Article published online: 2021-06-03

Original Article

# Evaluation of Pulmonary Infiltrate in Febrile Neutropenic Patients of Hematologic Malignancies

**Chandan K Das, Ajay Gogia, Lalit Kumar, Atul Sharma, Sanjay Thulkar[1], Immaculata Xess[2], Karan Madan[2]**

*Departments of Medical Oncology, [1]Radiology and [2]Microbiology, All India Institute of Medical Sciences, New Delhi, India*

## Abstract

**Background:** Pulmonary infection is the major risk during neutropenia induced by chemotherapy as well as stem cell transplantation. In spite of potent new-generation antifungal and broad-spectrum antibiotics, one-third of patients usually die from infectious complications. Early diagnosis and prompt administration of appropriate therapy improve the survival. **Materials and Methods:** We prospectively carried out the study to identify the infectious etiology of pulmonary infiltrates in febrile neutropenia patients by imaging and bronchoscopy. Bacterial culture, fungal culture, galactomannan and molecular diagnosis for pneumocystis, and other infectious agent were carried out in the bronchoalveolar lavage (BAL) fluid and blood. **Results:** A total of 27 patients were evaluated. Half of the patients belonged to acute leukemia (46%). We had a diagnostic yield of 65% with the most common isolates being Gram-negative bacteria and *Aspergillus* species. **Conclusion:** Gram-negative organisms were the predominant infectious agents of pulmonary infection. Our finding emphasizes the importance of BAL in evaluating pulmonary infiltrates in neutropenic patients with hematological malignancies.

**Keywords:** *Hematological malignancies, infection, pulmonary infiltrate*

## Introduction

Pulmonary infections represent the most common and dreaded infectious complications occurring during neutropenia phase of patients with cancer. The incidence of pneumonia in high-risk patients (e.g., patients with acute leukemia or stem cell transplant [SCT]) is 17%–24%.[1,2] In spite of potent mold-active antifungal as well as broad-spectrum antibiotic therapy, the clinical response is 60%–65%, whereas the infection-related fatality rate in these patients may be as high as 38%.[2] Thus, pulmonary infections are associated with a significant prognostic deterioration in patients with cancer. The Gram-positive organism is the predominant etiologies isolated.[1] The attributed mortality is high, particularly in patients affected by an invasive pulmonary mycosis. In patients with invasive pulmonary aspergillosis, the survival rates had been decimal (10%) in patients undergoing SCT.[3] Early detection of pulmonary infiltrates has been demonstrated to improve the outcome of (prompt) systemic antifungal treatment. Much effort has been made during the past 15 years to optimize diagnostic procedures to provide an early diagnosis of lung infections in patients with malignancies.[4] We carried out the study to determine the etiology of pulmonary infiltrates in febrile neutropenia episodes and correlate the radiological appearance of pulmonary infection and microbiologically documented infection of febrile neutropenia.

## Materials and Methods

This was a prospective study done at the Medical Oncology Ward, All India Institute of Medical Sciences (AIIMS), New Delhi, during November 1, 2014, to June 30, 2016. All febrile neutropenia episodes of hematological malignancy and hematopoietic SCT patients admitted during the study period in the Medical Oncology Wards fulfilling the inclusion and exclusion criteria were included. Patients with nonhematological malignancy with febrile neutropenia with pulmonary infiltrates and with preexisting pulmonary and cardiac dysfunction were excluded. The study approved by the Ethics Committee of AIIMS, New Delhi. After obtaining written informed consent, eligible patients were enrolled in the study and enrolment details related to personal and demographic profile, underlying disease, and clinical

**How to cite this article:** Das CK, Gogia A, Kumar L, Sharma A, Thulkar S, Xess I, *et al.* Evaluation of pulmonary infiltrate in febrile neutropenic patients of hematologic malignancies. Indian J Med Paediatr Oncol 2019;40:386-90.



**Submitted:** 18-Feb-2018
**Revised:** 19-May-2018
**Accepted:** 21-Jun-2018
**Published:** 04-Dec-2019

***Address for correspondence:***
*Dr. Ajay Gogia, Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi, India.*
*E-mail: ajaygogia@gmail.com*

**Access this article online**

**Website:** www.ijmpo.org

**DOI:** 10.4103/ijmpo.ijmpo_39_18

**Quick Response Code:**

presentation were noted. High-resolution computerized tomography (HRCT) was done after enrolment. The imaging findings were reviewed by an independent radiologist. Bronchoscopy was done and bronchoalveolar lavage (BAL) fluid isolated for microbiological investigation on those patients with pulmonary infiltrate on imaging. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and Mycoses Study Group (EORTC/MSG) Consensus Group criteria was used.[5]

## Results

A total of 55 patients were evaluated in the span of study duration. Half (51%) of the reasons for ineligibility in our patients were hemodynamically instability and low platelet count. Due to the risk of severe bleeding and unsustainability of bronchoscopy procedure, most of our patients they rendered were ineligible. We had enrolled 27 patients after written consent. One patient failed at bronchoscopy procedure due to respiratory distress. Of the 26 analyzable patients, majority of the patients belonged to acute myeloid leukemia (32%) and non-Hodgkin's lymphoma (32%), acute lymphoid leukemia (18%), Hodgkin's lymphoma (14%), and multiple myeloma (4%). We enrolled mostly adult patients with febrile neutropenia (88%), the median age being 37 years. Sixty-eight percent of our patients were male and the gender ratio was 2.14:1. The average duration of illness was 9.8 days. The median duration of onset of febrile neutropenia to bronchoscopy was 8.8 days. Fever was present in all patients. As most of our patients, the clinical focus was the pulmonary infection, respiratory distress present in 69% of patients at initial presentation. Another focus of infection was diarrhea (19%) and perianal soft-tissue infection (7%). Other clinical signs and symptoms at presentation were bleeding in 27% of patients; decreased urine output as defined by <1 ml/kg/h any time during hospital stay was 38%. Baseline characteristics of all patients are given in Table 1.

### Laboratory characteristics

Patients were evaluated regarding the complete blood count, renal function test, and hepatic function tests. All our patients were febrile neutropenia; 90% of our patients were anemic (<8 g/dL) requiring transfusion. The median leukocyte count was $1 \times 10^9$/L (range 0.2–1.45 × $10^9$/L. The median platelet count was $30 \times 10^9$/L (20–50 × $10^9$/L) and 27% of all patients presented with bleeding at the presentation from any site. As acute kidney injury (AKI) is the most common complication of sepsis, 10% of our patients identified as AKI and three of our patients required hemodialysis. As the acute leukemic patients generally nutritionally debilitated, the median albumin level of our patients was 2.9 g/dL. Hepatic dysfunction due to sepsis or leukemia or drug-induced presented in 10% patients.

**Table 1: Baseline characteristics of 26 febrile neutropenic patients**

| Parameter | Observation (range) |
|---|---|
| Age (year) | 37.5±19.2 (2-65) |
| Sex (male:female) | 2.1:1 |
| Presentation duration (days) | 9.8±5.2 (4-24) |
| Fever duration (days) | 8.8±4.4 (4-20) |
| Fever (%) | 26/26 (100) |
| Tachypnea/respiratory distress (%) | 18/26 (69) |
| Perianal/soft-tissue infection (%) | 2/26 (7) |
| Loose stool/vomiting (%) | 5/26 (19) |
| Decreased urine output (%) | 10/26 (38) |
| Bleeding (%) | 7/26 (27) |

### Imaging evaluation

HRCT was carried out on the patients with febrile neutropenia with pulmonary infection. The objective findings were lobar/lobular consolidation (50%), nodule (27%), ground glass opacity (23%), and effusion (11.5%) All the radiologic images were reviewed by independent radiologists. After radiologic review, 39% were classified as bacteria and 31% of the population classified as a fungal infection. Thirteen per cent of the patients were classified as mixed infection as per radiology.

### Bronchoalveolar lavage quality assessment

BAL quality assessment was done using physical as well as microbiological techniques. Chamberlin's criteria were used for quality assessment. Inadequate BAL sample was found in 5% of all samples collected. The complications of BAL are as follows: The procedure of bronchoscopy was well tolerated by the patients and the problems encountered (tachycardia – 11, hypoxia – 4, and throat pain – 8) were mild and reversible. One patient developed episodes of epistaxis postbronchoscopy, which was managed with conservative treatments.

### Serum and bronchoalveolar lavage galactomannan

Galactomannan was analyzed using enzyme-linked immunosorbent assay and 46% of our patients diagnosed as EORTC-MSG probable/possible invasive aspergillosis group. Serum galactomannan test came positive (optical density (OD) > 0.5) in 8/26 (30.7%) and BAL galactomannan positive (OD >1) in 4/26 (15.3%). A total of 17 microbiological isolates identified by BAL bacterial culture and 8 organisms isolated by blood culture. BAL fungal stain and culture identified two *Aspergillus flavus* species and one *Aspergillus terreus* species. We also stained and cultured the entire specimen for TB GeneXpert and Ziehl–Neelsen stain and Lowenstein–Jensen media culture but none of them. We did stain for *Norcardia* and *Actinomycosis* and anaerobic culture as a case-to-case basis. Cytomegalovirus polymerase chain reaction (PCR) was done for two patients. PCR for *Pneumocystis carinii* came positive for one patient [Table 2]. We correlate between the

**Table 2: Species distribution of microbiologically documented patients**

| Microbiological etiology isolated | *n* (percentage of isolated etiology) |
|---|---|
| *Acinetobacter* | 2/17 (11.7) |
| *Escherichia coli* | 2/17 (11.7) |
| *Klebsiella pneumonia* | 2/17 (11.7) |
| *Pseudomonas* | 2/17 (11.7) |
| *Burkholderia* | 1/17 (6) |
| Mixed Gram-negative bacteria | 4/17 (23 |
| Gram-positive bacteria | 0/17 (0) |
| *Aspergillus flavus* | 2/17 (11.7) |
| *Aspergillus terreus* | 1/17 (6) |
| *Pneumocystis jirovecii* | 1/17 (6) |

radiologic findings with the microbiological determination. Patients with fungal pneumonia the diagnostic etiology by radiology review a positive correlation exists with serum or BAL galactomannan elevation ($r$ = +0.46) and with documented fungal isolation ($r$ = +0.37). Patients were followed up up to 30-day postadmission. More than half of our patients recovered with antibiotic and inotrope support and 41% of our patients died. For majority of cases, the cause of death was due to multiorgan failure. The most common diagnosis at death was the refractory shock (80%), respiratory failure (15%), and pulmonary hemorrhage (5%).

## Discussion

Chemotherapy for hematological malignancies cause profound suppression of immune system and adversely affects the gastrointestinal mucosal integrity, and hence, they are at a heightened risk for invasive infection due to colonizing bacteria or fungi that translocate across intestinal mucosal surfaces. Profound prolonged neutropenia is most likely to occur in the preengraftment phase of allogeneic hematopoietic cell transplantation, and patients undergoing induction chemotherapy for acute leukemia are at risk of serious infection as compared to another chemotherapy schedule.

Pulmonary infection is the most common site of infection in patients with hematologic malignancies with febrile neutropenia.[2,6] We carried out the present study to evaluate the pulmonary infection in neutropenic patients using BAL and compare with the conventional method of diagnosis, e.g., clinical, radiology, blood, and BAL culture. The uniqueness of study population as it included the selected group of febrile neutropenic patients with hematologic malignancy. Fever in neutropenic patients is an emergency as it is almost always indicative of an underlying infective etiology. However, localizing signs may be subtle or absent. Respiratory signs were present in three-quarter of the patients in the present study, indicating that signs and symptoms of respiratory infection are blunted in many of these patients, as they are immunosuppressed. In contrast to the global trends of Gram-positive bacteria as the predominant infecting agent in febrile neutropenic patients, most of our isolated were Gram-negative organism 13/17 (76%). Gram-positive bacteria were not isolated separately in our study. This may be partly due to the fact that effective antibiotics active against Gram-positive bacteria were incorporated early as part of empirical antibiotic therapy and the pattern of infection has a significant geographic variation. Among the Gram-negative pathogens isolates, in 4/13 patients, extended-spectrum beta-lactamases positive bacteria were isolated. This points out to the emergence of these types of organisms as an important cause of infection in these patients. This also highlights the importance of using antibiotics that are capable of neutralizing the β-lactamase, produced by these organisms and incorporating them into upfront empirical antibiotic combinations. Therefore, each institution must have an antibiotic policy based on local prevalence and sensitivity patterns. In this aspect, BAL forms an important diagnostic tool for these patients to optimize antimicrobial treatment. In 2 out of 17 patients in whom organism was isolated, multiple bacteria or fungus were grown simultaneously. This may represent actual infection with more than one bacterium or may be due to contaminants. One of the disadvantages of the fiber optic bronchoscopy (FOB) is the possible contamination during its introduction through the nasal passage. Therefore, it is important to be careful during the procedure of collection and transport of the BAL specimen. Surveillance cultures from the upper airways and correlation with the BAL isolates may be helpful in distinguishing between contamination from the upper airway and true infection of the lower respiratory tract. Quantitative estimation of the cultures also would be helpful in this regard.

Invasive mycoses are one of the major causes of mortality in patients with febrile neutropenia. Patients undergoing treatment for hematologic malignancies have an estimated cause-specific mortality due to invasive fungal infections (IFI) of 35%.[3,7,8] In an EORTC/MSG study, factors significantly associated with the development of IFI/invasive mold infection are prolonged neutropenia, prolonged use of systemic corticosteroid, T-cell suppressive therapy, and recent SCT (<6 months before episode).[9] Similarly, relative or absolute T-cell deficiency or suppression by drugs is the major risk factor for the development of symptomatic pneumocystis infection.[10] Fungi could be grown in culture from three patients. However, none of the patients stained positive for fungi from the direct KOH examination indicates the relative insensitivity of KOH preparation. Twenty-two patients have received amphotericin-B as part of empirical treatment before bronchoscopy, which might have been a reason for KOH preparation being negative. The sensitivity of the organism to antifungals drugs was not done in our study. Strong clinical or radiological evidence of fungal

infection should be treated with the full course of antifungal therapy, as BAL cultures can be sterile for fungi, especially if the patient has already been started on antifungal therapy empirically. In our study, one patient came positive for *P. carinii*. The radiology was corroborative of these findings. She recovered from the *Pneumocystis pneumonia* after starting of trimethoprim-based therapy.

In neutropenic patients, only about 10% of conventional chest radiographs show abnormalities, whereas CT in these patients reveals pathological findings in 50% of cases.[11] For evaluation of pneumonia, HRCT with subsequent guided BAL has been recommended as the most sensitive technique.[12] HRCT is the preferred sequence of choice due to its thin collimation, more sensitive in detecting small nodule <5 mm, and no contrast media exposure. The relative sensitivity and specificity of HRCT to detect bacterial infection were 84.78% and 93.84%, while the for the fungal infection, it is 95.2% and 96.7%, respectively.[13] We correlate between the radiologic findings with the microbiological determination. In patients with fungal pneumonia, the diagnostic etiology by radiologic review, a positive correlation exists with serum or BAL galactomannan elevation ($r$ = +0.46) and with documented fungal isolation ($r$ = +0.37). The possible reasons for the lower strength of correlation were due to the low yield of fungal culture and low sample size.

The median duration of days between onset of symptoms and bronchoscopic evaluation was 9.8 days. This delay was due to the fact that most of our patients who developed pneumonitis had a hemodynamically unstable and poor performance status for withstanding the bronchoscopy procedure. Furthermore, we had to ensure a platelet count of at least 50,000/mm$^3$ before bronchoscopy. Most of our patients (90%) received single donor platelet before bronchoscopy; this was difficult to achieve as most of the patients had received intensive cytotoxic therapy and subsequently were severely myelosuppressive. Therefore, in achieving an adequate platelet count, the procedure was often delayed. A well-coordinated approach and aggressive platelet support should help in decreasing the time interval between onset of symptoms and BAL. Overall, the bronchoscopy procedure was well tolerated with minor reversible complications. We had a diagnostic yield of 65% similar as compared to the previously published study [Table 3].[14] However, the therapeutic utility or the change in the management was low as we usually start our therapy empirically. The identification of organisms ensured that the complete duration of antimicrobial therapy could be given to these patients as part of definitive therapy. Therefore, the actual benefit to the patients may have been higher than indicated. Furthermore, if these organisms are not eradicated fully, they could form part of resistant colonization. These could be the potential source of further morbidity in future chemotherapy.

**Table 3: Comparison of previous study evaluating pulmonary infiltrate in febrile neutropenic patients**

| Study | Gilbert *et al*.[14] | Present study |
|---|---|---|
| Sample size | 144 | 26 |
| Population | Hematopoietic stem cell transplant population | Hematologic malignancy and stem cell transplant |
| Diagnostic yield | 52.5% | 65% |
| Etiology | Bacterial (31%), fungal (15%), alveolar hemorrhage (11%) | 76% Gram-negative<br>17.6% fungal<br>0% Gram-positive/TB |
| Changes in therapy | 59% | 25% |
| Comments | 11% noninfectious causes | Anaerobe: Negative<br>TB: Negative |

TB – Tuberculosis

## Conclusion

Evaluation of pulmonary infiltrates in febrile neutropenia patients helps in optimizing antimicrobial therapy. Knowledge of prevalence of organisms and their sensitivity patterns would also help in formulating effective empiric antibiotic protocols. This would help in decreasing the morbidity and also in cutting the cost of antibiotic treatment. Our finding also emphasizes the importance of appropriate empirical antimicrobial therapy, which forms the mainstay of treatment for these patients. Our finding suggests that BAL has got several potential advantages in evaluating patients with hematological malignancies. However, it must be emphasized that the effectiveness of BAL depends on several local factors. The presence of good microbiological and cytopathological backup is crucial in analyzing the specimen. HRCT accurately correlates with the microbiological isolation. In summary, our experience with FOB and BAL in patients with hematological malignancies pulmonary infiltrates is encouraging. It has been a learning experience, and the results obtained would be of benefit in planning further studies.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

## References

1. Jagarlamudi R, Kumar L, Kochupillai V, Kapil A, Banerjee U, Thulkar S. Infections in acute leukemia: An analysis of 240 febrile episodes. Med Oncol 2000;17:111-6.
2. Kumar L, Kochupillai V, Bhujwala RA. Infections in acute myeloid leukemia. Study of 184 febrile episodes. J Assoc Physicians India 1992;40:18-20.
3. Auberger J, Lass-Flörl C, Ulmer H, Nogler-Semenitz E, Clausen J, Gunsilius E, *et al.* Significant alterations in the epidemiology and treatment outcome of invasive fungal

infections in patients with hematological malignancies. Int J Hematol 2008;88:508-15.

4. Maschmeyer G, Carratalà J, Buchheidt D, Hamprecht A, Heussel CP, Kahl C, *et al.* Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients (allogeneic SCT excluded): Updated guidelines of the infectious diseases working party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). Ann Oncol 2015;26:21-33.
5. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, *et al.* Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46:1813-21.
6. Hammond SP, Marty FM, Bryar JM, DeAngelo DJ, Baden LR. Invasive fungal disease in patients treated for newly diagnosed acute leukemia. Am J Hematol 2010;85:695-9.
7. Morgan J, Meltzer MI, Plikaytis BD, Sofair AN, Huie-White S, Wilcox S, *et al.* Excess mortality, hospital stay, and cost due to candidemia: A case-control study using data from population-based candidemia surveillance. Infect Control Hosp Epidemiol 2005;26:540-7.
8. Dasbach EJ, Davies GM, Teutsch SM. Burden of aspergillosis-related hospitalizations in the United States. Clin Infect Dis 2000;31:1524-8.
9. Hoenigl M, Strenger V, Buzina W, Valentin T, Koidl C, Wölfler A, *et al.* European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) host factors and invasive fungal infections in patients with haematological malignancies. J Antimicrob Chemother 2012;67:2029-33.
10. Sepkowitz KA, Brown AE, Armstrong D. *Pneumocystis carinii* pneumonia without acquired immunodeficiency syndrome. More patients, same risk. Arch Intern Med 1995;155:1125-8.
11. Heussel CP, Kauczor HU, Heussel GE, Fischer B, Begrich M, Mildenberger P, *et al.* Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: Use of high-resolution computed tomography. J Clin Oncol 1999;17:796-805.
12. Boersma WG, Erjavec Z, van der Werf TS, de Vries-Hosper HG, Gouw AS, Manson WL. Bronchoscopic diagnosis of pulmonary infiltrates in granulocytopenic patients with hematologic malignancies: BAL versus PSB and PBAL. Respir Med 2007;101:317-25.
13. Kang M, Deoghuria D, Varma S, Gupta D, Bhatia A, Khandelwal N. Role of HRCT in detection and characterization of pulmonary abnormalities in patients with febrile neutropenia. Lung India 2013;30:124-30.
14. Gilbert CR, Lerner A, Baram M, Awsare BK. Utility of flexible bronchoscopy in the evaluation of pulmonary infiltrates in the hematopoietic stem cell transplant population -- A single center fourteen year experience. Arch Bronconeumol 2013;49:189-95.