

## 2046: Fungal Infection Pre-Infusion Data

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Fungal infections are significant opportunistic infections affecting transplant patients. Because these infections are quite serious, it is important to collect additional information on them. The Fungal Infection Pre-Infusion Data Form (Form 2046) captures information regarding the diagnosis, treatment, and response to treatment of any proven or suspected fungal infections diagnosed prior to receiving a HCT or cellular therapy. This form must be completed when one of the fungal infections listed below has been reported on the Baseline Form (Form 2000). One form will be completed for each applicable infection reported.

The following infections will cause a Fungal Infection Pre-Infusion Data Form (Form 2046) to come due when reported on the Baseline Form (Form 2000):

- *Aspergillus flavus*
- *Aspergillus fumigatus*
- *Aspergillus niger*
- *Aspergillus*, NOS
- *Aspergillus terreus*
- *Aspergillus ustus*
- *Blastomyces* (dermatitidis)
- *Candida albicans*
- *Candida non-albicans*
- *Cryptococcus gattii*
- *Cryptococcus neoformans*
- *Fusarium* (all species)
- *Histoplasma* (capsulatum)
- *Mucorales* (all species)
- *Rhizopus* (all species)
- *Scedosporium* (all species)
- *Zygomycetes*, NOS
- Suspected fungal infection

For reference, definitions of some common terms concerning fungal infections are provided below. These definitions are for clarification only and should not be considered to be reporting criteria or instructions.

**Fungemia:** the presence of fungus (mold or yeasts) in blood cultures.

**Proven invasive fungal infections:** based on EORTC published recommendations<sup>1</sup> as follows:

A. Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage (molds) or showing encapsulated budding yeasts or *Candida* species showing pseudohyphae or true hyphae (yeasts); or

B. Cultures of specimens obtained by a sterile procedure from a normally sterile site (excludes bronchial

lavage, sinus specimen, and urine) with clinical or radiologic evidence of abnormality growing mold, 'black yeast', or yeast.

Probable invasive fungal infections: based on EORTC published recommendations<sup>1</sup> requires presence of one each of host factors, clinical features, and mycological features:

#### A. Host Factors

1. Receipt of allogeneic HCT.
2. Treatment with steroids of at least 0.3mg/kg/day prednisone equivalent for 3 weeks or longer.
3. Treatment with T-cell immunosuppressants (cyclosporine, tacrolimus), monoclonal antibodies (alemtuzumab), or nucleoside analogues (fludarabine) in the past 90 days.

#### B. Clinical Features

1. Lower respiratory tract disease includes CT findings of one of the following:
  - a. dense, well-circumscribed lesions with or without a halo;
  - b. air-crescent sign; or
  - c. cavity.
2. Tracheobronchitis with evidence of ulceration, nodule, pseudomembrane, plaque, or eschar on bronchoscopy.
3. Sinonasal infection with; CT documenting acute sinusitis and at least one of the following:
  - a. acute localized pain (including radiation to the eye);
  - b. nasal ulceration with black eschar; or
  - c. bone destruction of the sinuses.

#### C. Mycological Features

1. Direct: Fungal elements of mold or culture of specific mold from sputum, bronchoalveolar lavage, bronchial brushings, or sinus aspirate.
2. Indirect: Galactomannan antigen detected in serum, plasma, bronchial lavage fluid, or cerebrospinal fluid or Beta-D-glucan detected in serum.

Disseminated infections with Histoplasmosis, Blastomycosis, or Coccidiomycosis:

- A. Culture of any of these organisms from an affected site or from the blood.
- B. Histopathology or direct microscopic demonstration of the appearance characteristic of these dimorphic (can exist in both a yeast and mold [hyphae] form based on external conditions) fungi;
- C. Demonstration of coccidioidal antibody in CSF or a 2-dilution rise in 2 consecutive blood samples in the appropriate setting; or
- D. Presence of a host factor (see above) plus an appropriate clinical picture with mycological evidence such as a positive *Histoplasma* antigen test from urine, blood, or cerebrospinal fluid.

**Disseminated *Cryptococcus*:** cryptococcal antigen detected in the cerebrospinal fluid.

## Links to Form Sections

[Q1-25: Infection Episode](#)

[Q26-31: Treatment of Infection](#)

<sup>1</sup> *Clin Infect Dis.* 2008 June 15; 46(12): 1813–1821

## Manual Updates

Sections of the Forms Instruction Manual are frequently updated. The most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.

If you need to reference the historical Manual Change History for this form, please reference the retired manual section on the [Retired Forms Manuals](#) webpage.

Date	Manual Section	Add/Remove/Modify	Description
9/10/2020	2046: Fungal Infection Pre-Infusion Data	Add	Red warning box added to question 31 to explain the “unknown” option should never be used: <i>The “Unknown” option should never be used to report the status of the infection. The options on the form will be revised with the next revision of this form.</i>
8/25/2020	2046: Fungal Infection Pre-Infusion Data	Add	Instruction added on when to use the “Unknown” option for the diagnostic methods of assessment in questions 3-25: <i>Methods of Assessment - A fungal infection may be identified by multiple assessments near the time of diagnosis. A description of each method of assessment is provided below. Report “Yes” for all assessments which were positive for signs of the fungal infection being reported on this form. Report “no” for assessments which were never performed or were never considered to be positive for the fungal infection being reported on this form. If the significance of the test result is not clear, obtain documentation from the recipient’s physician confirming whether the assessment was considered positive. Report “No” for assessments with results which are determined to be equivocal or indeterminate. The “Unknown” option should be used sparingly and only when there is no information on how the fungal infection was diagnosed.</i>
8/25/2020	2046: Fungal Infection Pre-Infusion Data	Add	Clarification added to question 26 on when to report fungal prophylaxis as treatment: <i>Report “Yes” if the recipient received any antifungal treatment from seven days prior to the date of diagnosis (refer to question two) through the day of infusion (Day 0 for HCT or cellular therapy). If the recipient did not receive any antifungal therapy during this time frame, report “No” and go to question 31. If the dose of fungal prophylaxis was increased to a therapeutic dose during the specified time window (seven days prior to the diagnosis date through the day of infusion), report “Yes.”</i>

5/1/ 18	2046: Fungal Infection Pre- Infusion Data	Modify	Version 2 of the 2046: Fungal Infection Pre-Infusion Data section of the Forms Instructions Manual released. Version 2 corresponds to revision 5 of the Form 2046.
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*Last modified: Sep 11, 2020*

# Q1-25: Infection Episode

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## Question 1: Organism

This field is auto-populated to match the fungus reported on the Baseline Form (Form 2000). Review the value to ensure it is accurate. A Fungal Infection Pre-Infusion Data Form will come due for each applicable infection reported on the Baseline Form (Form 2000) so it is imperative to identify the fungal infection to which this form will correspond.

If multiple infections of the same fungus are reported during the same reporting period, the center must complete a Fungal Infection Pre-Infusion Data Form (Form 2046) for each infection instance, or episode, reported.

## Question 2: Date of Infection Diagnosis

This field is auto-populated to match the date reported on the [Baseline Form](#). Review the value to ensure it is accurate. See the Baseline section of the manual for further instructions on reporting the date of diagnosis.

If multiple infections of the same fungal organism are reported in the same reporting period, the diagnosis date in question two will clarify for which infection episode the form is being completed.

## Question 3-25: Diagnostic Testing

Report all testing that had positive results and which indicated the fungal infection was present. Do not report negative or indeterminate / equivocal testing in this section. As indicated in the instructions for question one, if the recipient was diagnosed with multiple fungal infections prior to infusion, multiple Fungal Infection Pre-Infusion Data Forms must be completed (one for each organism). Ensure the testing reported in these questions only reflects the assessments used to identify the infection / organism being reported on this form. For reporting purposes, only report methods performed and samples collected (or sites assessed for radiological findings) within 14 days (+ / -) of the diagnosis date reported in question two.

[Links to specific instructions](#)

[Methods of Assessment](#)

[Site / Sample Source](#)

### Methods of Assessment:

A fungal infection may be identified by multiple assessments near the time of diagnosis. A description of each method of assessment is provided below. Report “Yes” for all assessments which were positive for signs of the fungal infection being reported on this form. Report “no” for assessments which were never performed or were never considered to be positive for the fungal infection being reported on this form. If the significance of the test result is not clear, obtain documentation from the recipient’s physician confirming whether the assessment was considered positive. Report “No” for assessments with results which are determined to be equivocal or indeterminate.

The “Unknown” option should be used sparingly and only when there is no information on how the fungal infection was diagnosed.

**Radiographic Findings:** includes all imaging assessments. Examples include x-ray, CT scan, PET scan, and MRI. These assessments are capable of identifying the presence of a fungal infection, but cannot identify specific organisms. Refer to the clinical interpretation of an imaging assessment to determine whether the test was considered positive for the infection being reported. If the provider’s notes do not specify whether the test was positive, obtain documentation from the physician clarifying how the assessment should be reported.

**Pathology:** samples obtained from the recipient via biopsy or fine needle aspirate are evaluated via microscopy without incubation. Presence and classification is assessed solely by microscopy. If a sample is grown in culture or stained, report these test methods under the more specific options below. Generally, the results / interpretation section of the pathology report will specify whether the assessment was positive or negative for signs of a fungal infection. If this is not the case, refer to the provider notes and obtain clarification from the recipient’s physician if both the pathology report and provider notes are not clear.

**Culture:** samples taken from the recipient are incubated in media supporting fungal growth. Presence of infection is assessed by colony formation / growth and classification is done via microscopy following incubation. Results are typically found in the microbiology / virology section of the medical record. The culture report will document whether growth is detected (positive) or not detected (negative). Staining may also be performed to classify the infection following incubation. Report the results of any staining techniques in the more specific methods below.

**KOH / Calcofluor / Giemsa stain:** samples taken from the recipient (usually fluids such as sputum or wash samples) are exposed to a stain which binds to structures specific to fungal cells. The sample is evaluated via microscopy to determine whether stained cells are present (positive result) or absent (negative result).

**KOH:** potassium hydroxide also referred to a “fungal wet prep.”

**Calcofluor:** white stain which binds to fungal cell walls causing them to appear bright green / blue.

**Giemsa stain:** often used to identify *Histoplasma*.

**Galactomannan Assay:** a sample (i.e., serum, bronchial lavage, bronchial wash or CSF) taken from the recipient are exposed to galactomannan-specific antibodies followed by antibody-specific enzymes (ELISA method). Galactomannan is a molecule specific to *Aspergillus*. The enzyme activity is quantified and the test is considered positive if the activity is above the upper limit of normal (as indicated on the test report). If the report is unclear regarding whether the result is considered positive, negative, or equivocal, contact your center’s laboratory to confirm.

**1,3-Beta-D-glucan (Fungitell) assay:** a sample (i.e., serum, bronchial lavage, bronchial wash or CSF) taken from the recipient is exposed to beta-d-glucan-specific antibodies followed by antibody-specific enzymes (ELISA method). Beta-d-glucan is a molecule found on a multiple fungi including *Candida* and *Aspergillus*. The enzyme activity is quantified and the test is considered positive if the activity is above the

upper limit of normal (as indicated on the test report). If the report is unclear regarding whether the result is considered positive, negative, or equivocal, contact your center's laboratory to confirm.

**PCR Assay:** samples taken from the recipient are manipulated using polymerase chain reaction techniques. Presence and classification of fungi are assessed by identifying DNA sequences unique to specific fungi. Reports can generally be found in the microbiology / virology section or the molecular pathology section of the medical record. The lab report will document whether an infection is detected (positive) or not detected (negative). If the report is unclear, contact your center's laboratory to confirm.

### Sites / Sample Source:

For each method of assessment which showed evidence of the fungal infection being reported, indicate every site or sample source where the infection was detected. Do not report sites yielding negative or indeterminate / equivocal results. Note the time window provided in the initial instructions for questions 2-35.

### Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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*Last modified: Dec 22, 2020*

## Q26-31: Treatment of Infection

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### Question 26: Did the recipient receive any therapy between 7 days prior to the date of infection diagnosis and the date of infusion?

Report “Yes” if the recipient received any antifungal treatment from seven days prior to the date of diagnosis (refer to question two) through the day of infusion (Day 0 for HCT or cellular therapy). If the recipient did not receive any antifungal therapy during this time frame, report “No” and go to question 31.

If the dose of fungal prophylaxis was increased to a therapeutic dose during the specific time window (seven days prior to the diagnosis date through the day of infusion), report “Yes.”

### Question 27-30: Antifungal Drugs

One instance of questions 27-30 must be completed for each drug administered during the time window indicated in the instructions for question 26. For each drug given, indicate the specific drug in questions 27-28 and then specify the start date in questions 29-30. If the exact start date is not known, but the year the drug was started is known, refer to [General Instructions, General Guidelines for Completing Forms](#), for information about reporting partial or unknown dates. If an estimated date is reported, check the “Date Estimated” box next to question 30.

If an antifungal drug was started greater than seven days prior to the date of infection diagnosis and was continued to within seven days of the diagnosis date, report seven days prior to the diagnosis date as the date the medication was started and check the “Date estimated” box next to question 30.

### Antifungal Drug Reporting Scenarios:

A. If a patient was diagnosed with *Aspergillus fumigatus* on 1/15/2016, go back to 1/8 to determine the medications the patient was receiving. If the patient is on drug “X” (e.g., fluconazole) on 1/8 but you also note the patient was receiving the drug on a prior visit on 1/3, please record the start date for drug “X” as 1/8 and mark “Date estimated”.

B. If the patient was diagnosed with *Aspergillus fumigatus* on 1/15/2016, and it is noted in a clinic note dated 1/19 that the patient was started on drug “Y” (e.g., posaconazole) “a few days ago” on the form, please record the start date for drug “Y” as 1/19 and mark “Date estimated”.

### Question 31: What was the status of the infection?

Report the status of the fungal infection immediately prior to the start of the preparative regimen (or infusion if no preparative regimen was given) based on the primary care provider’s clinical judgement. If the status of the infection is not documented in the primary care provider’s note summarizing their last evaluation prior to the start of the preparative regimen, obtain documentation from the provider indicating which option to report. For reporting purposes, centers should indicate “Ongoing” if the infection is still present but cannot be considered improved or resolved.



The “Unknown” option should never be used to report the status of the infection. The options on the form will be revised with the next revision of this form.

**Section Updates:**

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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*Last modified: Dec 22, 2020*