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Article Title: Limited utility of routine chest X-ray in initial evaluation of neutropenic fever in patients with haematological diseases undergoing chemotherapy.

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ABSTRACT

Background

Routine chest X-Ray (CXR) is recommended for neutropenic fever(NF) management however its role is relatively understudied in haematology patients.

Methods:

Retrospective, single-centre analysis of haematology patients admitted with NF between January 2011-December 2015. Baseline demographics, treatment details and outcomes were collected from electronic patient records. CXRs underwent independent radiology review. Primary endpoints were proportion of NF episodes in which CXR detected a probable chest infection in the absence of respiratory symptoms/signs, and/or resulted in a change in antibiotic management.

Results:

Four hundred and thirty-five episodes were identified; CXR was performed in 75% of patients (65% within 2 days of NF). In 4/164 (2.4%) of asymptomatic patients, CXR was consistent with infection, in contrast to 19/119 (16%) patients with clinical signs of respiratory infection. Only 3/283 (1.1%) CXRs resulted in a change to antibiotics. CXR consistent with infection was not associated with increased mortality or increased admission length, although there was an association with ICU admission (OR:7.61, 95%CI:2.04–28.31).

Conclusion:

In haematology patients with NF, CXR rarely detected chest infection or changed management in patients with no respiratory symptoms or signs. CXR in our institution is no longer part of routine assessment of NF in the absence of these features.

Introduction

Patients receiving myelosupressive therapies for haematological conditions are at significant risk of NFneutropenic fever (NF) which can lead to life threatening complications such as overwhelming sepsis and death.[1] Guidelines for investigation of NF recommend a thorough initial assessment to identify potential sources of infection, investigation with blood cultures, urinalysis, serum biochemistry, liver function tests and a routine chest X-ray (CXR) even in the absence of respiratory symptoms and signs.[2-4]

Despite these guidelines, there is little evidence supporting routine diagnostic CXR in NF. Two small series of solid and haematological cancer patients with NF reported CXR detection of chest infection in less than 3% of patients with no respiratory symptoms or signs.[5,6] The low detection rate of chest infection in NF patients is also reflected in paediatric febrile neutropenic populations.[7,8] One meta-analysis found that a febrile neutropenic child with no signs or symptoms had a 1.9% probability of having chest infection.[7]

To our knowledge, no large study of adult cohorts has reported the impact of CXR on management decisions or outcomes according to CXR results. Addressing this issue is relevant as while a CXR is considered relatively inexpensive, it contributes to the overall healthcare bill, exposes patients to additional radiation and may require immunocompromised patients to be removed from a filtered 'clean air' environment.

With the support of our institution's (Austin Health) 'Choosing Wisely' initiative, this study investigated the utility of CXR both in diagnosis and in management decisions for patients with haematological conditions complicated by NF.

Methods

Patients

Data was collected from a large tertiary referral centre. Eligible patients were aged 16 years or above, undergoing recent (within last 2 months) myelosuppressive chemotherapy for an underlying haematological condition, with NF (defined as temperature: $\geq$37.5°C and neutropenia: <1.5 x 10^9/L) between 1st January 2011 to 31st

December 2015. For the purposes of this study, NF episodes were further stratified based on Infectious Diseases Society of America definition (oral temperature ≥ 38.3°C and profound neutropenia of < 0.5 x 10^9/L at presentation). [2] Patients with known intercurrent pneumonia prior to the episode of NF were excluded.

The institutional guidelines recommend posaconazole anti-fungal prophylaxis in high-risk patients (defined as patients with acute leukaemia receiving intensive induction therapy) but no routine antibiotic prophylaxis. All patients with NF either on the ward or presenting to the emergency department were recommended to undergo clinical assessment, blood cultures, urinalysis, CXR, haematology and biochemistry analysis followed by prompt administration of intravenous broad spectrum antibiotics.

Data collection

Patients were identified from the hospital database via a search of cases admitted under the institutional haematology unit for NF. Patients included those who presented to the emergency department with NF and patients (including newly diagnosed) who were admitted for myelosupressive therapy and subsequently developed NF. Data were collated from electronic patient records and included patient demographics, haematological diagnosis, treatment details, documented pulmonary comorbidities, and details of NF at the time of initial presentation (neutrophil count, clinical assessment findings including respiratory symptoms/signs of dyspnoea, chest pain, cough, crepitations, wheeze, reduced air entry, elevated respiratory rate, hypoxia, vital signs, antibiotic therapy, inpatient hospital stay duration and treatment received). Initial CXR results were recorded in addition to documented change in antibiotic treatment subsequent to chest imaging. Only routine CXR performed for initial NF evaluation (within 2 days of NF diagnosis) were analysed. Known and unchanged pre-existing lung lesions were not recorded as abnormal. CXRs were reviewed by a blinded independent radiologist. CXRs were scored by the radiologist as highly suspicious for infection, (defined as features consistent with consolidation, collapse, parenchymal opacities or pleural effusions not attributable to underlying malignancy), versus indeterminate (abnormalities present but not consistent with infection) versus normal.

Statistical analysis

Baseline demographics characteristics, abnormal CXR results and changes in antibiotic management were summarised as (interquartile ranges and ranges) for continuous characteristics and as counts (proportions) for categorical characteristics. Two-tailed Fisher exact test was used to compare the proportions of abnormalities in standard CXR vs portable CXR.

Due to the nature of repeated measures, where individual patients may be observed on multiple occasions, unadjusted random-effect logistic regression models with patients as a random effect were used to test the individual associations between absence or presence of abnormal CXR and gender, age, history of asthma, history of chronic obstructive pulmonary disease (COPD), smoking history, cancer type, admissions where haematopoietic (autologous or allogenic) stem cell transplant was performed, neutrophil count ($\geq 0.5 \times 10^9$/L versus $< 0.5 \times 10^9$/L), neutrophil nadir of 0, temperature (37.5°C - 38.3°C versus ≥38.3°C) and respiratory symptoms or signs.

Similarly, the association between absence or presence of abnormal CXR and ICU admission, inpatient mortality and admission length were tested using unadjusted random-effect regression models with patients as random effect (logistic models for binary outcomes and a negative binomial regression model for admission length). Effect sizes were presented as either Odds Ratios (ORs) or Incidence Rate Ratios (IRRs) with corresponding 95% confidence intervals. IRR quantifies the factor change in the expected LOS, for example, IRR=1.2 represents a 20% increase in expected count of days spent in the hospital by patients with abnormal CXR compared to patients without abnormal CXR.

The study was approved by the local institutional review board (LNR/15/AUSTIN/431).

Results

Four hundred and forty-five episodes from 318 haematology patients with NF were documented. Figure 1 summarises the process by which 283 episodes were deemed eligible for analysis. Of the 152 episodes where routine CXR was not performed at baseline, there was one episode where CT chest was performed within 48 hours. Forty-four CXR and 9 CT chest imaging were performed after 48 hours of NF, indications included persistent fevers and central line insertion placement checks. Patient demographics, CXR and antibiotic management details are described in Table 1.

Table 2 summarises the relationship between CXR results and presence of respiratory symptoms/signs. Only 4/164 (2.4%) CXRs in asymptomatic patients demonstrated radiological features of respiratory infection. Conversely, in symptomatic patients, 19/119 (15.9%) CXRs had infective features. There was no statistically significant difference (p=0.40) in frequency of abnormalities detected between portable CXR (13/132) and standard CXR (10/148).

Table 3 summarises the results of the regression analysis to identify variables significantly associated with an abnormal CXR. Having at least one respiratory sign or symptom was the only variable associated with an increased chance of having an abnormal CXR. No single comorbidity nor type of underlying disease were associated with an increased risk.

NFNFIn terms of patient outcomes, an abnormal CXR was associated with a statistically significant increase in ICU admissions (OR 7.61, p=0.002, 95% Confidence Interval (CI): 2.04 – 28.31) but not an increased length of hospital admission (IRR 1.07; p=67; 95%CI: 0.80 – 1.42), or increased inpatient mortality (OR 3.89; p=0.25; 95%CI: 0.39 – 39.03).

In 3/283 (1.1%) episodes an abnormal CXR resulted in a change of antibiotic treatment, all in patients with respiratory features. Conversely in the remaining 20 episodes where CXR was consistent with infection, no change in antibiotic management occurred based on the results.

Discussion

Driven by local and international guidelines, CXR is still commonly performed routinely in patients with NF. This real-world study analysed the effect of this investigation on management of haematology patients with NF in the modern era of antibiotics. Interestingly, despite being included in local guidelines, only 65% of patients in this cohort had CXR within 2 days of presentation, suggesting physicians are already using clinical judgement in ordering CXR at baseline rather than adhering to rigid protocols.

The study had two predominant relevant findings: an abnormal CXR in the absence of respiratory symptoms/signs was rarely observed and CXR results seldom influenced antibiotic management. No association was identified between an abnormal CXR and increased admission length or inpatient mortality. These results are consistent with smaller series in predominantly solid-cancer cohorts,[5,6] and in haematopoietic stem cell transplant patients.[9] Of note, the latter study in transplant patients (n=825) reported that in the absence of respiratory symptoms in NF patients, 0/379 CXRs identified pulmonary infiltrates.

Importantly, our study included patients with mild to moderate neutropenia and/or low grade fever as these patients are underrepresented in previous studies yet are commonly investigated and treated according to published NF guidelines. Importantly, there was no significant association (OR 0.81, p=0.62, 95%CI: 0.35 – 1.91) with abnormal CXR findings when patients met the standard NF definition (temperature ≥38.3°C and neutrophil count <0.5 $x10^9$/L) versus low-risk NF patients (temperature 37.5-38.3°C and neutrophils 0.5-1.5$x10^9$/L).

One of the limitations of this study is the high proportion of AP and portable CXRs. Despite the well-known poorer imaging quality associated with AP projection, such modalities are utilised in patients with NF who often cannot be moved due to their immunocompromised state and hence, these results reflect routine clinical care. NFAnother limitation of the study is that in 25% of NF episodes, chest imaging was not performed, and an additional 10% of NF patients underwent chest imaging more than 48 hours after the NF episode with reasons for omission of early CXR poorly documented.

The low rates of infection identified on CXR, lack of association between CXR findings and patient outcomes and absence of changes in management based on CXR results alone serve to highlight the limited benefit of routine CXR in NF patients presenting without respiratory compromise. Based on our data, these results are applicable even to profoundly neutropenic patients. As a consequence, we suggest that CXR could be omitted from routine assessment of NF in the absence of clinical respiratory features in patients with haematological conditions.

Conflicts of interest:

All authors (OE, ZL, AB, GC, AG, LC, EH) declare that they have no conflict of interest.

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Tables and Figures:

Figure 1: Flow diagram of study sample episodes and CXR performed

Table 1: Baseline, CXR and antibiotic management characteristics

Table 2: Relationship between clinical respiratory presentation and CXR results

Table 3: Odds ratio for association with an abnormal CXR

Figure 1: Flow diagram of study sample episodes and CXR performed

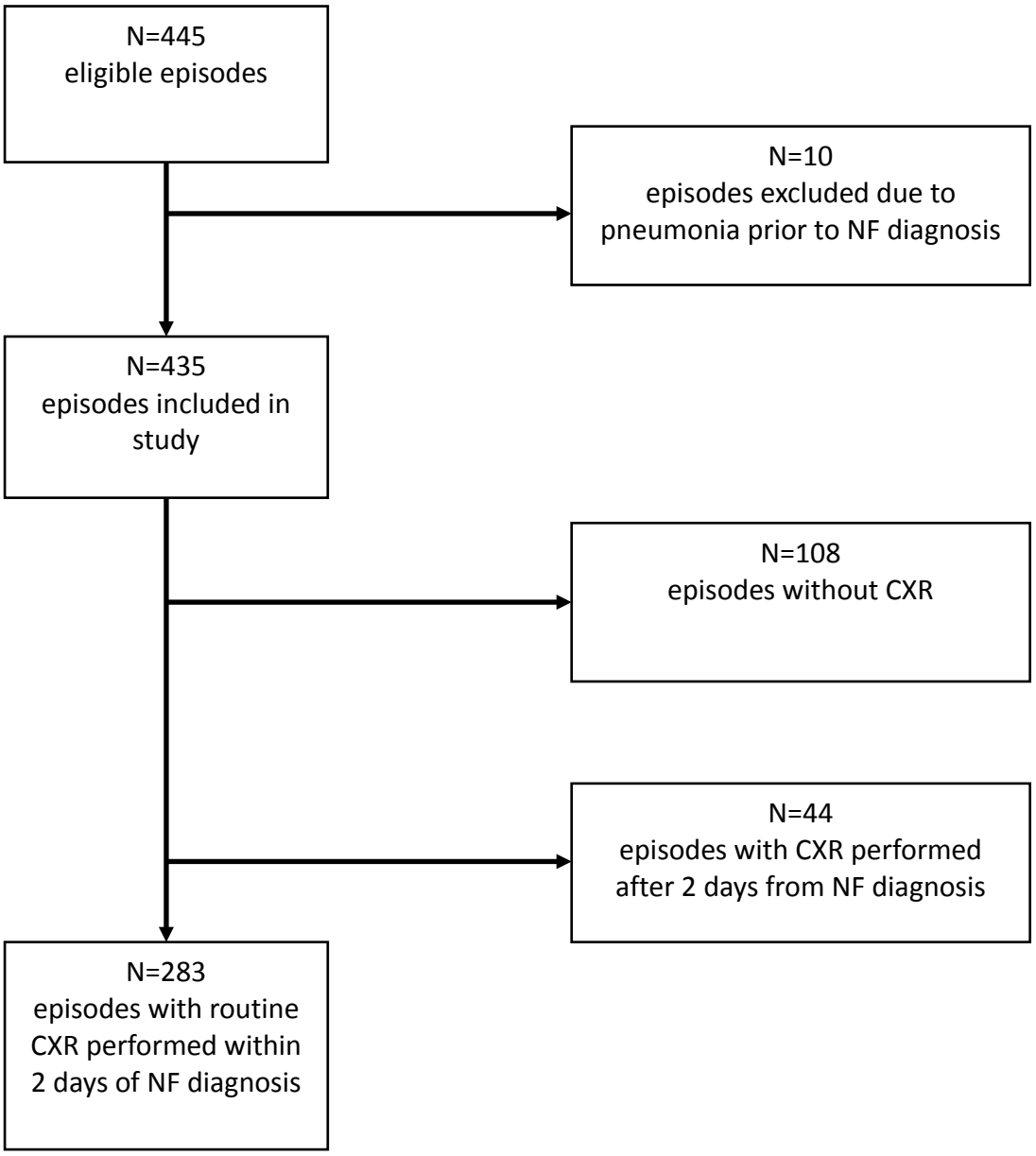

Table 1: Baseline, CXR and antibiotic management characteristics

	N (%)
Febrile neutropenia episodes identified	435
Routine CXR within 2 days of NF diagnosis (Eligible episodes)	283 (65)
Median age in years (min, q1, q3, max)	58 (17, 46, 66, 90)
Gender	
Male	163 (58)
Female	120 (42)
Haematological condition	
Leukaemia	125 (44)
Acute myeloid leukaemia	79 (28)
Acute lymphocytic leukaemia	24 (8)
Chronic lymphocytic leukaemia	15 (5)
Lymphoma	110 (39)
Myeloma	43 (15)
Other	5 (2)
History of pulmonary disease –	
Past/current smoker and COPD	115 (41)
Current Smoker	24 (8)
Asthma	29 (10)
COPD	15 (5)
Other	22 (8)
Haematopoietic stem cell transplant admission	46 (16)
Autologous	45 (16)
Allogeneic	1 (0.3)
Median days between NF and last chemotherapy treatment in days (min, q1, q3, max)	10 (0, 8, 13, 70)
Documented fever ≥38.3°C	194 (69)
Neutrophil count <0.5x10^9/L	227 (80)
Fever ≥38.3°C and neutrophils <0.5x10^9/L	161 (57)
Median neutrophil nadir during admission x10^9/L (min, q1, q3, max)	0 (0, 0, 0.1,1.5)
Median length of stay in days (min, q1, q3, max)	15 (1, 6, 23, 70)
Inpatient mortality	4 (1)
Cause of death:	

Sepsis/cardiogenic shock	3 (1)
Underlying disease	1 (0.4)
CXR Type	
AP	24 (8)
AP with portable x-ray machine	131 (46)
PA	124 (44)
PA with portable x-ray machine	1 (0.4)
Not recorded	3 (1)
Intravenous antibiotics	
Piperacillin-tazobactam	147 (52)
Piperacillin-tazobactam and other*	93 (33)
Cefepime	7 (2)
Cefepime and other	18 (6)
Other	17 (6)
No intravenous antibiotics	1 (0.4)
Agent added as a result of CXR	
Azithromycin	3 (1)

CXR=Chest X-Ray; AP=anteroposterior projection; PA=posteroanterior projection
*Other includes cefepime, ciprofloxacin, clindamycin, meropenem, vancomycin, azithromycin, teicoplanin, daptomycin, flucloxacillin, gentamicin and linelozid

Table 2: Relationship between clinical respiratory presentation and CXR results

	CXR consistent with infection	CXR indeterminate	CXR normal	Totals
Respiratory symptoms/signs present	19	3	97	119
Respiratory symptoms/signs absent	4	3	157	164
Totals	23	6	254	283

Table 3: Odds ratio for association with an abnormal CXR

Variable	Odds Ratio (p, 95% CI)
Gender	1.75 (0.23, 0.70 – 4.41)
Age	1.62 (0.37, 0.57 – 4.63)
Previous or current smoker	0.98 (0.97, 0.39 – 2.47)
History of Asthma	1.35 (0.65, 0.38 – 4.85)
History of COPD	1.81 (0.45, 0.38 – 8.56)
Haematopoietic stem cell transplant admission	0.22 (0.14, 0.03 – 1.65)
Neutrophils $<0.5x10^9$/L	0.53 (0.18, 0.21 – 1.36)
Neutrophil nadir of 0	1.10 (0.85, 0.43 – 2.75)
Fever ≥38.3°C and neutrophils $<0.5x10^9$/L	0.81 (0.62, 0.35 – 1.91)
Symptoms or signs*	**7.60 (<0.01, 2.51 – 22.98)**

COPD=Chronic Obstructive Pulmonary Disease