




# Approach to Acute Respiratory Illness in Children with Hematological Malignancy: A Prospective Study Evaluating Utility of CT Scan

Priyanka Aggarwal<sup>1</sup> Tapish Raipa<sup>2</sup> Ishan Kumar<sup>2</sup> Ashish Verma<sup>2</sup> Ram Chandra Shukla<sup>2</sup>  
Vineeta Gupta<sup>1</sup>

<sup>1</sup>Division of Pediatric Hematology-Oncology, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

<sup>2</sup>Department of Radiodiagnosis and Imaging, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Address for correspondence: Ishan Kumar, MBBS, MD, DNB, Department of Radiodiagnosis, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, Uttar Pradesh, India (e-mail: ishan.imsrd@bhu.ac.in).

Ind J Med Paediatr Oncol 2022;43:480–490.

## Abstract

**Introduction** Various pulmonary complications can occur in children with hematological malignancies including both infection and malignant disease infiltration of pulmonary parenchyma.

**Objectives** To assess the role of CT scan in determining the etiology of acute pulmonary complications in children with hematological malignancies.

**Materials and Methods** All children < 17 years with newly diagnosed hematological malignancy with respiratory symptoms (Group A) along with children who developed fever with persistent respiratory symptoms as well as worsening chest radiographs during treatment (Group B) and underwent CECT thorax, from February 2019 to July 2020 were enrolled. The final diagnosis was made on the basis of clinical history, laboratory as well as radiological investigations and treatment response.

**Results** Thirty-seven children with mean age of  $7.5 \pm 3.5$  years and male to female ratio of 1.3:1 who underwent CECT thorax were included in our study. For newly diagnosed cases, i.e., Group A ( $n=8$ ), the most common cause of respiratory symptoms as identified on CECT thorax was pulmonary tumoral infiltration ( $n=5$ ) followed by tuberculosis ( $n=3$ ). However, in Group B ( $n=29$ ) the cause of persistent respiratory symptoms was identified as infection ( $n=17$ ) followed by leukemic infiltration ( $n=12$ ). Thus, chest CT could accurately identify pulmonary tuberculosis, fungal pneumonia, bacterial infection, and pulmonary tumoral infiltrates.

**Conclusion** CT scan can be used as an adjunctive tool for prompt diagnosis and management of pulmonary complications in children with persistent respiratory symptoms as they are often non-specific.

## Keywords

- ▶ contrast-enhanced computed tomography
- ▶ leukemia
- ▶ lymphoma
- ▶ lungs
- ▶ pediatric

DOI <https://doi.org/10.1055/s-0042-1758539>.  
ISSN 0971-5851.

© 2022. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

## Introduction

Acute respiratory illness (ARI) in immunocompromised children remains a significant diagnostic challenge for both clinicians and radiologists. Pulmonary infection complicates ~75% of immunocompromised patients during their treatment.<sup>1</sup> Given the innumerable pathogens that can cause infectious complications in immunocompromised children, identifying a specific pathogen can be elusive.

In children developing complications secondary to chemotherapy-induced immune suppression, when combined with certain specific morphological findings and the type and duration of immune suppression, radiological investigations can aid with the decision-making process. Chest radiography is the initial imaging modality of choice for the diagnostic assessment of patients presenting with ARI; however, there is low sensitivity and low specificity regarding the type of specific pathogens.<sup>2</sup> Chest CT has been demonstrated to confer a higher degree of sensitivity and specificity for identifying the underlying cause of pulmonary involvement.

Contrast-enhanced CT chest should be done to evaluate the lungs, mediastinum, and pleural/chest wall abnormalities and identify mediastinal and hilar lymph nodes, as opposed to axial HRCT (high-resolution CT), which is done for pulmonary pathologies only. Volumetric multidetector CT acquisition in most of the modern day scanners can generate reconstructed HRCT images, which obviate the use of traditional axial HRCT acquisition in pediatric patients. Apart from pulmonary infections, non-infectious causes such as malignant pulmonary infiltration, radiation-induced lung injury, pulmonary thromboembolic phenomenon, should also be considered while evaluating acute respiratory illness in this group.

The aim of this study was to assess the role of contrast-enhanced CT scan in determining the etiology of pulmonary complications in children with hematological malignancies presenting with ARI.

## Materials and Methods

This was a prospective observational study performed at the Division of Pediatric Hematology Oncology, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University from February 2019 to July 2020 (ethical clearance no. Dean/2018/EC/919). Thirty-seven children were included in this study who met our inclusion criteria.

### Inclusion Criteria

All children < 17 years with hematological malignancy who were

- ▶ Newly diagnosed with respiratory symptoms (group A)
- ▶ On chemotherapy and developed fever with persistent respiratory symptoms, i.e., respiratory symptoms present even after 7 to 10 days from start of treatment along with/without worsening chest radiographs (group B)

### Exclusion Criteria

- ▶ Unwillingness to participate in the study
- ▶ Hemodynamically unstable child

Children were investigated and empirical intravenous antibiotics, i.e., piperacillin-tazobactam and amikacin were started as per unit protocol. Investigations such as complete blood count, conventional blood culture, chest X-ray were sent for all children that had either of the two, i.e., fever, cough, or increased respiratory rate for age. Intravenous/oral fluconazole (antifungal) was added after 48 to 72 hours<sup>3</sup> if the child had clinical deterioration despite receiving empirical intravenous antibiotics. As pulmonary infection in immunocompromised children is most likely due to bacterial pathogens,<sup>2</sup> antibiotics was started and resolution of symptoms were expected to occur by 7 to 10 days (arbitrary) with antibiotics, followed by antifungals (as indicated) as per blood culture sensitivity pattern in the pediatric oncology ward. Patients responding to antibiotics in both the groups and having a normal follow-up chest X-ray at 7 to 10 days did not undergo chest CT. In both the groups, if after 7 to 10 days, there was no clinical improvement to empirical antibiotics, a repeat conventional blood culture, chest X-ray, and chest CT was done. The indications of chest CT in our study were persistent respiratory symptoms, irrespective of abnormality on chest X-ray at 7 to 10 days of antibiotics.

Chest CT findings were further corroborated by blood culture, gastric aspirate for Gene Xpert and galactomannan assay (based on availability) in infective cases. As gastric aspirate in children has been found to be equally effective and beneficial in *Mycobacterium tuberculosis* (MTB) detection with non-requirement for specific facilities as compared with bronchoalveolar lavage, it was used in this study for MTB detection.<sup>3</sup> CT-guided tissue biopsy from mediastinal mass was performed in most cases where malignant infiltration was suspected. Children whose parents did not consent for tissue biopsy, it was not done. Pulmonary infiltration was suspected if the clinical condition of the child was consistent with disease infiltration and child had sterile cultures. However, lung biopsy was not performed.

Data were collected with respect to age, gender, duration of symptoms, radiological findings on chest X-ray and chest CT, along with response to treatment. In infective cases, results of blood culture, gastric aspirate for Gene Xpert and galactomannan assay (based on availability) along with results of tissue biopsy in cases where malignant infiltration was suspected were also collected.

### CECT Protocol

CT chest was performed using a 128 slice light speed VCT (GE Medical System). Non-ionic contrast agent Iohexol (Omnipaque) of concentration 300 mgI/mL was administered using hand injector (with an optional use of power injector and bolus chase) in a calculated dosage (1–1.5 mL/kg) depending upon the child's weight. In patients with previous history of contrast allergy or high-risk of contrast allergy (previous anaphylactic reactions to food or medication), after injecting the first 1 mL of contrast agent, child was observed for a few seconds for any allergic reactions and again after half

an hour to see any delayed reaction. Scan delay of 25 to 30 seconds was kept following the administration of contrast for optimal enhancement of soft tissue. Images were then reconstructed using different reconstruction algorithm and evaluated in advantage workstation 4.4 and 4.7.

### Image Evaluation and Interpretation

All CT scans were evaluated by a radiologist with 7 years of experience. Following definitions were used for characterizing lesions seen on CT scan.<sup>4</sup>

- i. Consolidation is defined as homogenous increase in lung parenchymal attenuation with obscuration of airways and vessels.
- ii. Ground glass opacities (GGO) are defined when bronchovascular margins are preserved behind hazy area of homogeneously increased attenuation.
- iii. A nodule around the peripheral pulmonary arterial branches or 3 to 5 mm from the pleura, pulmonary vein or interlobular septa is defined as centrilobular nodule. Appearance of multiple areas of centrilobular nodules with a linear branching pattern was defined as "tree-in-bud" nodules. Nodules were termed as random if they lacked an architectural predominance.
- iv. Abnormal widening of the interlobular septa is defined as an interlobular septal thickening.
- v. Each parenchymal lesion localized to a particular lobe was evaluated in terms of presence and distribution of abnormality identified on CECT thorax.
- vi. Halo sign was defined as ground-glass opacity surrounding a nodule or, a mass or a rounded area of consolidation.

### Approach to Diagnosis

Following signs on CT were used to suggest the specific etiology of pulmonary findings.

- Bacterial pneumonia: Patients with segmental or lobar consolidation with/without pleural effusion
- Tuberculosis: Centrilobular nodules with tree in bud pattern, necrotizing mediastinal and hilar lymph nodes, empyema, cavitary consolidations, military pattern, and cavitary lesions.
- Fungal infection: Patchy consolidations and halo sign, cavitary nodules, consolidation with crescent of air.
- Viral pneumonia: bilateral multifocal GGO with patchy consolidations with perihilar distribution along bronchovascular bundles indicative of bronchopneumonia.
- Lymphoma/leukemic infiltrate: mediastinal mass with lung consolidation or randomly distributed nodule with bronchovascular bundle thickening or nodular pleural thickening

All children were followed and a repeat CECT was performed after the completion of treatment in children with tuberculosis and malignant pulmonary infiltration. The final etiological diagnosis was made on the basis of clinical history, laboratory investigations and treatment response was considered as an outcome measure in this study.

**Statistical Analysis:** SPSS software (Version 22.0. IBM Corp. Armonk, NY, USA) for windows was used for data entry

and analysis. All numerical variables are expressed as median with range. For comparison of categorical data chi square test was used. For categorical variables with cell values < 5, Fisher's exact test was used. A *p*-value < 0.05 was taken as significant.

**Ethics:** The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1964, as revised in 2013. Ethical clearance from Institute Ethical Committee of Institute of Medical Sciences, Banaras Hindu University, was obtained (Dean/2018/EC/919). Written informed consent was obtained from parents of all children included in our study.

### Results

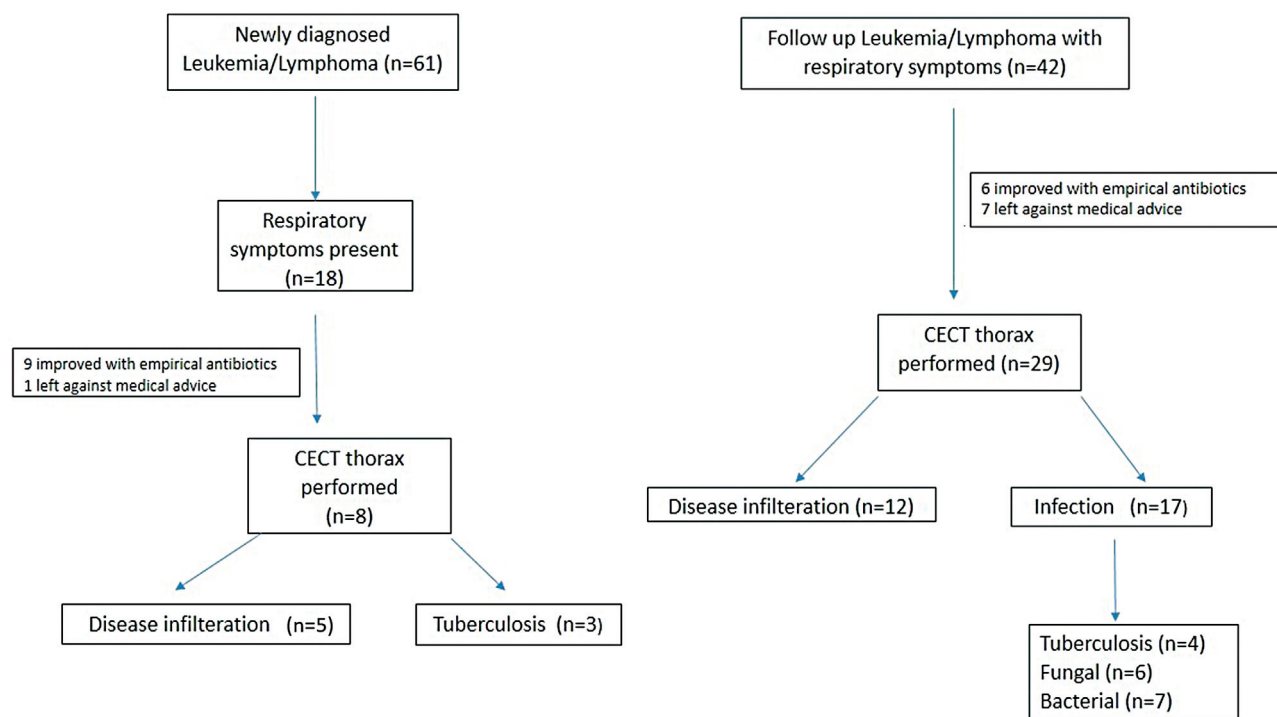
During the study period, a total of 103 children developed ARI and were divided in two separate groups (► **Fig. 1**). The first group (Group A) comprised of newly diagnosed leukemia/lymphoma (59.2% [*n* = 61]). Among them, 29.5% (*n* = 18) had respiratory symptoms at the start of treatment, of which 50% (*n* = 9) improved with empirical antibiotics, 5% (*n* = 1) abandoned treatment, and 44.4% (*n* = 8) underwent CECT thorax. The second group (Group B) consisted of children who developed respiratory symptoms while on different phases of chemotherapy 40.8% (*n* = 42). Among them, 14.3% (*n* = 6) improved with empirical antibiotics, 16.7% (*n* = 7) abandoned treatment, and 69% (*n* = 29) underwent CECT thorax. Our study included a total of 37 children (mean age 7.5 ± 3.5 years; male to female ratio of 1.3:1) who did not show improvement after primary treatment and had persistent respiratory symptoms. Of these 37 children, underlying hematological malignancy included acute lymphoblastic leukemia in 43.2% (*n* = 16), non-Hodgkin lymphoma in 24.3% (*n* = 9), acute myeloid leukemia in 21.6% (*n* = 8), and Hodgkin's lymphoma in 10.8% (*n* = 4) (► **Table 1**).

In the group A (*n* = 8), causes of persistent respiratory symptoms as identified on CECT chest were pulmonary metastatic infiltration in 62.5% (*n* = 5) cases followed by tuberculosis in 37.5% (*n* = 3), whereas in group B (*n* = 29), diagnosis included infection in 58.6% (*n* = 17) children followed by pulmonary metastatic infiltration in 41.3% (*n* = 12). Among the infections, CECT findings were consistent with pulmonary tuberculosis 23.5% (*n* = 4), fungal infection 35.3% (*n* = 6), and bacterial infection 41.2% (*n* = 7).

Among children who underwent chest CT in both groups, 24.3% children (*n* = 9) despite having a normal chest X-ray on day 7, underwent chest CT to elucidate the cause of respiratory distress. Chest CT was able to detect pulmonary changes, i.e., tubercular (*n* = 2) in group A and disease infiltration (*n* = 3), followed by pneumonia, i.e., fungal in (*n* = 3) and bacterial (*n* = 1) in group B.

### Pulmonary Tuberculosis

CECT suggested pulmonary tuberculosis in seven children who demonstrated centrilobular nodules with tree in bud appearance (*n* = 6) most frequently (► **Fig. 2A**), followed by



**Fig. 1** Flow diagram depicting patient enrolment.

**Table 1** Baseline characteristics of study population

Characteristics	
Age	7.5 ± 3.5 years
M:F ratio	1.3:1
Underlying pathology: n (%)	
ALL	16 (43.2%)
AML	8 (21.6%)
NHL	9 (24.3%)
HL	4 (10.8%)
Presenting symptoms: n (%)	
Fever	31 (83.7%)
Cough	17 (45.9%)
Rapid breathing	12 (32.4%)
Chest pain	1 (0.02%)
Etiological cause: n (%)	
Bacterial	7 (18.9%)
Fungal	6 (16.2%)
Tuberculosis	7 (18.9%)
Leukemic infiltration/disease	17 (46%)

segmental/subsegmental consolidation ( $n = 4$ ), and military tuberculosis with random nodules in one child. Other findings were pleural effusion ( $n = 3$ ), GGOs ( $n = 1$ ), and necrotic mediastinal lymph nodes ( $n = 3$ ). Gene Xpert (gastric aspirate) was sent for all these children that was positive in three children (Group A [ $n = 1$ ]; group B [ $n = 2$ ]). Antitubercular treatment (ATT) was started in all these seven children,

irrespective of Gene Xpert results. Five children improved following ATT, and two children died due to relapse of underlying malignancy (► **Table 2**).

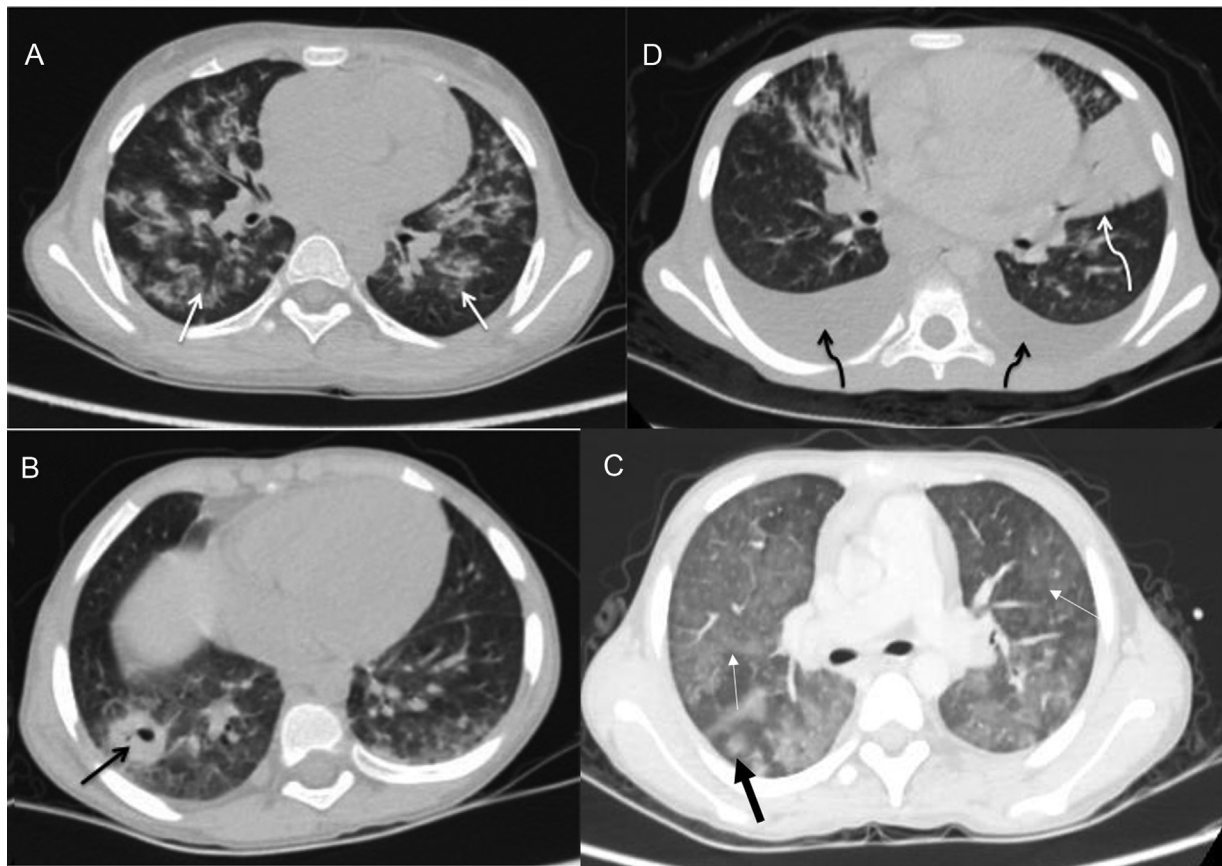
### Fungal Infection

Children with CT features of fungal infection ( $n = 6$ ) revealed segmental/sub segmental consolidation ( $n = 4$ ), GGO ( $n = 3$ ), halo sign ( $n = 3$ ), reverse halo sign ( $n = 1$ ), multiple cavitary lesions ( $n = 1$ ) and pleural effusion ( $n = 3$ ) (► **Fig. 2B, 2C**). Fluconazole (empirical antifungal) was started in all children ( $n = 37$ ) if there was no improvement in fever after adding antibiotics for 48 hours. Of the six children with CT features of fungal disease, galactomannan was positive in two children and *Candida* was isolated from blood in two children. Among these six children, in five children, antifungals were escalated, i.e., amphotericin B ( $n = 4$ ) and voriconazole ( $n = 1$ ). All six children responded to antifungals.

In bacterial pneumonia ( $n = 7$ ), findings included lobar/sublobar consolidation ( $n = 4$ ), segmental/sub-segmental consolidations ( $n = 3$ ), pleural effusion ( $n = 5$ ) and homogeneously enhancing (non-necrotic) mediastinal lymph nodes ( $n = 5$ ) (► **Fig. 2D**). In these children, antibiotics were escalated based on blood culture. If blood culture did not yield any organism, the antibiotics were escalated according to blood culture sensitivity pattern in the pediatric oncology ward. The most common organisms isolated were bacteria, i.e., MRSA ( $n = 2$ ), *E. coli* ( $n = 1$ ) and Co NS ( $n = 1$ ) followed by *Candida* ( $n = 2$ ).

### Pulmonary Metastatic Infiltrates

In cases of leukemic infiltrates ( $n = 7$ ), CT findings included bronchovascular thickening ( $n = 4$ ), GGO ( $n = 4$ ), random nodules ( $n = 5$ ), halo sign ( $n = 2$ ), pleural thickening with



**Fig. 2** Axial CECT images of four different patients showing (A) bilateral pulmonary infiltrates in form of centrilobular nodules (white arrows) with adjacent ground glass opacities representing tubercular involvement (B) bilateral pleural effusion (black curved arrow) and lobar consolidation in left lingular segments (white curved arrow) in bacterial infection and (C) cavitory lesion in the right lower lobe (black arrow) suggestive of fungal infection. (D) Bilateral ground glass opacities (white arrows) with halo sign (thick black arrow) in fungal infection.

effusion ( $n=2$ ), subsegmental consolidations ( $n=4$ ), discrete mediastinal nodes ( $n=6$ ), and mediastinal mass ( $n=1$ ). In cases of lymphoma with pulmonary infiltrates ( $n=10$ ), CT findings included segmental/sub-segmental consolidations ( $n=7$ ), pleural effusion with pleural thickening ( $n=4$ ), mediastinal mass ( $n=4$ ), discrete mediastinal nodes ( $n=6$ ), GGO ( $n=2$ ), and halo sign ( $n=2$ ). Patients with mediastinal mass ( $n=6$ ) underwent CT-guided biopsy that yielded the diagnosis. Hyperleukocytosis was seen in two children with relapsed ALL and one child with refractory NHL (► **Table 3**). Based on chest CT findings along with tissue diagnosis, in all these children ( $n=17$ ) empirical antibiotic/antifungal were stopped and chemotherapy was planned according to tissue biopsy report.

## Discussion

The results of our study prove that CECT of chest done at 7 to 10 days of onset of persistent respiratory symptoms can efficiently detect the pulmonary involvement by infective/tumoral infiltrates, even with the normal chest radiographs. Further, CT scan can provide clues toward underlying etiology, narrow down the differential consideration, and help initiate additional diagnostic measures.

Chest radiography remains the initial imaging modality of choice for the evaluation of immunocompromised patients

presenting with acute respiratory symptoms. However, radiographs can be normal in up to 10% of patients with lung pathology in immunocompromised patients.<sup>2</sup> Our experience also showed that even with normal lung radiographs, CT could detect the findings in nine patients (34%). The American College of Radiology (ACR) appropriateness criteria for imaging of chest in immunocompromised patients (both adult and pediatric) recommend CT with contrast as the next imaging modality with normal, equivocal, or non-specific chest radiographs or with those demonstrating multiple, diffuse, or confluent opacities. However, separate criteria do not exist for pediatric patients, especially regarding the time to obtain CT scan. Our study suggests that CT with contrast should be done if the child is not responding to empirical antibiotic therapy at 7 to 10 days of persistent respiratory symptoms.

Children with bacterial pneumonia ( $n=7$ ) had lobar/sublobar consolidations, along with pleural effusion ( $n=5$ ) on chest CT as has been also reported by Copley et al. Caution should be exercised when diagnosing bacterial infection as CT findings can overlap with various non-infective causes such as pulmonary hemorrhage and acute eosinophilic pneumonia in children.<sup>5</sup> Also, CT findings may overlap with atypical pneumonia including viral infections but the presence of ground glass opacification with consolidation, peribronchial thickening and lobular instead of

**Table 2** CECT findings of children who had respiratory distress due to infectious etiology

S.no	Age (y)	Diagnosis	Clinical presentation	Investigations	CECT findings	Treatment	Follow-up
1	7/M	ALL with pulmonary tuberculosis	Fever cough Rapid breathing for 20 days	Chest X-ray (day 7) Patchy opacity in right upper lobe, B/LCP angle blunting	Pleural R/M-high ADA lymphocytosis (91%) Patchy consolidation along with ground glass opacities, centrilobular nodules and bilateral pleural effusion was observed	Empirical antibiotics On the basis of CECT and pleural tap R/M suggesting TB, ATT was advised for 6 months	Clinical improvement observed following ATT
2	9/M	AML with fungal pneumonia	Cervical lymphadenopathy for 15 days Fever and cough for 5 days	Normal	Focal ground glass opacities with surrounding consolidation (reverse halo sign) and focal patchy opacity were observed	Empirical antibiotics Amphotericin B administered for 14 days.	Fever subsided and child clinically improved
3	12/M	ALL with fungal pneumonia /septic pulmonary embolism	Fever (during induction phase of chemotherapy)	Focal patchy opacities and left sided loculated effusion	Randomly distributed cavitary and non-cavitory nodule with left sided empyema and peripheral patchy consolidation with surrounding GGO were observed	Empirical antibiotics along with Amphotericin B.	Clinical response after Vancomycin administration
4	3/M	ALL with pulmonary tuberculosis	Cough and neck swelling for 15 days fever for 2 days	Opacity in right middle lobe and infiltrative pattern	Multiple bilateral centrilobular nodule with tree in bud appearance, focal GGO and right middle lobe atelectasis was observed	Empirical antibiotics Anti-tubercular drug was advised for 6 months	Clinical improvement observed after ATT intake
5*	4/M	ALL with pulmonary tuberculosis	on/off fever, Rapid breathing and cervical lymphadenopathy	Multiple reticular opacities	Multiple patchy consolidation in bilateral upper lobe with multiple ground glass opacities, centrilobular nodules with tree in bud appearance	ATT was advised for 6 months	Clinical improvement observed after ATT intake
6	2/F	ALL with pulmonary tuberculosis	Fever and cough for 20 days History of significant weight loss	Inhomogenous opacity in Right upper zone	Sublobar consolidation in right upper lobe, pleural effusion and mediastinal lymph nodes	Empirical antibiotics ATT was advised for 6 months	Clinical improvement observed after ATT intake.
7*	3/F	ALL with pulmonary tuberculosis	On/off fever for 22 days and cough for 5 days	right lung infiltrates	Diffuse ground glass opacities and patchy consolidation in bilateral upper and lower lobe, centrilobular nodule showing tree in bud appearance in B/L lower lobes and mediastinal lymph node was observed	Empirical antibiotics ATT advised	Child died due to progressive disease
8	6/M	NHL with Bronchopneumonia	On/off fever for 1 month	Normal	Lobar consolidation with centrilobular ground glass opacities and sub-centrimetric mediastinal lymph nodes	Empirical antibiotics	Fever improved following meropenem and vancomycin administration
9	1/F		On/off fever for 15 days	Normal		Empirical antibiotics	

(Continued)

Table 2 (Continued)

S.no	Age (y)	Diagnosis	Clinical presentation	Investigations	CECT findings	Treatment	Follow-up
		AML with fungal pneumonia			Blood c/s- sterile Gene X-pert- negative Galactomannan assay- Not done	Focal diffuse GGO and centrilobular nodule and mild pleural effusion s/o infective etiology	Child improved clinically after amphotericin B administration
10	4/M	NHL with bronchopneumonia	Fever and cough for 15 days	Bilateral inhomogenous opacities	B/L lobar consolidation with minimal pleural effusion was noted s/o infective cause	Empirical antibiotics	Clinical improvement after Teicoplanin and meropenem administration
11	12/M	ALL with fungal pneumonia	Fever for 12 days	Inhomogenous opacity in right mid zone	Randomly distributed multiple nodules with surrounding GGO and patchy consolidation in right middle lobe, subcentrimetric mediastinal lymph node and minimal pleural effusion noted	Empirical antibiotics Amphotericin-B administered following CECT findings and culture report	Clinical improvement after amphotericin B administration
12	4/M	ALL with Septic pulmonary embolism Vs fungal infection	Fever for 15 days	Normal	Multiple cavitary lesion with surrounding consolidation in B/L lung field with mediastinal lymph node	Empirical antibiotics with Fluconazole	Child improved after day 4 of fluconazole administration.
13	13/M	ALL with fungal pneumonia	Child fever for 20 days and cough for 15 days.	Bilateral inhomogenous opacities	Segmental consolidation with surrounding GGO in left upper lobe, and few centrilobular nodule with tree in bud appearance, and minimal pleural effusion	Empirical antibiotics with amphotericin B was administered for 2 weeks	Clinical improvement after amphotericin B administration
14*	7/M	ALL with fungal pneumonia	Fever for 10 days and poor oral intake for 1 month	Normal	Multiple random nodules with surrounding GGO, mild interstitial thickening and mediastinal lymph node	Empirical antibiotics with fluconazole. ATT advised following CT findings and positive Gene Xpert	Child improved following ATT administration.
15	5/F	AML with fungal pneumonia	Cough and rapid breathing for 4 days	Focal opacity	Patchy consolidation with surrounding GGO, focal and diffuse GGO and randomly distributed nodule was observed	Empirical antibiotics with fluconazole	Child responded to voriconazole
16	6/M	AML with bronchopneumonia	Fever and cough for 12 days	Consolidation, CP angle blunting	Lobar consolidation with pleural effusion and mediastinal lymph node was observed	Empirical antibiotics with fluconazole vancomycin was advised as per blood culture sensitivity	Clinical improvement after Vancomycin administration
17	16/F	AML with pulmonary tuberculosis.	Fever, cough for 25 days and rapid breathing for 10 days	Normal	Centrilobular nodule with tree in bud appearance and pleural effusion	Empirical antibiotics with fluconazole ATT was advised based on CECT findings and no	Clinically improvement following ATT intake for 6 months

Table 2 (Continued)

S.no	Age (y)	Diagnosis	Clinical presentation	Investigations	CECT findings	Treatment	Follow-up
18	12/F	AML with bronchopneumonia	Fever and rapid breathing for 4 days	Inhomogenous opacities	Segmental consolidation with pleural effusion, few centrilobular nodule and subcentrimetric mediastinal lymph node	response to antibiotics as well as antifungals Empirical antibiotics with fluconazole Vancomycin was advised as per blood culture sensitivity	Clinical improvement after vancomycin administration
19	8/F	ALL with bronchopneumonia	Fever and rapid breathing for 10 days	Consolidations	B/L segmental consolidation with perit bronchovascular nodule and few subcentrimetric mediastinal lymph node	Empirical antibiotics Imipenem was advised as per blood culture sensitivity	Clinical improvement after imipenem administration
20	9/F	AML	Fever and cough for 3 days	Consolidations	B/L lobar consolidation with pleural effusion and mediastinal lymph node.	Broad spectrum antibiotics was started.	Responded to the treatment.

\*Before starting chemotherapy. \*\* MRSA, methicillin-resistant *Staphylococcus aureus*.

segmental distribution<sup>4</sup> favor viral pneumonia which was not seen among any child in this study. Also, the absence of cavitary lesion, necrotic mediastinal lymph nodes and predominant tree-in-bud nodules pointed toward bacterial etiology.

The presence of centrilobular nodule with tree in bud appearance, segmental/sub-segmental consolidation (especially in upper lobes), have been described to be associated with pulmonary tuberculosis in immunocompromised host,<sup>5,6</sup> as was also seen in this study. Similar CT findings can also be seen in *Pneumocystis jiroveci*,<sup>7</sup> invasive pulmonary aspergillosis,<sup>7</sup> mucormycosis,<sup>8,9</sup> and candidiasis.<sup>8,9</sup> However, nodules or areas of consolidation with a surrounding halo of GGO representing pulmonary hemorrhage are cardinal features when considering a possibility of fungal pneumonia in neutropenic children.<sup>10</sup> Sometimes, areas of cavitation representing infarction also develop in the neutrophil recovery phase,<sup>11</sup> that are more frequently observed in *Candida* than *Aspergillus* infection. In our study, one of six children had multiple cavitary lesions that improved following fluconazole administration that favors the possible candida infection in this child.

The role of chest radiographs in detecting non-infectious complications such as tumor recurrence and pulmonary metastasis in children with history of malignancy, is limited. In this study, seven children who had disease infiltration (confirmed by CECT findings as well as clinical condition) showed inhomogeneous opacities on chest radiographs. The presence of pulmonary tumoral infiltration on CT scan is usually suggested by presence of a coexisting mediastinal mass (lymphoma) and lung consolidation or randomly distributed nodule with bronchovascular bundle thickening (leukemia), reflecting predilection of leukemic infiltrates for perilymphatic pulmonary interstitium or nodular pleural thickening<sup>12,13</sup>

Thus, we would like to emphasize that chest radiography still remains the imaging modality of choice for the diagnostic assessment of immunocompromised children presenting with acute respiratory illness.<sup>14</sup> It cannot only detect infectious complications such as pleural effusion, empyema, and pneumothorax<sup>14,15</sup> but serial chest radiographs along with pattern and distribution of abnormality can also aid in formulating a differential diagnosis.<sup>14,15</sup> However, they lack sensitivity to detect subtle abnormalities in symptomatic immunocompromised children. Also, chest radiographs are non-specific with regard to specific pathogen.<sup>1</sup> On the contrary, chest CT is more sensitive than chest radiography for detecting subtle pulmonary parenchymal abnormalities due to its superior spatial resolution and cross-sectional display of findings.<sup>14</sup> In a study by Heussel et al, CT could aid in diagnosing pneumonia in 60% of febrile neutropenic patient with normal chest radiograph at least 5 days before abnormalities were visible on chest radiographs.<sup>16</sup> The results of our study emphasize that utilizing a chest radiograph as an initial modality and incorporation of CECT as a second-line modality is a cost-effective approach that can be utilized especially in low-income countries. Moreover, CT can obviate the need for specialized biochemical testing



**Table 3** CECT findings of children that had malignant disease infiltration

S no.	Age (y)/ Sex	Diagnosis	Clinical presentation	Investigations	Chest X-ray	CECT findings
1	8/F	Relapsed ALL	On/off fever, neck swelling, cough and rapid breathing	Hyperleukocytosis	Normal	Multiple diffusely spread patchy ground glass opacities (GGO) with mild interstitial thickening in bilateral lungs and moderate pleural effusion and enlarged mediastinal lymph node.
2	13/M	Relapsed ALL	Fever and difficulty in breathing	Blood C/S - Sterile Gene X-pert - negative	Normal	Subpleural patchy opacities with interstitial thickening, and subcentrimetric random nodules
3	6/F	Relapsed ALL	On/off fever and lymphadenopathy	Hyperleukocytosis	Normal	Multiple randomly distributed nodule with surrounding GGO, nodular thickening of interlobular fissure and enlarged mediastinal lymph node
4	10/M	Relapsed ALL	On/off fever and cough	Blood C/S - sterile	Widened mediastinum, Inhomogeneous opacities	Multiple mediastinal lymph node with subsegmental patchy consolidation, random nodules and focal GGO
5	11/M	Relapsed ALL	On/off fever and rapid breathing	Blood C/S - Sterile	Mediastinal widening	Conglomerated mediastinal lymph nodes with adjacent subsegmental consolidation and pericardial effusion, randomly distributed multiple soft tissue density nodule, mild pleural thickening and bony erosion of sixth rib.
6*	2/F	NHL	Fever and lymphadenopathy	Blood C/S - Sterile	Right upper lobe opacity. Widened mediastinum	Near complete thrombosis of SVC, proximal right subclavian and B/L brachiocephalic vein. Randomly distributed nodule with few showing surrounding GGO, right upper lobe segmental consolidation and bilateral pleural effusion with mild pleural thickening. Few subcentrimetric mediastinal lymph nodes.
7	11/M	Relapsed AML	Fever and cough	Blood C/S - Sterile Gene X-pert - negative	Inhomogeneous opacity	Focal patchy consolidation, multiple diffuse patchy GGO with mild interstitial thickening and subcentrimetric mediastinal lymph nodes.
8*	13/M	NHL	Fever chest pain and rapid breathing		Lung opacity. CP angle blunting	Anterior and superior mediastinal mass with right upper lobe consolidation and moderate pleural effusion.
9*	9/M	HL	Fever, neck swelling for 7 months	Blood C/S - Sterile Gene X-pert - Negative.	Inhomogeneous opacity	Patchy consolidation, bilateral nodular pleural thickening and mediastinal lymph nodes
10	5/M	Refractory NHL	Fever		Inhomogeneous opacity	Focal subsegmental consolidation, Soft tissue density random nodule and hilar lymph nodes.
11*	8/M	HL	Fever, rapid breathing and lymphadenopathy		Consolidation with inhomogeneous opacity	Subsegmental consolidation, centrilobular nodule with surrounding mild GGO with mediastinal lymph node
12	4/F	Refractory NHL	Rapid breathing		Bronchopneumonia, bilateral CP angle blunting	Segmental consolidation, bilateral nodular pleural thickening with pleural effusion and mediastinal lymph nodes
13	6/F	Refractory HL	Fever, rapid breathing and lymphadenopathy	.	Mediastinal widening	Large mildly enhancing mediastinal mass with necrosis, nodular thickening of pleura with pleural effusion

Table 3 (Continued)

S no.	Age (y)/ Sex	Diagnosis	Clinical presentation	Investigations	Chest X-ray	CECT findings
14	6/F	Relapsed NHL	On/off fever, cough and rapid breathing		Mediastinal widening	Mediastinal enhancing mass occupying superior and anterior mediastinum, pleural thickening and mediastinal lymph nodes
15	8/F	Refractory NHL	Fever and rapid breathing.	Hyperleukocytosis	Bilateral inhomogenous opacities	Segmental consolidation, B/L diffuse focal GGO with interstitial thickening and calcified enlarged mediastinal lymph nodes
16	7/M	Refractory NHL	Fever, cough and rapid breathing	Blood C/S - Sterile Gene X-pert - negative.	Mediastinal widening.	Anterior mediastinal enhancing mass with bilateral minimal pleural and pericardial effusion. Patchy ground glass opacities present
17*	7/F	HL	Neck swelling for 6 months	Blood C/S - Sterile Gene X-pert - Negative	Inhomogenous opacities	Middle lobe segmental consolidation, halo sign and cervical non-necrotic lymph nodes

\*Before starting chemotherapy.

which can eventually decrease the overall cost incurred to the patients.

The major limitation in this study was our small cohort size and lack of detailed microbiological/histopathological assessment through lung biopsy. In the majority of cases, our diagnosis was based on response to antibiotics and clinical follow-up. Also, we did not screen for viral infections due to a high cost of PCR based test to detect the same. The strength of this study was, however, its prospective nature. Therefore, we suggest that there is a need for multicentric prospective studies that can evaluate the role of CT scan in diagnosing etiology of persistent respiratory symptoms in pediatric immunocompromised patients in a resource limited setting.

## Conclusion

In conclusion, chest CT can be a useful adjunctive tool when the etiology for ARI is not clear and resources are limited. Chest CT has the ability to identify the presence of pulmonary disease with high sensitivity, along with vital diagnostic information about the pattern of involvement as well as the most likely etiological pathogen.

### Data, Materials and/or Code Availability

Data are available with the corresponding author and can be shared on reasonable request.

### Ethics Approval

The study was approved by the institutional ethics committee of Institute of medical Sciences, Banaras Hindu University.

### Funding

None.

### Conflict of Interest

None declared.

### Consent

Written informed consent was obtained from all the patients included in this study.

## References

- Cereser L, Zuiani C, Graziani G, et al. Impact of clinical data on chest radiography sensitivity in detecting pulmonary abnormalities in immunocompromised patients with suspected pneumonia. *Radiol Med (Torino)* 2010;115(02):205–214
- Lee C, Colletti PM, Chung JH, et al; Expert Panel on Thoracic Imaging. ACR Appropriateness Criteria® acute respiratory illness in immunocompromised Patients. *J Am Coll Radiol* 2019;16(11S): S331–S339
- Baghaei P, Tabarsi P, Farnia P, et al. Utility of gastric lavage for diagnosis of tuberculosis in patients who are unable to expectorate sputum. *J Glob Infect Dis* 2011;3(04):339–343
- Davis K, Wilson S. Febrile neutropenia in paediatric oncology. *Paediatr Child Health (Oxford)* 2020;30(03):93–97
- Copley SJ. Application of computed tomography in childhood respiratory infections. *Br Med Bull* 2002;61(01):263–279

- 6 Jung JI, Lee DG, Kim YJ, Yoon HK, Kim CC, Park SH. Pulmonary tuberculosis after hematopoietic stem cell transplantation: radiologic findings. *J Thorac Imaging* 2009;24(01):10–16
- 7 Demirkazik FB, Akin A, Uzun O, Akpınar MG, Ariyürek MO. CT findings in immunocompromised patients with pulmonary infections. *Diagn Interv Radiol* 2008;14(02):75–82
- 8 Nam BD, Kim TJ, Lee KS, Kim TS, Han J, Chung MJ. Pulmonary mucormycosis: serial morphologic changes on computed tomography correlate with clinical and pathologic findings. *Eur Radiol* 2018;28(02):788–795
- 9 Franquet T, Giménez A, Hidalgo A. Imaging of opportunistic fungal infections in immunocompromised patient. *Eur J Radiol* 2004;51(02):130–138
- 10 Brook O, Guralnik L, Hardak E, et al. Radiological findings of early invasive pulmonary aspergillosis in immune-compromised patients. *Hematol Oncol* 2009;27(02):102–106
- 11 Austin JH, Müller NL, Friedman PJ, et al. Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. *Radiology* 1996;200(02):327–331
- 12 Tanaka N, Matsumoto T, Miura G, et al. CT findings of leukemic pulmonary infiltration with pathologic correlation. *Eur Radiol* 2002;12(01):166–174
- 13 Heyneman LE, Johkoh T, Ward S, Honda O, Yoshida S, Müller NL. Pulmonary leukemic infiltrates: high-resolution CT findings in 10 patients. *AJR Am J Roentgenol* 2000;174(02):517–521
- 14 Reynolds JH, Banerjee AK. Imaging pneumonia in immunocompetent and immunocompromised individuals. *Curr Opin Pulm Med* 2012;18(03):194–201
- 15 Kisebo HN, Boon SD, Davis JL, et al. Chest radiographic findings of pulmonary tuberculosis in severely immunocompromised patients with the human immunodeficiency virus. *Br J Radiol* 2012;85(1014):e130–e139
- 16 Heussel CP, Kauczor HU, Heussel G, Fischer B, Mildemberger P, Thelen M. Early detection of pneumonia in febrile neutropenic patients: use of thin-section CT. *AJR Am J Roentgenol* 1997;169(05):1347–1353