

American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: Acute Respiratory Illness in Immunocompromised Patients

Variant 1: Cough, dyspnea, chest pain, fever.

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	9		☼
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Variant 2: Negative, equivocal, or nonspecific chest radiograph.

Radiologic Procedure	Rating	Comments	RRL*
CT chest without IV contrast	9		☼☼☼
CT chest with IV contrast	3	Consider this procedure if hemoptysis is present.	☼☼☼
CT chest without and with IV contrast	1		☼☼☼
Ga-67 scan lung	1	Consider this procedure if PJP is suspected.	☼☼☼☼
Tc-99m DTPA scan lung	1	Consider this procedure if PJP is suspected.	☼☼
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Variant 3: Positive chest radiograph, multiple, diffuse, or confluent opacities.

Radiologic Procedure	Rating	Comments	RRL*
CT chest without IV contrast	7		☼☼☼
Transthoracic needle biopsy	5	Consider this procedure if a serious opportunistic infection is suspected.	Varies
CT chest with IV contrast	3	Consider this procedure if hemoptysis is present.	☼☼☼
CT chest without and with IV contrast	1		☼☼☼
Ga-67 scan lung	1	Consider this procedure if PJP is suspected.	☼☼☼☼
Tc-99m DTPA scan lung	1	Consider this procedure if PJP is suspected.	☼☼
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Variant 4: Positive chest radiograph, noninfectious disease suspected.

Radiologic Procedure	Rating	Comments	RRL*
CT chest without IV contrast	8		☼☼☼☼
CT chest with IV contrast	5	Consider this procedure if neoplasm or pulmonary embolus is suspected. Consider this procedure if hemoptysis is present.	☼☼☼☼
Transthoracic needle biopsy	5	Consider this procedure if thoracic malignancy suspected.	Varies
CT chest without and with IV contrast	1		☼☼☼
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

ACUTE RESPIRATORY ILLNESS IN IMMUNOCOMPROMISED PATIENTS

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Summary of Literature Review

Introduction/Background

There are many causes of immunodeficiency likely to be encountered by today's physician. With advances in medical techniques such as solid organ and stem cell transplantation, cancer therapy, and immunosuppressive therapy, along with the continued presence of the human immunodeficiency virus (HIV), the number of immunocompromised patients in our health care system has increased in recent decades [1]. Other causes of immunosuppression seen in medicine today include hematologic malignancies, congenital immunodeficiency syndromes, and the mildly impaired host states, such as diabetes mellitus, advanced age, malnutrition, alcoholism, chronic debilitating illness, and chronic obstructive lung disease [2,3]. Determining the most likely pathogen causing pneumonia in these patients can be difficult given the diverse causes of immunosuppression. Based on the patient's underlying disease or related therapy, it helps to determine what major component of the immune system has been damaged (ie, T-cell, B-cell, phagocytosis, complement system, or splenic function). Knowledge of what immune defect has occurred, as well as the time course from its occurrence to the onset of patient symptoms, often aids in establishing a definitive diagnosis or more specific differential diagnosis [4-6].

Acute respiratory illness (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, and weight loss) and some of which are organ specific (eg, cough, shortness of breath, and chest pain). In immunocompromised individuals, the respiratory system is one of the most frequently involved organ systems that results in complications, often initially manifesting with symptoms of ARI. Of all pulmonary complications in patients with immunodeficiency, pulmonary infections comprise nearly 75%, many of which progress along a rapid and potentially fatal course [1,6]. Noninfectious causes of ARI in the immunocompromised population should also be considered, however, and include such entities as pulmonary edema, drug-induced lung disease, atelectasis, malignancy (including post-transplant lymphoproliferative disorder), radiation-induced lung disease, alveolar hemorrhage, diffuse alveolar damage, organizing pneumonia, rejection of lung transplantation, and thromboembolic disease [3,6].

Overview of Imaging Modalities

Despite modern advances in computed tomography (CT) technology, the chest radiograph remains the first-line modality in the diagnostic evaluation of immunocompromised patients presenting with ARI. The morphology and distribution of abnormalities on the chest radiograph, along with changes on serial radiographic examinations, can aid in arriving at a differential diagnosis. Chest radiographs also demonstrate the presence of complicating features of pneumonia, such as empyema or abscess [7]. The well-known shortcomings of the chest radiograph, however, are its lack of specificity with regard to actual pathogens and its overall low sensitivity for detectable abnormalities in immunosuppressed patients with symptomatic disease [1].

CT is more sensitive and specific than chest radiography for detecting subtle pulmonary findings. Although not recommended for the initial imaging evaluation of patients with ARI, the use of CT has been described in several scenarios regarding the immunocompromised host: to evaluate patients who are clinically symptomatic for ARI, but who have equivocal or normal chest radiographic findings; to better characterize abnormal but nonspecific chest radiograph findings; and to provide essential information for determining the appropriate method and site of lung biopsy [2]. Because the appearance and distribution of airspace abnormalities are better characterized with

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the improved resolution provided by CT, certain diseases such as *Pneumocystis jirovecii* pneumonia (PJP, previously known as *Pneumocystis carinii* pneumonia), invasive pulmonary aspergillosis, and *Cytomegalovirus* (CMV) can be identified on CT with a higher degree of confidence than they can on radiography [8-12]. Recognizing the CT patterns associated with these infections allows for the critical initiation of early empiric therapy, often based on a presumptive radiologic diagnosis, all the while waiting for more definitive microbiologic data, which may not be available for days or weeks [2,5].

Although chest radiography and chest CT are the mainstay imaging modalities in evaluating the immunocompromised host with ARI, nuclear scintigraphy using gallium-67 (Ga-67) or Tc-99m diethylenetriamine penta acetate (DTPA) radiotracers have quite specific but rarely used indications in this setting. Ga-67 can be used to help diagnose *Mycobacterium avium intracellulare*, *Mycobacterium tuberculosis*, and lymphoma based on increased radiotracer activity in hilar and mediastinal lymph nodes. However, this finding is nonspecific, and distinguishing between a malignant and infectious or inflammatory etiology may require a tissue diagnosis. Additionally, Ga-67 can be used to evaluate for the presence of PJP within the lungs in cases where conventional imaging has turned up normal or equivocal findings. Studies by Moser et al and Temeh et al showed gallium scintigraphy to be more sensitive and specific for the presence of PJP than both chest radiography [13] and chest CT [14] in acquired immune deficiency syndrome (AIDS) patients.

Discussion of Imaging Modalities by Variant

Variant 1: Cough, dyspnea, chest pain, fever

When immunocompromised patients present with symptoms of acute onset fever, cough, and shortness of breath, chest radiography should be the first radiologic examination performed [15]. The chest radiograph typically identifies pulmonary infection if present, although it can be normal in up to 10% of symptomatic patients with proven disease and up to 39% of AIDS patients with PJP [5]. Although the chest radiograph has been shown to be of little value in predicting the causative organisms of pulmonary infections, it remains useful in determining the extent of pulmonary disease and in screening for associated complications [15]. For patients with acute onset cough and fever or a single focal, segmental, or lobar airspace opacity on chest radiograph, bacterial pneumonia is the most likely etiology of pulmonary infection.

Fungal pneumonias, PJP, tuberculosis (TB), and noninfectious causes of ARI such as atelectasis and edema are also in the differential diagnosis, although their clinical presentations often differ [5]. If the initial chest radiograph suggests edema, serial chest radiography with concomitant diuresis, for example, would be helpful in confirming cardiogenic pulmonary edema and differentiating it from infectious causes of ARI. There are many clinical scenarios in the immunocompromised patient, such as isolated segmental pneumonia or presumed pulmonary edema, where further radiologic imaging with CT may not be needed unless the patient's clinical picture worsens or fails to improve with therapy.

Variant 2: Negative, equivocal, or nonspecific chest radiograph

One important limitation of the chest radiograph is its low overall sensitivity in detecting pulmonary infection, a problem compounded in the immunocompromised patient whose weakened immune system often struggles to mount an adequate inflammatory response. Indeed, the chest radiograph in an immunosuppressed patient with cough, dyspnea, chest pain, and fever may be equivocal or even negative despite a high suspicion for pulmonary disease [1]. In this setting, chest CT has been shown to offer a distinct advantage in sensitivity for detecting subtle parenchymal abnormalities [2,16,17]. In one study by Heussel et al [18], 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. The advantage likely lies in the ability of cross-sectional imaging to provide 3-D volumetric data, as opposed to the low-resolution 2-D data provided by radiography. With the improved resolution of CT, even subtle parenchymal abnormalities that would escape detection on the chest radiograph become manifest. The appearance and distribution of lung abnormalities on CT, coupled with information of the patient's clinical presentation, are often quite helpful in formulating a differential diagnosis [5,7,15,16,19-27].

In patients whose primary immune defect is HIV infection, a normal or near-normal chest radiograph can occasionally occur when they are infected with TB [28], nontuberculous mycobacteria, or PJP [5,29]. In the setting of an HIV infection, if there is a high clinical suspicion of a pulmonary infection along with a normal or near-normal chest radiograph, a CT may be warranted to assess for subtle pulmonary parenchymal disease [5,30]. Findings of parenchymal and nodal TB in the thorax can be readily evident on CT in the setting of a normal or

near-normal chest radiograph [31]. In a series by Aderaye et al [32], 7.2% of patients with HIV and pulmonary TB had normal chest radiographs. Among patients with culture-positive TB and normal chest radiographs in this series, 90% had negative smears for acid-fast bacilli. In patients with nontuberculous mycobacterial infections, relatively subtle findings of small airways disease including mild bronchiectasis, peribronchial thickening, foci of mucoid impaction, and air trapping may be evident only on CT [5]. A review by Kanne et al [29] found that PJP findings on chest radiography are often nonspecific and that up to one-third of patients infected with PJP may actually have normal chest radiographs. Patients with PJP and normal chest radiographs often have only subtle findings on CT, such as patchy ground-glass opacities and small nodules or cysts [33].

Although Hidalgo et al found CT to be more sensitive and specific than nuclear medicine studies for diagnosing PJP, as well as being cheaper and faster to perform, there is some literature supporting the use of performing Tc-99m DTPA and Ga-67 lung scans when PJP is suspected [34,35]. A classic study by Barron et al [36] involving AIDS patients showed that Ga-67 lung scans have an overall sensitivity of 94% and specificity of 74% for PJP. When the chest radiograph is negative or equivocal at the time of admission, however, the sensitivity of Ga-67 drops to 86%, though the specificity improves to 85%. Leach et al [37] noninvasively detected PJP in 34 of 36 patients using Tc-99m DTPA lung scanning, thereby reducing the need for bronchoscopy to confirm the diagnosis. Despite the medical literature supporting the use of nuclear medicine to establish the diagnosis of PJP, CT is the modality which most efficiently and reliably depicts the findings of the disease, such as bilateral ground-glass opacities with a perihilar predominance, smooth interlobular septal thickening, and bilateral lung cysts often with a subpleural, upper lobe distribution [5,12].

Variant 3: Positive chest radiograph, multiple, diffuse, or confluent opacities

Chest CT also is indicated in the immunocompromised patient when the radiograph is positive and shows multiple, confluent, or diffuse airspace opacities. In this situation, although the chest radiograph may serve as an effective screening or triaging modality, its inherent low resolution makes it a suboptimal examination to determine the detailed morphology of the opacities, as well as the pattern and distribution of disease, thereby making it an unsuitable standalone study. For example, in febrile patients having undergone recent stem cell transplantation, the ability of CT to detect halos of ground glass-opacity around scattered pulmonary nodules is essential in making the early presumptive diagnosis of invasive aspergillosis, allowing initiation of empiric antifungal therapy and improved prognosis [5,38].

Common patterns of disease found on chest CT in patients with ARI include pulmonary nodules, tree-in-bud nodules, parenchymal consolidation, and ground-glass opacities [2]. These patterns are described in the literature to define the CT appearances of many pulmonary infections in the immunocompromised host, including PJP [9,11,12,29,39], invasive pulmonary aspergillosis [8,10,12,38-43], mucormycosis [39,42], candidiasis [39,41], CMV pneumonia [11,43,44], human metapneumovirus [45,46], and mycobacterial pneumonias [23,24,43]. Some researchers even advocate the use of high-resolution chest CT so that lung parenchymal abnormalities can be best characterized in terms of morphology and patterns of disease, allowing better prediction of the underlying etiologic agents in this vulnerable population [40].

Knowledge of common pulmonary pathogens, their characteristic appearances on chest CT, their associations with specific immunosuppressive states (eg, solid organ transplantation, stem cell transplantation, chronic steroid use, etc.), and their usual time course to infect relative to therapy are all important elements when considering a differential diagnosis [2,5]. The well-recognized patterns of disease that CT is able to detect, taken together with the appropriate clinical and laboratory data, go a long way in piecing together the diagnostic puzzle.

In some clinical scenarios of patients with ARI, transthoracic or transbronchial biopsy may be an appropriate action to allow for the identification of the specific organism causing the airspace opacities. Early identification of the underlying pathogen allows for prompt and appropriate treatment of the pneumonia in these vulnerable patients [47,48]. When a biopsy is being considered, CT allows for optimal characterization of the potential target lesions and determination of the safest route and equipment to be used [42].

Variant 4: Positive chest radiograph, noninfectious disease suspected

Noninfectious pulmonary disease may be suspected in the immunocompromised patient with ARI. For example, these patients sometimes receive cytotoxic medications over the course of their treatment that can produce respiratory symptoms. Additionally, cancer and cancer therapy are both recognized risk factors for venous thromboembolism, a well-established and dreaded complication affecting the circulatory system, which can lead to symptoms of shortness of breath and chest pain [49]. The improved resolution provided by chest CT provides a

much more definitive assessment of any nonspecific opacities found on chest radiography that are suspected to be noninfectious based on the patient's clinical presentation [6]. Noninfectious complications that can contribute to ARI in immunocompromised hosts can include pulmonary edema, drug-induced lung disease, atelectasis, malignancy, radiation-induced lung disease, alveolar hemorrhage, diffuse alveolar damage, organizing pneumonia, rejection of lung transplantation, graft-versus-host disease, and thromboembolic disease [3,6].

The cross-sectional imaging provided by CT allows for optimal characterization of abnormalities discovered on chest radiography. In patients with prior thoracic malignancy, recurrence of the primary cancer or development of a secondary lung tumor should always remain a suspicion when the chest radiograph is abnormal. In a similar fashion, metastatic disease to the lungs can occur from nonthoracic primary sites.

Studies have shown CT to be more sensitive than radiography in detecting drug-induced lung injury from such agents as bleomycin, busulfan, carmustine, and cyclophosphamide [50,51]. Chest CT has been shown for years now to be the most efficient and effective means to evaluate for suspected acute pulmonary embolism [52,53].

Summary of Recommendations

- Chest radiography is indicated early in the evaluation of the immunocompromised patient with ARI. If the radiograph demonstrates a single, focal airspace abnormality and the patient presents with symptoms of an acute bacterial pneumonia, further imaging with CT may not be needed.
- If the radiograph is normal, equivocal, or nonspecific, but clinical suspicion for disease is high, CT can be performed to evaluate for subtle pulmonary abnormalities or to better characterize nonspecific radiographic disease.
- The ability to recognize patterns of airspace disease on chest CT plays an essential role in refining a differential diagnosis—a particular advantage over the nonspecific chest radiograph.
- CT is also indicated for the planning of image-guided (or transbronchial) biopsy and/or therapy of intrathoracic abnormalities noted on chest radiographs.
- Nuclear scintigraphy has a very specific but rarely used role in the evaluation of immunocompromised patients with ARI.

Summary of Evidence

Of the 53 references cited in the *ACR Appropriateness Criteria[®] Acute Respiratory Illness in Immunocompromised Patients* document, 2 are categorized as good quality therapeutic studies. Additionally, 51 references are categorized as diagnostic references including 1 well-designed study, 3 good quality studies, and 16 quality studies that may have design limitations. There are 31 references that may not be useful as primary evidence.

The 53 references cited in the *ACR Appropriateness Criteria[®] Acute Respiratory Illness in Immunocompromised Patients* document were published between 1985–2013.

While there are references that report on studies with design limitations, 6 well-designed or good quality studies provide good evidence.

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, both because of 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 to 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.

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”.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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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.