

**American College of Radiology  
ACR Appropriateness Criteria®  
Acute Respiratory Illness in Immunocompromised Patients**

**Variant 1:** Acute respiratory illness in immunocompromised patients. Cough, dyspnea, chest pain, or fever. Initial imaging.

| Procedure                              | Appropriateness Category | Relative Radiation Level |
|--|--------------------------|--------------------------|
| Radiography chest                      | Usually Appropriate      | ⊕                        |
| CT chest with IV contrast              | May Be Appropriate       | ⊕⊕⊕                      |
| CT chest without IV contrast           | May Be Appropriate       | ⊕⊕⊕                      |
| MRI chest without and with IV contrast | Usually Not Appropriate  | ○                        |
| MRI chest without IV contrast          | Usually Not Appropriate  | ○                        |
| CT chest without and with IV contrast  | Usually Not Appropriate  | ⊕⊕⊕                      |
| FDG-PET/CT skull base to mid-thigh     | Usually Not Appropriate  | ⊕⊕⊕⊕                     |

**Variant 2:** Acute respiratory illness in immunocompromised patients. Normal, equivocal, or nonspecific chest radiograph. Next imaging study.

| Procedure                              | Appropriateness Category | Relative Radiation Level |
|--|--------------------------|--------------------------|
| CT chest without IV contrast           | Usually Appropriate      | ⊕⊕⊕                      |
| CT chest with IV contrast              | May Be Appropriate       | ⊕⊕⊕                      |
| MRI chest without and with IV contrast | Usually Not Appropriate  | ○                        |
| MRI chest without IV contrast          | Usually Not Appropriate  | ○                        |
| CT chest without and with IV contrast  | Usually Not Appropriate  | ⊕⊕⊕                      |
| FDG-PET/CT skull base to mid-thigh     | Usually Not Appropriate  | ⊕⊕⊕⊕                     |

**Variant 3:** Acute respiratory illness in immunocompromised patients. Abnormal chest radiograph, multiple, diffuse, or confluent opacities. Next imaging study.

| Procedure                                | Appropriateness Category | Relative Radiation Level |
|--|--------------------------|--------------------------|
| CT chest without IV contrast             | Usually Appropriate      | ⊕⊕⊕                      |
| CT chest with IV contrast                | May Be Appropriate       | ⊕⊕⊕                      |
| Image-guided transthoracic needle biopsy | May Be Appropriate       | Varies                   |
| MRI chest without and with IV contrast   | May Be Appropriate       | ○                        |
| MRI chest without IV contrast            | May Be Appropriate       | ○                        |
| FDG-PET/CT skull base to mid-thigh       | Usually Not Appropriate  | ⊕⊕⊕⊕                     |
| CT chest without and with IV contrast    | Usually Not Appropriate  | ⊕⊕⊕                      |

**Variant 4:****Acute respiratory illness in immunocompromised patients. Abnormal chest radiograph, noninfectious disease suspected. Next imaging study.**

| <b>Procedure</b>                         | <b>Appropriateness Category</b> | <b>Relative Radiation Level</b> |
|--|---------------------------------|---------------------------------|
| CT chest without IV contrast             | Usually Appropriate             | ☼☼☼                             |
| CT chest with IV contrast                | May Be Appropriate              | ☼☼☼                             |
| FDG-PET/CT skull base to mid-thigh       | May Be Appropriate              | ☼☼☼☼                            |
| Image-guided transthoracic needle biopsy | May Be Appropriate              | Varies                          |
| MRI chest without and with IV contrast   | May Be Appropriate              | ○                               |
| MRI chest without IV contrast            | May Be Appropriate              | ○                               |
| CT chest without and with IV contrast    | Usually Not Appropriate         | ☼☼☼                             |

# ACUTE RESPIRATORY ILLNESS IN IMMUNOCOMPROMISED PATIENTS

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## **Summary of Literature Review**

### **Introduction/Background**

The immunocompromised patient suffering from an acute respiratory illness (ARI) poses a significant challenge to both clinicians and imagers. The number of immunocompromised patients in our health care system continues to rise with advances in medical techniques, including solid organ and stem cell transplantation, chemotherapy, and immunomodulatory therapy, along with the continued presence of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). Other causes of immunosuppression include hematologic malignancies, congenital immunodeficiency syndromes, and mildly impaired host states, such as diabetes mellitus, alcoholism, and chronic obstructive pulmonary disease. Given the myriad of pathogens that can infect immunocompromised individuals, identifying the specific organism or organisms causing the lung disease can be elusive. Moreover, immunocompromised patients are often placed on prophylactic or empiric antimicrobial therapy, which further complicates diagnostic evaluation. Knowledge of the specific mechanism of the patient's immune system defect, as well as the time course from its occurrence to the onset of symptoms, often aids in establishing a definitive diagnosis or specific differential diagnosis.

ARI constitutes a group of signs and symptoms that develop over a brief interval (hours to weeks), some of which are constitutional (eg, fever, chills, weight loss), and some of which are organ specific (eg, cough, shortness of breath, chest pain). The respiratory system is frequently involved in complications encountered in immunocompromised states. Infections comprise nearly 75% of all pulmonary complications in immunosuppressed patients, and many progress along a rapid and potentially fatal course [1,2]. Noninfectious causes should also be considered when an immunocompromised patient presents with ARI, including such entities as pulmonary edema, drug-induced lung disease, atelectasis, malignancy, radiation-induced lung disease, pulmonary hemorrhage, diffuse alveolar damage, organizing pneumonia, lung transplant rejection, and pulmonary thromboembolic disease [2].

### **Discussion of Procedures by Variant**

#### **Variant 1: Acute respiratory illness in immunocompromised patients. Cough, dyspnea, chest pain, or fever. Initial imaging.**

##### **Radiography Chest**

Chest radiography is the initial imaging modality of choice for the diagnostic assessment of immunocompromised patients presenting with ARI [3]. The chest radiograph typically shows the presence and extent of pulmonary infection, although radiographs can be normal in up to 10% of patients with proven disease [4]. The pattern and distribution of abnormalities on the chest radiograph, along with changes on serial radiographic examinations, can aid in formulating a differential diagnosis. Chest radiographs may also show the presence of complications of infectious pneumonia, such as empyema or abscess [3,5]. The well-known limitations of chest radiography; however, are the lack of specificity with regard to specific pathogens and overall low sensitivity for detecting subtle abnormalities in immunocompromised patients with symptomatic disease [1].

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### **CT Chest**

Chest CT plays an important role in the diagnostic workup of immunocompromised patients with ARI. Chest CT is more sensitive than chest radiography for detecting subtle pulmonary parenchymal abnormalities [3]. In addition, because of its superior spatial resolution and cross-sectional display of findings, CT provides enhanced characterization of pulmonary parenchymal abnormalities. However, in most clinical scenarios, CT should not be the initial imaging study performed in the evaluation of these patients. Even in immunosuppressed patients, bacterial pneumonia is still the most likely etiology of pulmonary infection [2]. Further radiologic imaging may not be needed unless the patient's clinical picture worsens or fails to improve with therapy.

### **MRI Chest**

There is no relevant literature regarding the use of thoracic MRI in the initial imaging evaluation of ARI in immunocompromised patients. However, MRI should not be the initial imaging study performed in the evaluation of these patients. Even in immunosuppressed patients, bacterial pneumonia is still the most likely etiology of pulmonary infection [2]. Further radiologic imaging may not be needed unless the patient's clinical picture worsens or fails to improve with therapy.

### **FDG-PET/CT Skull Base to Mid-Thigh**

There is no relevant literature regarding the use of PET using the tracer fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)/CT in the initial imaging evaluation of ARI in immunocompromised patients. Accordingly, FDG-PET/CT should not be the initial imaging study performed in the evaluation of these patients. Even in immunosuppressed patients, bacterial pneumonia is still the most likely etiology of pulmonary infection [2]. Further radiologic imaging may not be needed unless the patient's clinical picture worsens or fails to improve with therapy.

### **Variant 2: Acute respiratory illness in immunocompromised patients. Normal, equivocal, or nonspecific chest radiograph. Next imaging study.**

#### **CT Chest**

Chest radiographs in immunocompromised patients with ARI may be equivocal or even normal despite a high suspicion for pulmonary disease [1]. In this setting, chest CT has been shown to confer a distinct improvement in sensitivity for detecting subtle parenchymal abnormalities [4]. In one study, CT performed in febrile neutropenic patients with normal chest radiographs showed pneumonia in 60% of cases at least 5 days before the abnormalities became visible on chest radiographs [6]. In another study in patients with pulmonary tuberculosis, 11% of HIV-positive patients had normal chest radiographs [7]. Similarly, up to one-third of patients infected with *Pneumocystis jirovecii* may have normal chest radiographs [8]. In addition, because of its superior spatial resolution and cross-sectional display of findings, CT provides enhanced characterization of pulmonary parenchymal abnormalities, which is often helpful in formulating a differential diagnosis.

#### **MRI Chest**

CT is preferable to MRI in immunocompromised patients with ARI who have normal, equivocal, or nonspecific chest radiographs. CT remains superior to MRI in the detection and characterization of pulmonary parenchymal infection [9,10]. However, MRI can be considered as an alternative imaging modality, albeit less sensitive. Moreover, once a diagnosis of infection has been established, MRI can be used as a reasonable alternative to CT for follow-up of parenchymal disease [10-12].

#### **FDG-PET/CT Skull Base to Mid-Thigh**

There is no relevant literature regarding the use of FDG-PET/CT in the evaluation of immunocompromised patients with ARI who have normal, equivocal, or nonspecific chest radiographs. Therefore, FDG-PET/CT should be rarely utilized in this clinical scenario. Furthermore, many pulmonary infections typically have high FDG uptake and, thus, may be mistaken for malignancy [13].

### **Variant 3: Acute respiratory illness in immunocompromised patients. Abnormal chest radiograph, multiple, diffuse, or confluent opacities. Next imaging study.**

#### **CT Chest**

Further investigation with CT is warranted in immunocompromised patients with ARI who have chest radiographs showing multiple, diffuse, or confluent opacities. In this patient population, multiple or diffuse opacities or nodules have a higher probability of representing an atypical opportunistic infection rather than community-acquired bacterial pneumonia [4,14]. CT provides enhanced characterization of pulmonary parenchymal abnormalities that are due to its superior spatial resolution and cross-sectional display of findings. Consequently, certain infections can be identified on CT with a higher degree of confidence than on radiographs

[15-17]. Common CT patterns of disease in patients with ARI include pulmonary nodules, tree-in-bud pattern, lung consolidation, and ground-glass opacities [4]. These patterns have been described in the literature to represent the appearances of a number of pulmonary infections in the immunocompromised host, including *P. jirovecii* [8,15,16], invasive pulmonary aspergillosis [15,17-20], mucormycosis [21,22], candidiasis [22,23], cytomegalovirus pneumonia [15,24,25], human metapneumovirus [26-28], and mycobacterial pneumonias [29-32]. CT shows the detailed morphology of parenchymal opacities, as well as the pattern and distribution of disease. For example, in febrile patients having undergone recent stem cell transplantation, the ability of CT to detect halos of ground-glass opacity around pulmonary nodules is helpful in making the early presumptive diagnosis of invasive aspergillosis, thus prompting initiation of empiric antifungal therapy with improved prognosis [17,19]. Furthermore, CT may show the presence of infection complications, such as empyema or abscess that may not be visible on radiographs.

### **MRI Chest**

CT is preferable to MRI in immunocompromised patients with ARI who have chest radiographs showing multiple, diffuse, or confluent opacities. CT remains superior to MRI in the detection and characterization of pulmonary parenchymal infection [9,10]. However, when the aerated parenchyma is replaced by consolidation, nodules, or masses, MRI can be considered as an alternative imaging modality, albeit less sensitive. Recent studies have shown that MRI can be used for the diagnosis of pulmonary infection [9,12,33]. Newer pulse sequences on 3T scanners may further enhance the diagnostic performance of MRI [11,34,35]. Therefore, as technology continues to improve, MRI represents a promising imaging modality for the workup of immunocompromised patients with abnormal chest radiographs. Moreover, once a diagnosis of infection has been established, MRI can be used as a reasonable alternative to CT for follow-up of parenchymal disease [10-12].

### **FDG-PET/CT Skull Base to Mid-Thigh**

There is no relevant literature regarding the use of FDG-PET/CT in the evaluation of immunocompromised patients with ARI who have chest radiographs showing multiple, diffuse, or confluent opacities. Therefore, FDG-PET/CT should be rarely utilized in this clinical scenario. Furthermore, many pulmonary infections typically cause high FDG uptake and, thus, may be mistaken for malignancy [13].

### **Image-Guided Transthoracic Needle Biopsy**

Image-guided transthoracic needle biopsy may play a role in the identification of the specific organism(s) producing pulmonary parenchymal abnormalities in certain clinical scenarios of immunocompromised patients with ARI. Though the diagnostic yield of transthoracic biopsy in detecting infections is significantly less than in detecting malignancies, the underlying pathogen is identified a significant minority of the time, which allows for prompt and appropriate treatment of the infection in these vulnerable patients [36,37]. Transthoracic biopsy demonstrates the greatest value in the diagnosis of fungal infections, even in the presence of normal sputum and blood cultures [36,38,39]. Even if chest radiography reveals the parenchymal opacities, CT should typically still be performed prior to contemplating transthoracic needle biopsy, as certain lesions may be more amenable to bronchoscopic biopsy if they are in close proximity to the airways. If a CT-guided transthoracic biopsy is planned, the interventionalist can also use the preprocedural CT to determine the optimal patient position and biopsy route.

### **Variant 4: Acute respiratory illness in immunocompromised patients. Abnormal chest radiograph, noninfectious disease suspected. Next imaging study.**

#### **CT Chest**

Further investigation with CT is warranted in immunocompromised patients with ARI who have chest radiographs showing pulmonary parenchymal opacities but noninfectious disease is suspected. Immunosuppressed patients are susceptible to a variety of noninfectious pulmonary diseases. Because of its superior spatial resolution and cross-sectional display of findings, CT provides enhanced characterization of pulmonary parenchymal abnormalities, which may assist in formulating a differential diagnosis. Noninfectious causes of ARI in immunocompromised hosts include pulmonary edema, drug-induced lung disease, atelectasis, malignancy (including post-transplant lymphoproliferative disorder), radiation-induced lung disease, pulmonary hemorrhage, diffuse alveolar damage, organizing pneumonia, lung transplant rejection, graft-versus-host disease, and pulmonary thromboembolic disease [2]. For example, many chemotherapeutic and immunomodulatory agents may result in pulmonary toxicity [40]. CT is more sensitive than chest radiography in detecting drug-induced lung injury from agents such as bleomycin, busulfan, carmustine, and cyclophosphamide [40,41]. In patients with a history of pulmonary malignancy, recurrence of the primary tumor or development of lung metastases should always be considered when chest radiography shows nodular opacities; similarly, metastases from an

extrathoracic primary often manifest as nodules. An organizing pneumonia pattern of lung injury is a well-known complication in immunocompromised patients, particularly as a manifestation of lung transplant rejection and chronic graft-versus-host disease following allogeneic hematopoietic stem cell transplantation [42-44]. Finally, both malignancy and its treatment are risk factors for deep venous thrombosis, which may lead to pulmonary thromboemboli and pulmonary infarcts [45].

### **MRI Chest**

There is no relevant literature regarding the use of MRI in the evaluation of immunocompromised patients with ARI, abnormal chest radiographs, and suspicion of noninfectious disease. However, there may be certain clinical scenarios in which MRI can be used as a reasonable alternative to CT. Given that MRI can characterize infectious consolidations, nodules, and masses, it may depict similar findings in noninfectious conditions.

### **FDG-PET/CT Skull Base to Mid-Thigh**

FDG-PET/CT may occasionally be beneficial in the evaluation of immunocompromised patients with ARI, chest radiographs showing pulmonary parenchymal opacities, and clinical suspicion of noninfectious disease. In patients with a history of pulmonary malignancy, recurrence of the primary tumor or development of lung metastases should always be considered when chest radiography shows nodular opacities; similarly, metastases from an extrathoracic primary often manifest as nodules. However, FDG-PET/CT should be interpreted cautiously, as many pulmonary infections typically cause high FDG uptake and, thus, may be mistaken for malignancy [13]. Certain immunodeficient conditions, such as HIV/AIDS, render patients extremely susceptible to both malignancies and opportunistic infections. AIDS-defining malignancies that may manifest in the lungs include Kaposi sarcoma and non-Hodgkin lymphoma. With regard to these neoplasms, FDG-PET/CT may assist in the specific diagnosis, staging or restaging of disease, and monitoring of therapeutic response [46]. FDG-PET/CT is also an accurate diagnostic modality for the staging and follow-up of patients with post-transplant lymphoproliferative disorder [47]. For these and other clinical scenarios, FDG-PET/CT provides diagnostic information without requiring intravenous (IV) contrast and may be advantageous in patients with renal compromise that is due to chronic immunosuppressive therapy [47].

### **Image-Guided Transthoracic Needle Biopsy**

Image-guided transthoracic needle biopsy may play a role in the diagnosis of pulmonary disease in immunocompromised patients with ARI, chest radiographs showing pulmonary parenchymal abnormalities, and clinical suspicion of noninfectious disease. In a study of patients with known hematologic malignancy and undiagnosed parenchymal lesions, CT-guided transthoracic biopsy yielded a diagnosis of malignancy 63% of the time [48]. Malignancy may also be diagnosed in patients without a history of neoplastic disease, occurring in 10% of HIV patients with solitary pulmonary nodules [49]. Even in patients for whom infection is the primary diagnostic consideration for ARI, certain malignancies, such as lung cancer and post-transplant lymphoproliferative disorder, may occasionally be diagnosed [36,50]. Even if chest radiography shows the parenchymal opacities, CT should typically still be performed prior to contemplating transthoracic needle biopsy, as certain lesions may be more amenable to bronchoscopic biopsy if they are in close proximity to the airways. If a CT-guided transthoracic biopsy is planned, the interventionalist can also use the preprocedural CT to determine the optimal patient position and biopsy route.

### **Summary of Recommendations**

- **Variante 1:** Radiographs of the chest are usually appropriate for the initial imaging of immunocompromised patients with acute respiratory illness including cough, dyspnea, chest pain, or fever.
- **Variante 2:** CT chest without IV contrast is usually appropriate as the next imaging study for immunocompromised patients with acute respiratory illness who have had a normal, equivocal, or nonspecific chest radiograph.
- **Variante 3:** CT chest without IV contrast is usually appropriate as the next imaging study for immunocompromised patients with acute respiratory illness who have had a chest radiograph showing multiple, diffuse, or confluent opacities.
- **Variante 4:** CT chest without IV contrast is usually appropriate as the next imaging study for immunocompromised patients with acute respiratory illness who have had an abnormal chest radiograph but noninfectious disease is suspected.

## Supporting Documents

The evidence table, literature search, and appendix for this topic are available at <https://acsearch.acr.org/list>. The appendix includes the strength of evidence assessment and rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents go to [www.acr.org/ac](http://www.acr.org/ac).

## Appropriateness Category Names and Definitions

| Appropriateness Category Name     | Appropriateness Rating | Appropriateness Category Definition  |
|-----------------------------------|------------------------|--|
| Usually Appropriate               | 7, 8, or 9             | The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.  |
| May Be Appropriate                | 4, 5, or 6             | The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal. |
| May Be Appropriate (Disagreement) | 5                      | The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.                   |
| Usually Not Appropriate           | 1, 2, or 3             | The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.  |

## Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#) document [51].

| Relative Radiation Level Designations |                                     |   |
|---------------------------------------|-------------------------------------|---|
| Relative Radiation Level*             | Adult Effective Dose Estimate Range | Pediatric Effective Dose Estimate Range |
| ○                                     | 0 mSv                               | 0 mSv                                   |
| ⊕                                     | <0.1 mSv                            | <0.03 mSv                               |
| ⊕⊕                                    | 0.1-1 mSv                           | 0.03-0.3 mSv                            |
| ⊕⊕⊕                                   | 1-10 mSv                            | 0.3-3 mSv                               |
| ⊕⊕⊕⊕                                  | 10-30 mSv                           | 3-10 mSv                                |
| ⊕⊕⊕⊕⊕                                 | 30-100 mSv                          | 10-30 mSv                               |

\*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as “Varies”.

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.