intervention. Patient 1 had delayed HLH diagnosis, trigger search, and treatment from use of HLH-2004 diagnostic criteria and erroneous testing. Patient 1 only met HLH-2004 criteria upon readmission for relapse, near the time of death. Patient 2 experienced a shorter delay from use of HLH-2004 diagnostic criteria, and underwent successful trigger identification and treatment with long-term survival. However, perceived very poor prognosis nearly prevented definitive trigger therapy, and erroneous testing caused difficulty discerning secondary infection or HLH relapse. This led to the discovery that erroneous testing was occurring. Both patients illustrate that use of the HScore criteria, rather than HLH-2004 criteria, would have led to earlier diagnosis of HLH and search for underlying triggers. B) QI intervention and retrospective analysis timeline diagram. Erroneous testing found in the clinical environment led to the QI project. Although active education ended in July 2016, efforts to improve testing continue. Unsuccessful systems interventions included an HLH order set and decision support tool. Removal of mistaken tests was simpler, and expected to be more effective as an engineering control. Scale of retrospective inclusion period is not constant, as illustrated with dark dashed line. C) Participant flow diagram of eligible patients in the cohort for retrospective review. Abbreviations: HLH=hemophagocytic lymphohistiocytosis, IVIG=intravenous gamma globulin, IL2=interleukin-2, NK=Natural killer cell quantitative flow cytometry.
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### Supplemental Digital Content 3. Characteristics of potential HLH.

| HLH Criteria                       | No.* | %     | Median† | Range‡ |
|------------------------------------|------|-------|---------|--------|
| Hemoglobin (<9 g/dL)†              | 11/13| 84.6% | 7.3     | 5.9-10.9 |
| Platelet (<100 x10^9/L)†           | 9/13 | 69.2% | 45      | 2-87   |
| ANC (<1 x10^9/L)†                  | 2/13 | 15.4% | 3.98    | 0-17.31 |
| Fever (≥38.5°C)                    | 11/13| 84.6% | 39.5    | 37.8-41.0 |
| Splenomegaly (cm)                  | 4/12 | 33.3% | 9.8     | 5.8-16.9 |
| Triglyceride (≥265 mg/dL)†         | 5/13 | 38.5% | 232     | 124-481 |
| Ferritin (≥500 ng/mL)†             | 13/13| 100.0%| 10157   | 782-70529 |
| Ferritin, <500 ng/mL               | 0/13 | 0.0%  |         |        |
| Ferritin, 501-3000 ng/mL           | 3/13 | 23.1% |         |        |
| Ferritin, >3000 ng/mL              | 10/13| 76.9% |         |        |
| Fibrinogen (≤150 mg/dL)†           | 0/13 | 0.0%  | 344     | 202-722 |
| sIL2R (≥2400 U/mL)                 | 5/10 | 50.0% | 2303    | <406-12686 |
| Hemophagocytosis                   | 1/7  | 14.3% |         |        |
| First marrow                       | 1/7  | 14.3% |         |        |
| Subsequent marrow                  | 0/1  | 0.0%  |         |        |
| NK function                        | N/A  | -     |         |        |
| Genetic testing                    | N/A  | -     |         |        |
| Symptom duration (weeks)           | 13/13| -     | 2       | 0-150  |
| HScore†                            | 13/13| -     | 207     | 173-243 |
| Age (years)                        | 13/13| -     | 45      | 22-73  |
| Follow up (days)                   | 13/13| -     | 42      | 2-1092 |
| Sex, male                          | 7/13 | 53.8% |         |        |
| Race                               |      |       |         |        |
| White                              | 5/13 | 38.5% |         |        |
| Black                              | 3/13 | 23.1% |         |        |
| Other                              | 5/13 | 38.5% |         |        |
| Acute Kidney Injury†               | 8/13 | 61.5% |         |        |
| Stage 1                            | 0/13 | 0.0%  |         |        |
| Stage 2                            | 1/13 | 7.7%  |         |        |
| Stage 3                            | 7/13 | 53.8% |         |        |

Legend: ANC= absolute neutrophil count, sIL2R= soluble interleukin-2 receptor, NK= natural killer cell, N/A= not tested. Spleen size is anterior-posterior dimension in centimeters. † Within 7 days of admission, * number with Hscore ≥169 who met criteria/number evaluable. ‡ Median and range shown for all patients with Hscore ≥169, who did not meet HLH-2004 criteria.
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| Supplemental Digital Content 4. Individual triggers and treatments for HLH and potential HLH. | # | Treatment | Survival (Days) |
|---|---|---|---|
| **Autoimmune, n=5** | | | |
| Lupus | 1 | CS, rituximab | >1342 |
| Evan syndrome | 1 | CS, rituximab, mycophenolate | >413 |
| ANCA-negative vasculitis | 1 | IVIG, HLH-94 | 15 |
| Anti-GBM disease | 1 | CS | 59 |
| Sjogren's disease, prior HLH | 1 | CS, alemtuzumab → Allo-BMT | >2096 |
| **Idiopathic, n=7** | | | |
| Alive at last follow up | 2 | IVIG, HLH-94 with tacrolimus; IVIG, HLH-94 with tacrolimus → tocilizumab → Investigational Therapy | >603; >472 |
| Deceased at last follow up | 5 | IVIG; HLH-94; HLH-94; HLH-94; HLH-94; HLH-94; HLH-94 | 3-512 |
| **EBV, n=9** | | | |
| Alive at last follow up | 2 | IVIG, rituximab, HLH-94; IVIG, acyclovir, HLH-2004, rituximab, etanercept → Allo-BMT | >2129; >2616 |
| Deceased at last follow up | 7 | CS, acyclovir; CS, IVIG, acyclovir; cyclophosphamide, HLH-94, acyclovir → FLACC; HLH-94, rituximab, CS, IVIG, ganciclovir; IVIG, HLH-94, acyclovir, rituximab; HLH-94, rituximab | 8-973 |
| **Infectious (non-EBV), n=17** | | | |
| Acute abdomen with bowel perforation | 2 | Surgery, broad spectrum antimicrobials; CS, surgery, broad spectrum antimicrobials | >688; >458 |
| Acute abdomen with bowel perforation, H. pylori positive and CMV viremia | 1 | Ganciclovir, broad spectrum antimicrobials, H. pylori treatment, abscess drainage | 110 |
| HIV | 2 | CS, IVIG, ART; CS, ART | >816; 68 |
| MRSA bacteremia | 2 | CS, IVIG, vancomycin; vancomycin | >709; 23 |
| HHV8+ Castleman’s disease, HIV | 1 | CS, rituximab, ganciclovir, IVIG, ART | >98 |
| CMV viremia with Still's disease | 1 | CS, anakinra, ganciclovir → foscarnet | >367 |
| Disseminated Histoplasmosis | 1 | CS, liposomal amphotericin B | >207 |
| Herpes simplex virus and S. pneumoniae meningitis | 1 | IVIG, HLH-94 (x3 doses), acyclovir, antimicrobials | >1011 |
| Candidemia | 1 | Micafungin, indwelling catheter removal | >5 |
| Influenza B | 1 | Oseltamivir | >878 |
| Mycobacterium szulgai bacteremia with MDS | 1 | Broad spectrum antimicrobials | 17 |
| Visceral leishmaniasis | 1 | Liposomal amphotericin B | >39 |
| Ehrlichiosis | 1 | CS, doxycycline | >884 |
| CMV viremia with parvovirus myocarditis | 1 | CS, IVIG, ganciclovir | >40 |
## Supplemental Digital Content 4, continued. Individual triggers and treatments for HLH and potential HLH.

| HLH Trigger | # | Treatment | Survival (Days) |
|-------------|---|-----------|-----------------|
| **Malignancy, Hodgkin Lymphoma, n=2** |  |  |  |
| Hodgkin Lymphoma with HIV | 2 | ART, CS, cyclophosphamide ↔brentuximab vedotin→ nivolumab; ART, CHOP | >314; 61 |
| **Malignancy, B-cell, n=11** |  |  |  |
| CLL post Allo-BMT | 1 | IVIG | 15 |
| CLL post ibrutinib initiation | 2 | CS, cyclophosphamide; HLH-94 | 28; 38 |
| T-cell rich B-cell lymphoma | 2 | IVIG, HLH-94 ↔ R-CHOP; HLH-2004 ↔ R-CHOP | >1347; >775 |
| Diffuse large B-cell lymphoma | 3 | IVIG, HLH-94 ↔ R-CHOP; R-ESHAP; R-CHOP | 418; 38; >387 |
| Intravascular B cell lymphoma | 2 | CS, IVIG1; comfort measures care | 3; 13 |
| EBV negative PTLD | 1 | Reduction of immunosuppression | >39 |
| **Malignancy, T/NK-cell, n=8** |  |  |  |
| Peripheral T-cell lymphoma, NOS | 3 | CS, IVIG, cyclosporine, 2rituximab; IVIG, HLH-2004 ↔ CHOP; CS, cyclophosphamide ↔brentuximab vedotin | 11; 171; 99 |
| Cutaneous gamma-delta T-cell lymphoma post Allo-BMT | 1 | HLH-94 | 72 |
| NK/T-cell lymphoma | 2 | CS, cyclophosphamide, XRT, denileukin diftitox; ICE | 45; 16 |
| NK cell leukemia | 1 | CS, splenectomy | >398 |
| Aggressive NK cell leukemia | 1 | CS, cyclophosphamide | 12 |
| **Malignancy, other hematologic, n=3** |  |  |  |
| Kaposi sarcoma, HIV, and HHV8 inflammatory syndrome | 1 | CS, ART, ganciclovir, HLH-94 ↔ 3rituximab | 20 |
| Histiocytic sarcoma | 1 | HLH-94 ↔ 3CHOEP → Allo-BMT | 861 |
| AML, s/p induction | 1 | IVIG | 18 |
| **Surgical, n=1** |  |  |  |
| Post salpingectomy | 1 | CS | 1 |
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Supplemental Digital Content 4, continued. Individual triggers and treatments for HLH and potential HLH.

| Potential HLH Trigger                  | #  | Treatment                              | Survival (Days) |
|---------------------------------------|----|----------------------------------------|-----------------|
| Autoimmune, n=6                       |    |                                        |                 |
| Lupus                                 | 2  | CS; CS                                 | >475; >305      |
| Autoimmune hepatitis, sickle cell crisis | 1  | CS                                     | 2               |
| DRESS                                 | 1  | CS                                     | >1091           |
| Multicentric Castleman's Disease      | 1  | Rituximab                              | >245            |
| Aplastic anemia, platelet reaction    | 1  | Broad spectrum antimicrobials          | >977            |
| Infectious, n=6                       |    |                                        |                 |
| Aplastic anemia, candidemia and nocardia pneumonia | 1  | Liposomal amphotericin B→ voriconazole | 42              |
| Ehrlichiosis                           | 2  | Doxycycline; CS, doxycycline          | >12; >155       |
| Leptospirosis                         | 1  | CS, broad spectrum antimicrobials^1    | 25              |
| EBV                                   | 1  | CS, ganciclovir                        | >3              |
| Parvovirus with sickle cell crisis    | 1  | IVIG, red cell exchange                | 3               |
| Malignancy, n=1                       |    |                                        |                 |
| Monoblastic AML with cytarabine syndrome | 1  | CS                                     | 28              |

Legend: Treatments and survival for individual cases separated with semicolon. Survival with > indicates patient was alive at last known follow up. Please note that there are no FDA approved treatments labeled for use in HLH, all treatments are off-label. ANCA= anti-neutrophil cytoplasmic antibodies, HIV= human immunodeficiency virus, GBM= glomerular basement membrane, MRSA= methicillin resistant staphylococcus aureus, CMV= Cytomegalovirus, EBV= Epstein-Barr virus, HHV8= human herpes virus, AML= acute myeloid leukemia, CLL= chronic lymphocytic leukemia, allo-BMT= allogenic bone marrow transplant, PTLD= post-transplant lymphoproliferative disease, CS= corticosteroid, ART= antiretroviral therapy, IVIG= intravenous gamma globulin, XRT= radiotherapy, DRESS= drug rash with eosinophilia and systemic symptoms, ATG-CSA= anti-thymocyte globulin and cyclosporine. HLH-94, HLH-2004, CHOP, R-CHOP, CHOP, R-ESHAP, ICE, FLACC refer to chemotherapy regimens. ^1Trigger discovered after patient death, ^2rituximab administered for EBV-positivity, ^3therapy changed after malignancy uncovered, ^4therapy changed due to relapse or refractory disease
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| Supplemental Digital Content 5. Potential HLH trigger identification methods. |
|-------------------------------|-----------------|-----------------|
| Method                        | Number (of 13)  | % cases         |
| Serologic test                | 5               | 38.5%           |
| Bone marrow                   | 1               | 7.7%            |
| Clinical, with exclusion      | 3               | 23.1%           |
| Lymph node biopsy             | 1               | 7.7%            |
| Liver biopsy                  | 1               | 7.7%            |
| Renal biopsy                  | 1               | 7.7%            |
| Respiratory testing/BAL       | 1               | 7.7%            |

Legend: From 13 patients with Hscore ≥169 during the first week of admission but not satisfying HLH-2004 criteria. BAL= bronchoalveolar lavage.