

**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 contrast	9		☼☼☼
CT chest with contrast	3		☼☼☼
CT chest without and with contrast	1		☼☼☼
Ga-67 scan lung	1	If PCP is suspected.	☼☼☼☼
Tc-99m DTPA scan lung	1	If PCP 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 contrast	7		☼☼☼
Transthoracic needle biopsy	5	If serious opportunistic infection is suspected.	NS
CT chest with contrast	3		☼☼☼
CT chest without and with contrast	1		☼☼☼
Ga-67 scan lung	1	If PCP is suspected.	☼☼☼☼
Tc-99m DTPA scan lung	1	If PCP 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 contrast	8		☼☼☼
CT chest with contrast	5	If neoplasm or pulmonary embolus is suspected.	☼☼☼
Transthoracic needle biopsy	5	If thoracic malignancy suspected.	NS
CT chest without and with 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

There are many causes of immunodeficiency likely to be encountered by today's physician. In recent decades, with advances in medical techniques such as solid organ and stem cell transplantation, cancer therapy, and immunosuppressive therapy, along with the spread of the human immunodeficiency virus (HIV), the number of immunocompromised patients in our health care system has greatly increased [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]. Given the diverse causes of immunosuppression, it is most helpful to diagnose potential infections by thinking in terms of defects in the basic types immune processes (phagocytosis, humoral or B-cell, complement system, cell-mediated or T-cell, and postsplenectomy), and then determining which has occurred, given the clinical situation at hand. By understanding the immune defect caused by the immunosuppression, the list of likely infecting organisms becomes much shorter [3-4].

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 (such

as fever, chills, and weight loss) and some of which are organ specific (such as 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 as 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 [3-4]. Noninfectious causes of ARI in immunocompromised hosts include pulmonary edema, drug-induced lung disease, atelectasis, malignancy, radiation-induced lung disease, diffuse alveolar hemorrhage, and pulmonary embolus [5].

Overview of Imaging Modalities

Despite modern advances in computed tomography (CT) technology, the chest radiograph remains first-line 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 [3-4]. 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 [2,6]. Because the appearance and distribution of airspace abnormalities are better characterized with the high spatial resolution provided by CT, certain diseases such as *Pneumocystis jirovecii* pneumonia (PCP), invasive pulmonary aspergillosis and cytomegalovirus (CMV) can be identified on CT with a higher degree of confidence than they can on radiography [7-10]. 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].

Chest radiography and chest CT are the mainstay imaging modalities in evaluating the immunocompromised host with ARI, although nuclear scintigraphy using gallium-67 (Ga-67) or DTPA-Tc tracer can also be performed. In this clinical setting, Ga-67 can be used to help diagnose

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Mycobacterium avium intracellulare, *Mycobacterium tuberculosis*, and lymphoma based on increased radiotracer activity in hilar and mediastinal lymph nodes. Additionally, Ga-67 can be used to evaluate for the presence of PCP within the lungs in cases where conventional imaging has turned up normal or equivocal findings. Some studies have shown gallium scintigraphy to be more sensitive and specific for the presence of PCP than both chest radiography [11] and chest CT [12] in 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 [3,5-6]. The chest radiograph typically identifies abnormalities if present, although it can be normal in up to 10% of symptomatic patients with proven disease [6] and up to 25% of AIDS patients with PCP [5]. Despite its shortcomings, it remains useful as a screening test for chest disease, as a tool to begin formulating a differential diagnosis, and as a triaging examination to consider additional imaging with chest CT. For patients with acute onset cough and fever, a single focal, segmental, or lobar airspace opacity on chest radiography suggests bacterial pneumonia as the most likely etiology of pulmonary infection.

Fungal pneumonias, PCP, 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 is suggestive of 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. Clearly there are many clinical scenarios, such as a focal lobar 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

The main limitation of the chest radiograph is its low sensitivity in detecting pulmonary infection, a particular problem in patients with weakened and delayed immune systems. Indeed, the chest radiograph in patients 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 subtle parenchymal abnormalities [2,13-15]. One study by Heussel et al 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 [2]. The advantage likely lies in its ability to provide cross-sectional imaging and volumetric data, as opposed to the low-resolution two-dimensional data provided by plain radiography. With the high spatial resolution of CT, even subtle parenchymal

abnormalities that would escape detection on the chest radiograph are typically quite apparent. 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 [13-14].

In patients whose primary immune defect is HIV infection, a normal or only subtly abnormal chest radiograph can occasionally occur when they are infected with TB [16], CMV pneumonia [17], or PCP [18], among other processes. If there is a high clinical suspicion of a pulmonary infection in the setting of a normal chest radiograph, a CT may be warranted to assess for subtle pulmonary parenchymal disease [19-20]. Miliary or disseminated TB or nodal disease can be readily evident on CT in the face of a normal or near-normal chest radiograph [16]. In a series by Aderaye et al [21] 7.2% of patients with HIV and 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. Small airways disease with mild bronchiectasis, peribronchial thickening, foci of mucoid impaction, and air trapping may be evident only on CT [22]. Patients who have a normal chest radiograph and PCP will usually have focal areas of ground-glass opacity evident on CT [23]. Cysts, reticular opacities, nodules, or cavities are common additional findings in patients with PCP [24].

Although Hidalgo et al found CT to be more sensitive and specific than nuclear medicine studies for diagnosing PCP, as well as being cheaper and faster to perform, there is some literature supporting the utility of performing DTPA-Tc and Ga-67 lung scans when PCP is suspected [25-26]. A classic study by Barron et al [27] involving AIDS patients showed that Ga-67 lung scans have an overall sensitivity of 94% and specificity of 74% for PCP, and when the chest radiograph is negative or equivocal at the time of admission, the sensitivity is 86% and the specificity is 85%. Leach et al [28] noninvasively detected 34 of 36 patients with PCP using DTPA-Tc lung scanning while inducing sputum, and they were thus able to reduce the need for bronchoscopy.

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 these situations with widespread parenchymal disease, the chest radiograph may serve as an effective screening or triaging modality, but its inherent low resolution makes it a suboptimal examination to determine the actual pattern and distribution of disease, thereby making it an unsuitable standalone study. For example, in febrile patients having undergone stem cell transplantation, the ability of CT to detect halos of ground glass-opacity surrounding bilateral pulmonary nodules is essential in making the early presumptive diagnosis of invasive aspergillosis [6].

Common patterns of disease found on chest CT include pulmonary nodules, tree-in-bud nodules, parenchymal consolidation, and ground-glass opacities [2]. These patterns are used in the literature to describe the characteristic CT appearances of many pulmonary infections in the immunocompromised host, including PCP [8,10,29], invasive pulmonary aspergillosis [7,9,29-35], mucormycosis [29,32], candidiasis [29-30,34], CMV pneumonia [10,33,36], nocardiosis [37], and mycobacterial pneumonias [33,35]. Some researchers even advocate the use of high-resolution chest CT (HRCT) so that lung parenchymal abnormalities can be characterized better in terms of these descriptive patterns of disease; this way, we may better predict the underlying etiologic agents [6].

Knowledge of the common organisms that infect the lung, their characteristic appearances on chest CT, their associations with specific immunosuppressive states (for example, solid organ transplantation vs stem cell transplantation vs chronic steroid use), and their usual time ranges of infection is essential when considering a differential diagnosis [2,4-5]. 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. Also, when a biopsy is required, CT allows for optimal characterization of the potential target lesions and determination of the safest route and equipment to be used [6,32].

Variant 4: Positive Chest Radiograph, Noninfectious Disease Suspected

The high spatial resolution provided by chest CT provides a much more definitive assessment of nonspecific radiographic opacities suspected to be noninfectious [6]. Common noninfectious causes of ARI in immunocompromised hosts include pulmonary edema, drug-induced lung disease, atelectasis, malignancy, radiation-induced lung disease, diffuse alveolar hemorrhage, and thromboembolic disease [5].

The cross-sectional imaging provided by CT allows for optimal characterization of abnormalities discovered on chest radiography. In patients with a history of prior lung 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. HIV-associated malignancies include non-Hodgkin's lymphoma, Kaposi's sarcoma, and lung cancer [5]. Kaposi's sarcoma, which occurs 20,000 times more frequently in AIDS patients than in the general population [38], can involve the lung parenchyma, airways, thoracic lymph nodes, and pleura. Although lung involvement with both Hodgkin's and non-Hodgkin's lymphoma is relatively low at the time of initial presentation, 20%-25% of patients eventually demonstrate parenchymal involvement [39-40].

Studies have shown CT to be more sensitive than radiography in detecting drug-induced lung injury from such agents as bleomycin, busulfan, carmustine, and methotrexate [41-43]. Chest CT has been shown for years now to be the most efficient and effective means to evaluate for suspected acute pulmonary embolism [44-45].

Summary

- 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 biopsy and/or therapy of intrathoracic abnormalities noted on chest radiographs.
- Nuclear scintigraphy likely has a limited role in the evaluation of immunocompromised patients with ARI.

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
O	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 NS (not specified).

Supporting Document(s)

- [ACR Appropriateness Criteria® Overview](#)
- [Procedure Information](#)
- [Evidence Table](#)

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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.