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**ENaC polymorphism p.W493R is associated with bronchiectasis but does not necessarily lead to aberrant ion conductance** http://ow.ly/S5Mwj

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# Lung positron emission tomography with FDG in patients with haematological malignancies and acute respiratory failure

*To the Editor*:

Diagnostic strategy in haematology patients with pulmonary infiltrates relies on different approaches [1, 2]. Over the past decade, the use of $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has been widely used to detect inflammatory and malignant processes, to evaluate the extent of a malignancy, and to ascertain response to therapy. Hot *et al.* [3] reported diagnostic contribution of FDG-PET in patient with invasive fungal infection. More recently, Veronesi *et al.* [4] reported PET findings in the diagnostic work-up of screening-detected lung nodules. PET-computed tomography (CT) was highly sensitive for the differential diagnosis of indeterminate nodules detected at baseline, nodules ⩾15 mm and solid nodules [4]. However, FDG-PET has never been evaluated in unselected patients with acute respiratory failure that complicates haematological malignancies.

TABLE 1 Clinical features, pulmonary diagnosis, $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) results and definite pulmonary diagnoses in patients with haematological malignancies and acute respiratory failure

| Case | Gender, age years | Malignancy | Definite diagnosis | CT findings | BAL findings | FDG-PET findings | Diagnostic test |
|---|---|---|---|---|---|---|---|
| **1** | Male, 41 | Haemophagocytic lymphohistiocytosis | Kaposi Sarcoma | Diffuse ground glass opacities | Alveolar haemorrhage | Diffuse and intense | Lung biopsy |
| **2** | Female, 73 | Myelodysplasia | Kaposi Sarcoma | Peribronchovascular nodules, diffuse ground glass opacities | Increased number of BAL cells, 90% macrophages | Diffuse and intense | Bronchial biopsy |
| **3** | Female, 32 | Hodgkin lymphoma | Tuberculosis | Segmental pneumonia | Increased number of BAL cells, 40% neutrophils, 30% lymphocytes | Focal and intense | Sputum |
| **4** | Male, 62 | Chronic myelomonocytic leukaemia | Pulmonary infiltration from the malignancy | Centrolobular nodules | Alveolitis with 90% neutrophils and myelomonocytic cells | Diffuse and moderate | BAL |
| **5** | Male, 63 | MALT lymphoma | Pulmonary infiltration from the malignancy | Diffuse ground glass opacities | Normal | Diffuse and moderate | Lung biopsy |
| **6** | Female, 54 | Intravascular large B cell lymphoma | Pulmonary infiltration from the malignancy | Peribronchovascular nodules, localised ground glass opacities | Normal | Diffuse and moderate | Bronchial biopsy |
| **7** | Female, 28 | Hodgkin lymphoma | Pulmonary infiltration from the malignancy | Diffuse ill-defined alveolar consolidation | Not performed | Diffuse and moderate | Marrow smear |
| **8** | Female, 59 | MALT lymphoma | Pulmonary infiltration from the malignancy | Diffuse ground glass opacities | Normal | Diffuse and moderate | Lung biopsy |
| **9** | Female, 54 | Diffuse large B cell lymphoma | Pulmonary infiltration from the malignancy | Peribronchovascular nodules | Alveolitis, tumoral B-cell infiltration | Diffuse and moderate | BAL |
| **10** | Male, 70 | Pleiomorph NHT lymphoma | Pneumocystis | Diffuse ground glass opacities | Not performed | Diffuse and moderate | Sputum |
| **11** | Male, 62 | Chronic lymphoid leukaemia | Pneumocystis | Diffuse ground glass opacities | Increased number of BAL cells, 80% lymphocytes | Diffuse and moderate | BAL |
| **12** | Male, 47 | Burkitt lymphoma | Invasive aspergillosis | Diffuse ill-defined alveolar consolidation | Not performed | Diffuse and moderate | Circulating galactomannan and sputum |
| **13** | Male, 12 | Acute myeloid leukaemia | Zygomycete pneumopathy | Ill-defined consolidation, halo sign | Necrotic cells | Focal and moderate | Biopsy |
| **14** | Female, 49 | Follicular lymphoma | Geotrichum pneumopathy | Not performed (severe ARDS) | Normal cells | Focal and moderate | BAL |
| **15** | Male, 46 | Mantle lymphoma | Invasive aspergillosis | Not performed | Not performed | Diffuse and moderate | Circulating galactomannan |
| **16** | Male, 68 | Diffuse large B cell lymphoma | Viral infection | Diffuse ground glass opacities | Not performed | Diffuse and moderate | Nasopharyngeal aspirate |
| **17** | Male, 71 | Myelodysplastic syndrome | Bacterial pneumonitis | Not performed | Not performed | Focal and mild | CT scan |
| **18** | Female, 73 | Chronic myelomonocytic leukaemia | Bacterial pneumonitis | Not performed | Not performed | Focal and mild | CT scan |
| **19** | Male, 63 | Chronic myeloid leukaemia | Cardiogenic pulmonary oedema | Not performed | Not performed | Normal | Echocardiography |
| **20** | Male, 80 | Chronic lymphoid leukaemia | Patent foramen ovale with anatomic shunt | Normal | Not performed | Normal | Contrast echocardiography |

CT: computed tomography; BAL: bronchoalveolar lavage; MALT: mucosa-associated lymphoid tissue; NHT: non-Hodgkin lymphoma; ARDS: acute respiratory distress syndrome. Parenchymal PET metabolic activity (maximum standardised uptake value): normal 0–2, focal and mild 2–4, moderate 4–8, intense >8.

We report the results from a prospective pilot study during which critically ill haematology patients with pulmonary infiltrates benefited from a FDG-PET in addition to routine diagnostic and therapeutic management. Diagnoses were made mostly by noninvasive tests and bronchoalveolar lavage (BAL) fluid analysis; in addition, six patients had bronchial or pulmonary biopsies. FDG-PET was performed between day 1 and day 5, and completed by two senior radiologists specialised in nuclear medicine. None of the patients was intubated at the time of PET-CT, and all received high flow oxygen or intermittent noninvasive mechanical ventilation. According to the level of maximum standardised uptake value (SUVmax), patients were classified as having normal (0–2), mild (2–4), moderate (4–8) or intense (>8) pulmonary parenchymal metabolic activity. Table 1 summarises individual demographic, clinical and FDG-PET data. No adverse effects were observed after isotope injection. Pulmonary lesion related to lymphoma and fungal or viral infection presented with moderate parenchymal activity, whereas bacterial pneumonia presented with focal and mild lung parenchymal activity. Intense lung parenchymal activity was observed with pulmonary tuberculosis (one patient) and pulmonary Kaposi sarcoma (two patients). Normal FDG-PET was associated with normal lungs but cardiac abnormalities (two patients).

The ability of lung PET-CT with a SUVmax >4 to detect pulmonary infiltration by the malignancy had a sensitivity of 100% and a specificity of 33.33%. Also, with a prevalence of malignant infiltration of 40%, the negative predictive value was 100% and the positive predictive value was 50%. Furthermore, the performances of lung PET-CT with a SUVmax >4 were identical than above to detect pulmonary infiltration by opportunistic infection (which prevalence was also 40%).

This preliminary evaluation of FDG-PET in haematology patients with acute respiratory failure depicts FDG-PET patterns that have not been previously reported. We are not able to provide a specific picture related to a single aetiology. However, since there is a direct relationship between diagnosis and prognosis in these patients [1], we believe that every emerging diagnostic strategy needs to be appraised and evaluated carefully to assess its possible contribution to diagnosis and treatments. Further description of FDG-PET patterns in unselected haematology patients with pulmonary involvement is warranted. This prospective evaluation may contribute to the identification of aetiology of pulmonary involvement, to report on the extent of the inflammatory or infectious process, and also to estimate diagnosis contribution of FDG-PET in patients not identified using conventional diagnostic methods. To do so, future studies will need to assess correlations with conventional CT and morphological and immunological features in cells recovered from BAL fluids. In this study of 20 patients, SUVmax was not correlated with the number and the type of BAL cells. Hence, diagnostic performance of lung PET-CT will need to be adjusted for accompanying inflammatory reaction in the normally aerated lung with respect to their neutrophil activation and on correlation of FDG-PET with conventional CT. Only such an evaluation would help determine whether PET-CT can replace conventional CT and bronchoscopy and BAL fluid cytological analysis. Last, patient follow-up using PET-CT may help correlate lung metabolic activity and respiratory situation, in order to assess whether patients are responsive to anti-inflammatory, anti-tumoural or anti-infectious agents.

In summary, these preliminary descriptive results provide interesting insights on the use of PET-CT in immunocompromised patients with pulmonary infiltrates. However, they raise more questions than they bring answers. Studies are needed to confirm these results on a larger scale. Also, investigations to assess diagnostic performance of PET-CT as compared to a well-accepted gold standard, such as pulmonary biopsy, are warranted.

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**Lung FDG-PET may help to identify aetiology of pulmonary infiltrates in immunocompromised patients** http://ow.ly/S24gC

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# Amoxicillin for clinically unsuspected pneumonia in primary care: subgroup analysis

*To the Editor:*

Antibiotic treatment is recommended for pneumonia [1, 2]. However, some studies have suggested that the milder spectrum of pneumonia in primary care does not have important adverse consequences if missed and, therefore, managed without antibiotics [3–5]. Better insight in the effects of antibiotics for pneumonia in primary care could improve patient information and management.

The aim of our study was to assess whether antibiotic treatment influenced outcome in patients presenting with acute lower respiratory tract infection (LRTI) with a radiologically proven, but clinically unsuspected, pneumonia compared to those without pneumonia.

This was a secondary analysis of a randomized, placebo controlled trial of amoxicillin for acute LRTI in 16 primary research networks in 12 European countries from October 2007 until April 2010. More details on this GRACE-10 study (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe, www.gracelrti.org) have been reported elsewhere [6]. Eligible patients were aged ⩾18 years who consulted their general practitioner (GP) for the first time with an acute cough (duration of ⩽28 days) as the main symptom. Exclusion criteria were clinically suspected pneumonia [7], based on focal chest signs (focal crepitations and bronchial breathing) and systemic features (high fever, vomiting and severe diarrhoea); pregnancy, allergy to penicillin, treatment with antibiotics in the previous month and immunodeficiency. The study was approved by ethics committees in all participating countries and all participants provided written informed consent.

Patients who agreed to randomisation were allocated to receive amoxicillin (1 g three times daily for 7 days) or placebo, by the GP dispensing sequentially numbered randomised containers.

GPs recorded patients' clinical signs, and comorbidities on a case report form. They also registered 14 baseline symptoms (cough, phlegm, shortness of breath, wheeze, runny nose, fever, chest pain, muscle aching, headache, disturbed sleep, feeling generally unwell, interference with normal activities/work, confusion/disorientation and diarrhoea) on a 4-point Likert-scale from "no problem" to "severe problem". Baseline symptom severity was calculated by summing the scores of the symptoms and rescaling them to make them range between 0 and 100. Patients filled in a daily symptom diary during their illness for up to 28 days for the same symptoms on a 7-point Likert scale (0=no problem, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad and 6=as bad as it could be). This diary was previously validated and shown sensitive to change [8]. If the diary was not returned after 4 weeks, brief information about symptom duration and severity were collected with either a short questionnaire or a standardised telephone call.

Chest radiographs were taken for each patient within 7 days of first presentation, but preferably within 3 days. Pneumonia was determined by radiologists, who were blind to all other information when they judged chest radiographs. In analysis reported here we defined pneumonia as all patients in whom the radiologist diagnosed pneumonia based on the chest radiograph [9].

Outcomes were duration of symptoms rated by patients as "moderately bad or worse" after initial presentation, symptom severity on days 2–4 after the index consultation, and worsening of illness, defined as a revisit to the GP with worsening symptoms, new symptoms, new signs, or illness necessitating admission to hospital within 4 weeks after the first consultation [6].

The effectiveness of the antibiotics was compared in patients with radiologically proven pneumonia compared to those without pneumonia for all three outcomes. Data were analysed using linear regression models. Cox regression was used for the duration of symptoms allowing for censoring, simple linear regression for