

The Utility of Routine Chest Radiography in the Initial Evaluation of Adult Patients With Febrile Neutropenia Patients Undergoing HSCT

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Abstract

Background: The routine use of chest radiographs (CXRs) in the initial evaluation of asymptomatic patients with febrile neutropenia undergoing hematopoietic stem cell transplant (HSCT) is controversial. **Objective:** The goal of this study was to document the incidence of pneumonia demonstrated on CXR during an initial febrile neutropenic episode in adult patients undergoing HSCT. **Materials and Methods:** Clinical records of 1083 adult patients undergoing autologous (n=766), allogeneic (n=269), or umbilical cord blood HSCT (n=48) between October 1, 2009, and December 31, 2012, were retrospectively reviewed. CXRs obtained at the initial febrile neutropenic episode were evaluated for radiologic features of pneumonia. The presence of clinical symptoms, length of stay (LOS), and readmission rates were assessed. **Results:** A total of 817 (75%) febrile neutropenic episodes were noted. Of the patients with neutropenic fevers, 455 (55%) had CXRs. Of the 76 patients with respiratory symptoms at the time of CXR, 24 (31.6%) had findings suggestive of pneumonia. None of the 379 CXRs performed in the absence of symptoms revealed an infectious process ($P=.0001$). Moreover, the mean LOS was 23.8 days for patients receiving a CXR compared with 22.2 days ($P=.04$) in patients without a CXR. Additionally, in patients who had CXRs, 15.7% were readmitted within 30 days compared with 7.4% in those without CXRs ($P=.0004$). **Conclusions:** Indiscriminate routine CXR at the time of first neutropenic fever in asymptomatic adults undergoing HSCT is unlikely to reveal an infectious process or change clinical practice, and may be associated with increased LOS and readmission rates. (J Natl Compr Canc Netw 2015;13:184–189)

Background

Most patients treated with myeloablative conditioning regimens before hematopoietic stem cell transplantation (HSCT) develop neutropenic fevers in the pre-engraftment period because of profound neutropenia.^{1,2} Fevers may signify potentially life-threatening

infections. The degree and duration of neutropenia depends on the intensity of the conditioning regimen and the source of donor stem cells.^{3,4}

Initial management of a febrile neutropenic episode involves obtaining at least 2 sets of blood cultures and immediate initiation of empirical broad-spectrum antibiotics with an antipseudomonal β -lactam agent.^{5,6} Current guidelines and evidence from retrospective trials in patients receiving chemotherapy or undergoing autologous and allogeneic HSCT suggest that additional investigational studies, particularly chest radiographs (CXRs), should be obtained in patients with clinical signs and symptoms suggestive of respiratory infection.^{7–11} However, the studies from which current guidelines were derived were primarily small, and involved pediatric populations. Because of the unique nature of adult transplant populations, the purpose of this quality improvement project was to investigate the incidence of pneumonia demonstrated on routine CXRs at the time of the initial febrile neutropenic episode in a group of patients undergoing autologous and allogeneic HSCT.

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Materials and Methods

We reviewed records of consecutive adult patients who underwent either myeloablative allogeneic, reduced-intensity/myeloablative umbilical cord blood transplantation (UCBT), or autologous HSCT at Dana-Farber/Brigham and Women's Cancer Center between October 1, 2009, and December 31, 2012. Patients undergoing reduced-intensity conditioning allogeneic HSCT were excluded from the analysis because they were typically discharged within 2 days of stem cell infusion. Fever was uniformly defined as an oral temperature greater than 100.4°F (38.0°C) or axillary temperature greater than 99.4°F (37.4°C). Neutropenia was defined as an absolute neutrophil count less than 500 cells/mL. Symptoms of respiratory illness were documented, including cough, shortness of breath, and chest pain. Physical examination findings concerning for a pulmonary process included tachypnea (respiratory rate >20 breaths per minute) and hypoxia (oxygen saturation <90%); rales, rhonchi, and/or decreased breath sounds were also noted. At the onset of first neutropenic fever, blood cultures were drawn from the periphery and from all central lines. All patients received intravenous antibiotic coverage with cefepime, ceftazidime, piperacillin/tazobactam, or imipenem after blood cultures were drawn. Historically, CXRs were automatically ordered as part of the initial febrile neutropenia workup. As of July 2012, CXRs were ordered according to physician preference, instead of according to strict adherence to guidelines. Most of the CXRs ordered for the inpatients were obtained within 24 hours of initiation of antibiotics. Baseline characteristics and patient demographics were retrieved from the Dana-Farber Cancer Institute (DFCI) HSCT repository. Data including the day of transplantation, patient-reported symptoms, physical examination, and culture results were obtained from the electronic and paper medical records. CXRs were reviewed by staff radiologists at Brigham and Women's Hospital at the time of study completion. Abnormal CXRs were compared with the pre-HSCT films of the patients. Radiologic findings consistent with pneumonia, including the presence of confluent consolidative radiodensities, air bronchograms, and a lack of evidence of volume loss suggestive of atelectasis, were all included as possible cases of pneumonia. Additional thoracic imaging was

obtained at the discretion of treating physicians. Descriptive statistics were used to compare baseline characteristics. Fisher exact test was used for 2 sample comparisons. Statistical significance was defined as a *P* value less than .05. Analyses were performed using SAS software.

Results

Patient Demographics

A total of 1083 patients were admitted for HSCT between October 1, 2009, and December 31, 2012; 766 patients were admitted for autologous HSCT, 269 were admitted for myeloablative allogeneic HSCT, and 48 were admitted for either myeloablative or nonmyeloablative UCBT. Of the 766 patients admitted for autologous HSCT, 452 had multiple myeloma, 227 had non-Hodgkin's lymphoma (NHL), and 87 had Hodgkin lymphoma. This subgroup included 476 men and 290 women, and the median age was 61 years (range, 21–77 years). Of the 269 patients admitted for allogeneic HSCT, 121 had acute myeloid leukemia, 49 had acute lymphoblastic leukemia, and 44 had myelodysplastic syndromes/myeloproliferative diseases; the remainder of the primary malignancies are discussed in Table 1. This subgroup included 145 men and 124 women, and the median age was 46 years (range, 21–66 years). Of the 48 patients admitted for double UCBT, most had acute myeloid leukemia (n=19) or NHL (n=13). This subgroup included 33 men and 15 women, and the median age was 53 years (range, 25–68 years). The primary malignancies of the patients admitted for HSCT are described in Table 1.

Febrile Neutropenia

A total of 825 febrile neutropenic episodes were noted in the 1083 patients (75.0%). Of the 766 patients who underwent autologous HSCT, 547 (71.4%) developed febrile neutropenia. Significantly more patients with lymphoma (276 of 314; 87.9%) developed neutropenic fevers than those with myeloma (271 of 452; 60.0%; *P*<.001). The median day of first neutropenic fever was day +6 (range, day –9 to +12), with day 0 being the day of stem cell infusion. The number of patients with febrile neutropenia in the allogeneic HSCT group was 240 of 269 (89%). The median day of first neutropenic fever was day +6 (range, day –8 to +13). In the

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Table 1 Primary Malignancies and Breakdown by Transplant Type

Primary Malignancies	Autologous	Allogeneic ^a	Umbilical Cord Blood ^b
ALL	–	49	3
AML	–	121	19
Aplastic anemia	–	15	0
CLL	–	5	2
CML	–	12	2
HLH	–	1	0
Non-Hodgkin's lymphoma	227	18	13
Hodgkin lymphoma	87	1	1
MDS/MPD	–	44	8
Multiple myeloma	452	3	0
Total	766	269	48

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HLH, hemophagocytic lymphohistiocytosis; MDS, myelodysplastic syndromes; MPD, myeloproliferative diseases.

^aPatients who received myeloablative bone marrow or peripheral blood stem cell transplant.

^bThese patients underwent either myeloablative or reduced-intensity conditioning.

UCBT group, 38 of 48 patients (79%) had febrile neutropenia, and the median day of first neutropenic fever was day +8 (range, day –7 to +16).

Chest Radiography

Of the 825 patients evaluated with febrile neutropenia, 455 (55.2%) had a CXR completed within 48 hours of their first temperature spike. Of the 547 patients undergoing autologous transplant who developed neutropenic fevers, 272 (49.7%) had CXRs, 30 of which were performed in the setting of either respiratory symptoms or abnormal findings on examination. Of these 30 CXRs, 10 showed significant radiologic findings leading to new or continued management for a pulmonary infection. No significant difference was seen in the percentage of patients with respiratory symptoms or findings on physical examination who subsequently had evidence of pneumonia on CXR (40% vs 20%; $P=.43$). Comparatively, none of the 242 CXRs ($P=.0001$) performed in asymptomatic patients were concerning for a new infection.

More patients with febrile neutropenia received CXRs after allogeneic HSCT than after autologous HSCT (153 of 240; 63.8%; $P=.002$). Only 41 patients who underwent allogeneic HSCT had documented respiratory findings, with 31 having physical findings suggestive of a pulmonary process and 10 having new symptoms, such as cough or shortness of breath. Of the 41 patients with findings, 12 (29%) had new

or worsening infiltrates on CXR. No significant difference was seen in the percentage of patients with respiratory symptoms or findings on examination who subsequently had evidence of pneumonia on CXR (50% vs 33%; $P=.45$). In contrast, none of the 112 CXRs ($P=.0001$) performed in the absence of symptoms was concerning for infection. In the UCBT group, 30 of 38 patients (78.9%) with febrile neutropenia underwent a CXR. This was significantly more than in the other 2 groups ($P=.002$). Of the 30 patients, 5 who had CXRs had either a cough or hypoxemia; of these, 2 had multifocal pneumonia on CXR. None of the other 25 films ($P=.023$) that were performed in the absence of symptoms revealed an infectious process. Table 2 summarizes the radiographic findings in the different groups.

Patient Outcomes

Length of stay (LOS) in the different populations was reviewed. In the patients who underwent myeloablative allogeneic or autologous HSCT, the shortest LOS was noted in the patients without an episode of febrile neutropenia, with a mean of 19.05 days. The mean LOS for patients who had fevers was 23.1 days ($P=.0001$). When specifically considering the 425 patients who received a CXR at the time of the first temperature spike, the mean LOS was 23.8 days compared with 22.2 days ($P=.04$) in the 362 patients who did not receive a CXR. In the patients who underwent

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Table 2 Evidence of PNA on CXR Obtained Within 48 Hours of Fever

	Total CXR Ordered	Reported PNA With Respiratory Symptoms or Signs	Reported PNA With No Respiratory Symptoms or Signs	P Value
Autologous transplant	272	10 of 30	0 of 242	.0001
Allogeneic transplant				
Myeloablative transplant ^a	153	12 of 41	0 of 112	.0001
Umbilical cord blood transplant ^b	30	2 of 5	0 of 25	.0230

Abbreviations: CXR, chest radiograph; PNA, pneumonia.

^aPatients who received peripheral blood or bone marrow transplants and did not receive umbilical cord blood transplants.

^bPatients received either reduced-intensity or myeloablative conditioning.

a UCBT, the shortest LOS of 30.7 days ($P=.04$) was documented in those without fevers. Among patients with febrile episodes, the mean LOS was 45.8 days in those who had CXRs at the time of initial temperature spike. This was similar to the mean LOS of 44.6 days ($P=.89$) noted in patients without documented CXRs.

Readmissions in the groups were also evaluated. In the patients who underwent myeloablative allogeneic and autologous HSCT, 19 of 248 patients (7.7%) without fevers during neutropenia and 94 of 787 (11.9%; $P=.06$) with fevers were readmitted within 30 days. Among those with fevers who underwent a CXR, 67 of 425 (15.7%) were readmitted, whereas only 27 of 362 (7.4%; $P=.0004$) without a CXR were readmitted within 30 days. Similarly, in the patients who received a UCBT, only 1 of 10 (10%) without neutropenic fevers were readmitted within 30 days compared with 12 of 38 (31.5%; $P=.24$) with fevers. In patients with fevers who received a CXR, 8 of 20 (40%) were readmitted compared with 4 of 15 (26.6%; $P=.49$) without CXRs.

Discussion

Patients undergoing HSCT are at particularly increased risk for infections as a result of prolonged neutropenia and deficiencies in cellular and humoral immunity. At Dana-Farber/Brigham and Women's Hospital, all patients who develop febrile neutropenia while receiving a stem cell transplant undergo an extensive evaluation consistent with NCCN and Infectious Diseases Society of America guidelines, involving a detailed history and physical examination, blood and urine cultures, and site-specific cultures and/or imaging.^{5,6,12} Before October 31, 2011, the practice at our institution was to include a rou-

tine CXR as part of the initial evaluation for patients with febrile neutropenia.

We conducted a retrospective investigation in a large cohort of adult patients that included both allogeneic and autologous HSCT recipients. Strikingly, none of the 379 CXRs obtained in asymptomatic individuals revealed radiographic findings of an infection. Moreover, all of the 24 patients with CXR findings concerning for infection had symptoms at the time that imaging was obtained. Importantly, most antibiotic regimens were not stopped or changed until the patient engrafted, regardless of CXR results.

The routine use of CXR in the initial evaluation of asymptomatic patients with febrile neutropenia is controversial. Minimal literature supports its utility, and the yield of conventional radiography is low in the early stages of pneumonia because of a diminished inflammatory response.^{10,13-15} The results presented herein were in concordance with those of most previous studies. Reports by several pediatric groups suggest that CXRs have limited benefit in children with routine febrile neutropenia after chemotherapy.⁸⁻¹⁰ In a study examining the utility of CXR during the initial febrile neutropenia episode in 81 pediatric patients receiving allogeneic HSCT, routine CXR only yielded evidence of a pulmonary infiltrate in 5 (6%) of the patients.⁷ Similar results have been demonstrated in adult patients with febrile neutropenia in both the ambulatory¹⁶ and inpatient setting.¹⁷ Oude Nijhuis et al¹⁶ found that only 2 of 109 (1.8%) CXRs were suggestive of pneumonia in ambulatory patients with febrile neutropenia without clinical signs of new pulmonary disease. Similarly, Navigante et al¹⁷ reported that only 2.3% of hospitalized oncology patients had CXR findings consistent with pneumonia in the absence of respiratory symptoms.

Contrary to the present findings, in a study of 61 adult patients who underwent autologous transplant, Roy et al¹⁸ reported that up to 31% of patients with abnormal CXRs had no clinical findings suggestive of pulmonary infection. The difference between the present results and those reported by Roy et al¹⁸ might be explained by the disparate patient populations and institution-specific antibiotic prophylactic protocols. At our institution, most of the patients who underwent autologous transplant had multiple myeloma, whereas most patients in the Roy et al¹⁸ study had breast cancer. All patients at our institution received prophylaxis with trimethoprim-sulfamethizole, levofloxacin, acyclovir, and nystatin or clotrimazole troches, whereas prophylaxis in the study by Roy et al¹⁸ included ofloxacin, acyclovir, and fluconazole, but did not include trimethoprim-sulfamethizole.

Looking specifically at the predictive values of respiratory symptoms, such as cough and shortness of breath, compared with respiratory signs on physical examination, such as rales and rhonchi, we found no significant difference in the percentage of patients with these findings who had evidence of pneumonia on CXR. Although the numbers are small, they suggest that CXRs should be considered in all patients with either a history of respiratory symptoms or abnormal physical examination findings.

It was also noted that both LOS and readmission rates in patients with fevers were significantly lower in those who did not undergo a CXR compared with those who did. A few factors could contribute to the differences in these important hospital metrics. The completion of radiologic studies depends on the availability of slots in radiology. A routine radiologic study ordered for fevers is usually completed and interpreted by a staff radiologist within 24 to 48 hours of order placement. Awaiting these results can lead to delays in care, such as changes or discontinuation of antibiotics. In addition, the development of new symptoms or signs without a cause elucidated on CXR requires further evaluation and possible intervention that may lead to further delays in discharge. With this, one may infer that the use of CXR during the initial febrile neutropenia episode in patients who underwent HSCT is a surrogate marker for acuity, which indirectly impacts LOS and readmission rates. This information could be used as part of a tool to predict discharge timing and risk of readmission.

The impact of LOS on outcome metrics such as cost has recently been evaluated in the HSCT population. In several studies, LOS has been shown to be a useful proxy for short-term costs.^{19,20} Each day a patient remains in the hospital impacts the overall cost, with baseline median costs ranging from \$55,000 to \$75,000 for an autologous HSCT and \$150,000 to \$175,000 for a myeloablative allogeneic HSCT.²¹ Furthermore, additional time in the hospital may increase the risk for hospital-associated complications, such as infection or venous thromboembolism.

Based on the initial observations that the utility of CXRs in diagnosing infection in the absence of symptoms was low and care outcomes were not improved as a result of the studies being ordered, we implemented an institution-wide policy limiting CXRs to symptomatic patients who underwent autologous HSCT. Using Lean Six Sigma and other process improvement techniques, the percentage of CXRs obtained at the initial febrile neutropenic episode in asymptomatic patients who underwent autologous transplant was reduced from 50% to 5% during the first 6 months of the intervention. Before this intervention, the 1-year cost associated with ordering CXRs in asymptomatic patients with febrile neutropenia who underwent autologous HSCT was \$43,420. The savings associated with reducing the percentage of unnecessary CXRs to 5% in asymptomatic autologous patients with febrile neutropenia was approximately \$38,858. Applying the same rationale, in 2012, a total of 236 allogeneic HSCTs were performed at DFCI; reducing the number of CXRs in the allogeneic population would have assumed a cost savings of approximately \$54,821.

In addition to promoting institutional cost savings, the reduction in routine CXRs will lead to less radiation exposure to patients undergoing possibly curative therapy. In 1996, an estimated 52 CT scans were performed per 1000 people, and in 2010 that number increased to 149 per 1000 people.²² Each CXR exposes a patient to 0.1 mSv of radiation. This is equivalent to 10 days of exposure to natural causes of radiation, such as radon.^{23,24} Although the risk of subsequent malignancy is extremely low as a result of one CXR, each additional radiologic study increases the total lifetime risk. In addition to the risks of radiation exposure, unnecessary anxiety is provoked when studies report false-positive or

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equivocal findings that require further workup or intervention. Unless these radiologic studies can be shown to be associated with improved detection of infection or disease or to improve outcomes, careful thought should be given to ordering studies that may not be medically necessary.

Conclusions

Indiscriminate routine CXR at the time of first neutropenic fever in asymptomatic patients who have undergone HSCT is unlikely to reveal an infectious process or change clinical practice. Moreover, a reduction in the number of unnecessary CXRs ordered can lead to cost savings and reduced radiation exposure without compromising patient care.

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