



Instructions for X-Linked Lymphoproliferative Syndrome (XLP) Post-HCT Data (Form 2134)

This section of the CIBMTR Forms Instruction Manual is intended to be a resource for completing the XLP Post-HCT Form.

E-mail comments regarding the content of the CIBMTR Forms Instruction Manual to: CIBMTRFormsManualComments@nmdp.org. Comments will be considered for future manual updates and revisions. For questions that require an immediate response, please contact your transplant center’s CIBMTR CRC.

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X-Linked Lymphoproliferative Syndrome Post-HCT Data

X-linked lymphoproliferative syndrome, also known as XLP or Duncan’s syndrome, is a rare inherited immunodeficiency. It is characterized by severe immune dysregulation, which generally manifests as an exaggerated immune response to infection. XLP belongs to the group of familial hemophagocytic lymphohistiocytosis syndromes. Patients typically present in childhood or early adolescence, often following infection with Epstein-Barr virus (which causes what is commonly known as “mono,” or infectious mononucleosis); up to 90% of XLP patients are seropositive for Epstein-Barr virus.¹ Following the response to the pathogen, the exaggerated proliferation of T-cells, B-cells, and macrophages may clinically manifest as hemophagocytic lymphohistiocytosis (HLH), dysgammaglobulinemia, and/or lymphoma.

XLP is divided into two specific types that are characterized by their clinical presentation and associated genetic abnormalities. XLP1 is defined by the *SH2D1A* mutation, which affects the signaling lymphocyte activation molecule (SLAM)-associated protein (SAP). XLP1 patients are more likely to present with fulminant infectious mononucleosis (FIM) and/or HLH following EBV, dysgammaglobulinemia, and/or lymphoma. Mutations in *BIRC4*, also known as x-linked apoptosis inhibitor protein (XIAP), define XLP2. Patients with XLP2 tend to present with colitis and/or splenomegaly; they may also present

following EBV infection with or without subsequent HLH. The common presentation of HLH following EBV suggests there may be a functional or molecular link between the SAP and XIAP proteins.²

This form must be completed for all recipients randomized to the Comprehensive Report Form (CRF) track whose primary disease is reported on Form 2400, question 357, as “disorders of the immune system” and question 628 as X-Linked Lymphoproliferative Syndrome. The X-Linked Lymphoproliferative Syndrome Post-HCT Data Form (Form 2134) must be completed in conjunction with each Post-HCT follow-up form (Forms 2100, 2200, 2300) completed. The form is designed to capture specific data occurring within the timeframe of each reporting period (i.e., between day 0 and day 100 for Form 2100, between day 100 and the six-month date of contact for Form 2200, between the date of contact for the six-month follow up and the date of contact for the one-year follow up for Form 2200, etc.).

¹Sumegi J, Huang D, Lanyi A, et al. Correlation of mutations of the SH2D1A gene and Epstein-Barr virus infection with clinical phenotype and outcome in X-linked lymphoproliferative disease. *Blood*, 2000;96(9):3118-25.

²Schmid JP, Canioni D, Moshous D, et al. Clinical similarities and differences of patients with X-linked lymphoproliferative syndrome type 1 (XLP-1/SAP deficiency) versus type 2 (XLP-2/XIAP deficiency). *Blood*, 2011;117(5):1522-9.

Key Fields

Accuracy of the Key Fields is essential for ensuring that:

- Data are being reported for the correct recipient.
- Outcomes data accurately reflects appropriate transplant type and product for each transplant center.
- Data are being shared with the correct donor center, cord blood bank, cooperative registry, or other agency.

The Key Fields precede the form body and are automatically populated in the FormsNet3SM application based on information provided on the CRID Assignment Form 2804. If errors are noted in the key fields, correct Form 2804 and then review it for accuracy. After Form 2804 has been corrected, verify data has been updated on all completed forms. If the data has not been updated automatically, centers will need to reprocess the completed forms to correct the key field data. If errors are noted in key fields for second or subsequent transplants, contact your CRC to make any necessary corrections to the transplant or product type. Transplant and product type will not be automatically populated on product or donor specific forms (Forms 2004, 2005, and 2006) and will need to be manually reported.

Disease Assessment Since the Date of Last Report

Question 1: Did the recipient have lymphoma at the time of HCT?

XLP is associated with a higher incidence of lymphoma, which may be secondary to EBV infection; however, not all lymphomas in the setting of XLP exhibit EBV clonality.

There is speculation that lymphoma risk is increased secondary to aberrant invariant natural killer T-cell (iNKT), NK, and T-cell cytotoxic function. The majority of lymphomas seen in XLP patients are T-cell lymphomas.

Specify if the patient had lymphoma at the time of transplant. If “yes,” continue with question 3; if “no,” continue with question 2.

Question 2: Did the recipient develop lymphoma or have persistent disease since the date of last report?

Indicate if the patient developed lymphoma during the reporting period or had persistent lymphoma carrying over from a previous reporting period. If “yes,” continue with question 3. If “no,” continue with question 4.

Question 3: Specify current status of lymphoma

Report the status of the patient’s lymphoma at last assessment during the reporting period. Disease response criteria are defined in Table 1 below.

Table 1. Lymphoma disease response definitions

Disease response	Definition
Complete remission (CR)	Complete disappearance of all known disease for ≥ 4 weeks.
Partial remission (PR)	$\geq 50\%$ reduction in greatest diameter of all sites of known disease <u>and</u> no new sites of disease.
Stable disease (SD)	$< 50\%$ reduction in greatest diameter of all sites of known disease.
Progressive disease (PD)	Increase in size of known disease <u>or</u> new sites of disease.
Not assessed	No assessment of patient’s disease during reporting period; this would indicate an absence of radiology or physical examination.
Unknown	Disease assessment was performed but is insufficient to determine disease status <u>or</u> results of evaluation(s) unknown <u>or</u> it is unknown if evaluations were performed.

Question 4: Did colitis persist or develop since the date of the last report?

Colitis refers to inflammation of the large intestine, often manifesting as diarrhea, abdominal pain and bloating, and melena (black “tarry” feces) or hematochezia (passage of fresh blood in feces).

Specify if the patient had colitis develop during the reporting period or persist from a previous reporting period. If “yes,” continue with question 5. If “no” or “unknown,” continue with question 7.

Question 5: What is the status of colitis?

Specify if colitis was active at the last assessment during the reporting period.

Question 6: Was the recipient receiving therapy for colitis?

Indicate if the patient received treatment for colitis at any time during the reporting period.

Question 7: Did vasculitis persist or develop since the date of the last report?

Vasculitis refers to inflammation of the vasculature (blood vessels), including both veins and arteries. Vasculitis may impact blood vessels of any size, from capillaries and arterioles to the great truncal vessels. It is typically caused by autoimmunity. If “yes,” continue with question 8. If “no” or “unknown,” continue with question 18.

Question 8: Central nervous system

CNS vasculitis refers to inflammation of the vasculature of the brain and/or spinal cord.

Specify if the patient had CNS vasculitis develop during the reporting period or persist from a previous reporting period. If “yes,” continue with question 9. If “no,” continue with question 11.

Question 9: What is the status of the CNS vasculitis?

Specify if CNS vasculitis was active at the last assessment during the reporting period.

Question 10: Was the recipient receiving therapy for CNS vasculitis?

Indicate if the patient received treatment for CNS vasculitis at any time during the reporting period.

Question 11: Pulmonary system

Pulmonary vasculitis involves inflammation of pulmonary vasculature. This can range from the great vessels, such as the pulmonary arteries, to the small alveolar capillaries.

Specify if the patient had pulmonary vasculitis develop during the reporting period or persist from a previous reporting period. If “yes,” continue with question 12. If “no,” continue with question 14.

Question 12: What is the status of the pulmonary vasculitis?

Specify if pulmonary vasculitis was active at the last assessment during the reporting period.

Question 13: Was the recipient receiving therapy for pulmonary vasculitis?

Indicate if the patient received treatment for pulmonary vasculitis at any time during the reporting period.

Questions 14-15: Other vasculitis involvement

Indicate if the patient had other vasculitis involvement. Specify involvement in question 15.

Question 16: What is the status of other vasculitis?

Specify if other vasculitis was active at the last assessment during the reporting period.

Question 17: Was the recipient receiving therapy for other vasculitis?

Indicate if the patient received treatment for other vasculitis at any time during the reporting period.

Question 18: Did the recipient have hemophagocytic lymphohistiocytosis (HLH) prior to transplant or did it present since the date of last report?

HLH is an abnormal proliferation of macrophages and histiocytes that leads to the phagocytosis of healthy circulating blood cells.

Indicate if the patient had HLH prior to transplant or developed HLH during the reporting period. If “yes,” continue with question 19. If “no,” continue with question 20.

If the recipient had HLH in the previous reporting period, but there was no evidence of HLH during the current reporting period, select “no.”

Question 19: Specify the status of the HLH disease since the date of last report

Specify if HLH was active or inactive (quiescent) at the last assessment during the reporting period.

Current Assessment of Immunologic Function Post-HCT

Question 20: Did the recipient receive supplemental intravenous immunoglobulins (IVIG)?

IVIG is a product made from pooled human plasma that primarily contains IgG. It is used to provide immune-deficient recipients with antibody function to prevent infection.

Indicate whether the recipient received IVIG during the reporting period. If “yes,” continue with question 21. If “no,” continue with question 22.

Question 21: Was therapy ongoing within three months of immunoglobulin testing?

Indicate whether the recipient received IVIG within three months prior to the immunoglobulin testing done during the reporting period. If IVIG was given within three

months of the immunoglobulin testing, the IgG level would not represent the recipient's native IgG. If "yes," continue with question 24. If "no," continue with question 22.

Questions 22-23: IgG

Indicate whether IgG level was "known" or "unknown" during the reporting period. If "known," report the laboratory value and unit of measure in question 23; if multiple tests were done, report the latest. If "unknown," continue with question 24.

Questions 24-25: IgM

Indicate whether IgM level was "known" or "unknown" during the reporting period. If "known," report the laboratory value and unit of measure in question 25; if multiple tests were done, report the latest. If "unknown," continue with question 26.

Questions 26-27: IgA

Indicate whether IgA level was "known" or "unknown" during the reporting period. If "known," report the laboratory value and unit of measure in question 27; if multiple tests were done, report the latest. If "unknown," continue with question 28.

Questions 28-29: IgE

Indicate whether IgE level was "known" or "unknown" during the reporting period. If "known," report the laboratory value in question 29; if multiple tests were done, report the latest. If "unknown," continue with question 30.

Question 30: NK cell function

Natural killer (NK) cells are cytotoxic lymphocytes implicated in viral response and tumor immunosurveillance. Patients with XLP often have normal numbers of NK cells, but the cells have functional defects. Indicate if the patient's immune studies revealed absent ($\leq 10\%$ lower limit of normal), decreased (11-50% lower limit of normal), or normal quantity of NK cells ($> 50\%$ lower limit of normal); if multiple NK studies were performed during the reporting period, report the latest results. If NK cell function was not assessed during the reporting period, indicate "unknown."

Laboratory Studies at the Time of Evaluation for This Reporting Period

Questions 31-32: Serum ferritin

Indicate whether serum ferritin level was "known" or "unknown" during the reporting period. If "known," report the value and unit of measure documented on the laboratory report in question 32. If there are multiple values from the reporting period, report the latest. If "unknown," continue with question 33.

Questions 33-34: Soluble interleukin-2 receptor (sIL-2R)

Indicate whether soluble interleukin-2 receptor levels were "known" or "unknown" during the reporting period. If "known," report the value and unit of measure documented on

the laboratory report in question 34. If there are multiple values from the reporting period, report the latest. If “unknown,” continue with question 35.

Questions 35-36: Triglycerides

Indicate whether triglyceride levels were “known” or “unknown” during the reporting period. If “known,” report the value and unit of measure documented on the laboratory report in question 36. If there are multiple values from the reporting period, report the latest. If “unknown,” continue with question 37.

Questions 37-38: Fibrinogen antigen assay (factor 1; fibrinogen activity; functional fibrinogen; fibrinogen antigen)

Indicate whether fibrinogen antigen levels were “known” or “unknown” during the reporting period. If “known,” report the value and unit of measure documented on the laboratory report in question 38. If there are multiple values from the reporting period, report the latest. If “unknown,” continue with question 39.

Question 39: Bone marrow aspirate/biopsy evidence of hemophagocytosis

Bone marrow aspirate and biopsy evidence of hemophagocytosis typically includes hypercellularity with markedly increased histiocytes and cytotoxic T-cells. Indicate if the pathologist interpretation of the marrow indicated the presence or absence of findings consistent with hemophagocytosis. If multiple evaluations were done during the reporting period, report the data from the latest. If bone marrow evaluation was not performed during the reporting period, indicate “not done.”

Questions 40-41: Specify the cerebrospinal fluid (CSF) findings

Indicate if protein and WBC count were elevated or normal in questions 40 and 41, respectively. If multiple evaluations were done during the reporting period, report the data from the latest. If CSF evaluation was not performed during the reporting period, indicate “not done.”

Signature

The FormsNet3SM application will automatically populate the signature data fields, including name and email address of person completing the form and date upon submission of the form.