

# Routine radiography does not have a role in the diagnostic evaluation of ambulatory adult febrile neutropenic cancer patients

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## Abstract

Cancer patients treated with chemotherapy are susceptible to bacterial infections. When an adult patient presents with febrile neutropenia, standard diagnostic care includes physical examination, laboratory diagnostics, chest X-ray (CXR) and sinus radiography. However, the yield of routine radiography in the diagnostic evaluation of ambulatory adult febrile neutropenic patients with normal findings at their physical examination is questionable. Two CXRs and one sinus X-ray were obtained in 109 and 106 febrile neutropenic episodes after chemotherapy in ambulatory adult patients who had no clinical signs suggesting pulmonary infection or sinusitis. We found that in only two of 109 (1.8%; 95% Confidence Interval (CI): 0.3–5.8%) febrile neutropenic episodes without clinical signs of new pulmonary disease, the CXR showed a consolidation suggesting pneumonia. In addition, in five of 88 (5.7%; 95% CI: 2.2–12.0%) febrile episodes in asymptomatic patients, sinus X-ray suggested sinusitis. In none of these seven episodes was a change of antibiotic therapy necessary. In the absence of clinical signs indicating pneumonia or sinusitis, the yield of CXR and sinus radiography in ambulatory adult cancer patients presenting with febrile neutropenia is minimal; CXR and sinus radiography should no longer be performed on a routine basis.

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## 1. Introduction

Cancer patients who are treated with chemotherapy show an increased susceptibility to bacterial infections due to disturbances in their innate immune system. Bodey and colleagues reported already more than 30

years ago that the most important factor for the increased infection risk is an absolute neutrophil count below  $0.5 \times 10^9/l$ , especially in cases of prolonged neutropenia ( $> 7$  days) [1]. Fever can be the first sign of a bacterial infection. However, fever may also be due to other causes such as viral infection, transfusion of blood products, tumour, or medication. Moreover, neutropenic patients with fever seem to be a heterogeneous population with variable risks for bacterial infection and medical complications [2,3]. Ambulatory patients with a shorter duration of neutropenia seem to be at a

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low risk for severe bacterial infections such as pneumonia and sinusitis [4,5].

Standard diagnostic evaluation of a patient with febrile neutropenia consists of history taking, performing a thorough physical examination, complete blood cell counts and bacterial cultures (blood, urine and stools when indicated). In addition, routine radiography consisting of chest X-ray (CXR) and sinus X-ray is mostly performed to increase the chance of finding a potential infectious focus [6,7].

However, the necessity of obtaining routine X-rays in all febrile neutropenic patients, regardless of the outcome of the history and physical examination, is debatable. In asymptomatic febrile neutropenic children, it has been described that the yield of CXR is very low [8–10]. In addition, conventional radiography is found to be quite insensitive in detecting consolidations in neutropenic patients in an early stage, which is mainly due to the fact that radiological signs of a bacterial infection during neutropenia may be reduced due to a diminished and delayed inflammatory response [8,11].

Because CXR and sinus radiography are still widely applied in daily practice, it is worthwhile to investigate the yield and therapeutic consequences of these routine radiographic diagnostics in outpatients after standard-dose chemotherapy. Therefore, the aim of this study was to evaluate whether CXR and sinus radiography should still be performed on a routine basis in all ambulatory adult cancer patients who present with febrile neutropenia.

## 2. Patients and methods

### 2.1. Patients

This study was performed at the department of Internal Medicine of the University Hospital, Groningen. Febrile neutropenic episodes in adult cancer patients presenting at the outpatient clinic between April 1999 and April 2002 were prospectively entered in this study (86 episodes in 72 patients). In addition, febrile neutropenic episodes in adult cancer patients who had been enrolled in two well documented studies investigating the role of growth factors in febrile neutropenia were included (34 episodes in 27 patients) [12,13].

All ambulatory adult patients with fever and chemotherapy-induced neutropenia without clinical signs suggesting pulmonary infection or sinusitis were considered to be eligible. Fever was defined as body temperature  $>38.5^{\circ}\text{C}$  once or  $>38.0^{\circ}\text{C}$  during an observation period of 6 h. Neutropenia was defined as granulocytes  $<0.5 \times 10^9/\text{l}$  or leucocytes  $<1.0 \times 10^9/\text{l}$ . Tachypnoea (breath rate above 20/min or 25% above baseline), rales and/or decreased breath sounds were defined as abnormal clinical signs on physical examination suggesting

pulmonary infection. In the absence of previous documented signs, they were suggestive for new infectious pulmonary disease. Clinical signs indicating sinusitis were headache and/or tapping pain and tenderness over the sinuses. Patients who had already received antibiotics or had undergone bone marrow or stem cell transplantation were excluded. The use of selective gut decontamination was not an exclusion criterion.

The study protocol was approved by the institutional review board.

### 2.2. Methods

All patients underwent a full medical history and physical examination at presentation, and laboratory diagnostics and bacterial cultures were performed. Two CXRs (posterior-anterior and lateral) and one sinus X-ray were obtained. The X-rays were assessed by different staff radiologists at the time of admission of the patient. At a later stage, one staff radiologist reviewed all X-rays again without knowledge of the outcome of the physical examination. All patients were hospitalised and received standard therapy consisting of broad spectrum intravenous (i.v.) antibiotics.

## 3. Results

A total group of 120 febrile neutropenic episodes in 99 patients were entered in this study. Hundred and nine febrile neutropenic episodes in 89 patients were included for the chest X-ray analysis (no clinical signs suspect for a pulmonary infection). Hundred and six febrile neutropenic episodes in 88 patients were included for the sinus X-ray analysis (no clinical signs indicating sinusitis). Patient characteristics are shown in Table 1.

Table 1  
Characteristics of the patients with episodes of fever and neutropenia

Characteristic	Number of episodes ( <i>n</i> = 120)
Age (years)	
Median (range)	45 (18–77)
Gender no. (%)	
Female	75 (63)
Male	45 (38)
Type of cancer no. (%) <sup>a</sup>	
Breast cancer	26 (26)
Haematological malignancy	26 (26)
Lung cancer	20 (20)
Testicular cancer	7 (7)
Other solid tumours	20 (21)

<sup>a</sup> In number of patients (*n* = 99).

### 3.1. Chest radiography

All of the enrolled 109 febrile neutropenic episodes were documented with two CXRs. In 36 of the 109 (33%) febrile neutropenic episodes, CXRs were abnormal. Thirty-four of these abnormal CXRs (94%) were due to other causes than bacterial pneumonia, i.e. the known malignant disease in 30 episodes, radiation fibrosis in one episode, and a known elevation of the right side of the diaphragm in three cases. In two of the 109 (1.8%; 95% Confidence Interval (CI): 0.3–5.8%) febrile neutropenic episodes, abnormalities on the CXR were diagnosed as consolidation suggesting pneumonia. No clinical signs of pulmonary infection were observed at presentation. One of the two positive X-rays was found in a patient with small-cell lung carcinoma arising from the left pulmonary hilus with metastases in the right lung. At presentation with febrile neutropenia, she had rhonchi over her left lung, but no other obvious signs of pneumonia. CXR showed a new consolidation suggesting pneumonia in the left pulmonary hilus next to the primary tumour. The other positive X-ray was in a patient who had obvious clinical and radiological signs of a sinusitis, and this was thought to be the reason for the febrile episode. However, CXR showed a possible new consolidation in the left lung as well. The outcome of the CXR in these patients did not alter the standard antibiotic therapy.

### 3.2. Sinus radiography

Eighty-eight of the enrolled 106 febrile neutropenic episodes (83%) were documented with a sinus X-ray. Nine of the 88 (10%) sinus X-rays obtained showed abnormalities. Four of them were abnormal due to causes other than sinusitis. One sinus X-ray showed the remains of a rhabdomyosarcoma whereas the others showed minimal mucosal swelling in one of the sinuses not sufficient for a radiological diagnosis of sinusitis. Five of the 88 (5.7%; 95% CI: 2.2–12.0%) sinus X-rays showed opacification suggestive of sinusitis. One of these positive sinus X-rays showed a right-sided sinusitis with multiple localisations. This patient had no clinical signs of sinusitis except fever. The day after admission, an anthroscopy of the right maxillary sinus was performed by the ear, nose and throat specialist, but no signs of sinusitis were found. One other patient had bilateral sinusitis with multiple localisations, while she clinically only suffered from a cold. 2 other patients had bilateral maxillary sinusitis and 1 patient had maxillary sinusitis on the right side. This last patient remained febrile on broad spectrum i.v. antibiotics, while at the same time her lymphoma showed rapid progression. This suggests that the febrile episode might have been due to tumour progression rather than sinusitis. Standard antibiotic therapy was not changed in

any of the patients, except for starting saline and xylo-methazolin nose drips in 3 patients and anthroscopy in 1 patient.

## 4. Discussion

Cancer patients who are neutropenic due to chemotherapy are highly prone to bacterial infections. Therefore, all patients with fever during a neutropenic period receive an elaborate diagnostic evaluation. Routine radiography has been part of this for a long time, despite little data about its utility. We questioned whether routine radiography adds extra information to the outcome of the physical examination in asymptomatic ambulatory adult cancer patients who present with febrile neutropenia.

Several groups studied the yield of routine chest radiography in children with febrile neutropenia after chemotherapy [8–10]. In total, it was found that only 4 of 330 (1.2%) had pneumonia confirmed on chest X-ray which was not suspected by physical examination. The conclusion of these studies was therefore that routine chest X-ray at diagnostic evaluation is unnecessary in the asymptomatic ambulatory paediatric patient. In adult febrile neutropenic patients, Jochelson and colleagues were the first to question the role of the routine chest X-ray [14]. They concluded after evaluating 75 episodes that the chest radiograph had a low diagnostic yield in febrile neutropenic patients with no signs or symptoms of pneumonia. In addition, Donowitz and colleagues concluded after their retrospective review of 195 febrile episodes in 127 patients that chest X-rays seem to be an important diagnostic tool in cases of persistent fever or recurrent fever, but had a marginal value during initial febrile episodes [15]. A more recent study shows that only 2.3% of the enrolled patients had a positive CXR suggesting pneumonia that was not suspected by history or physical examination [16].

Despite these results, routine radiography consisting of at least CXR and often sinus X-rays is still the standard of care in adult cancer patients who present with febrile neutropenia [7].

Our results show that in only two of the 109 (1.8%) evaluated febrile neutropenic episodes, the CXR yielded essential information to a negative physical examination. One of these episodes occurred in a patient with lung cancer. Because of the increased risk for bronchial obstruction by the primary tumour potentially leading to postobstruction infection, it is arguable that in lung cancer patients, CXRs should always be obtained, irrespective of the outcome of the physical examination. However, low sensitivity of X-ray for detecting consolidations in neutropenic cancer patients pleads against this.

High-resolution computed tomography (CT), on the other hand, seems to have much higher sensitivity [17].

Heussel and colleagues found that in neutropenic bone marrow or stem cell recipients with persistent fever despite antibiotic therapy, high-resolution CT showed consolidation suggesting pneumonia in up to 60% of the patients whereas the CXRs were still normal [18].

In only five of the 88 (5.7%) episodes in patients without clinical signs of sinusitis, the sinus X-ray suggested sinusitis. Mucosal swelling was often found. Whether this should be seen as a sign of bacterial infection remains uncertain, because it could also be related to chemotherapy-induced mucositis. Moreover, in all these patients a change of the standard antibiotic therapy was not necessary.

In view of the increased tendency for treating a subset of low-risk febrile neutropenic patients with oral antibiotics, possibly as outpatients, a thorough physical examination to look for an infectious focus is of imminent importance. When abnormalities are found further action in the form of imaging techniques like X-rays and/or high-resolution CT should be taken. However, when clinical signs suggestive of pneumonia or sinusitis are absent, the yield of radiography in most ambulatory adult cancer patients is minimal. Therefore, CXR and sinus X-ray should no longer be performed on a routine basis in asymptomatic patients with febrile neutropenia presenting in the outpatient clinic. Whether these conclusions apply for hospitalised febrile neutropenic patients as well needs to be investigated. Moreover, a more selective application of CXRs and sinus X-rays in cases of febrile neutropenia will lead to considerable cost savings.

#### 4.1. Conflict of interest statement

All authors disclosed any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

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