adequate penetration in affected tissue; non-resolving pulmonary infiltrates in TB patients do not necessarily preclude inadequate drug penetration.

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Treatment regimens yielding adequate blood concentrations may provide similarly adequate penetration in affected tissue http://ow.ly/p7f9F

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Neutrophilia independently predicts death in tuberculosis

To the Editor:

Experimental animal work indicates that neutrophils play a key role in the immune response to mycobacteria [1, 2]. They appear protective against early infection [3] but in established disease, neutrophilia associates with pathology [1, 4]. In humans, higher neutrophil counts at tuberculosis diagnosis predict slower sputum conversion to negative during therapy [5, 6], but the overall prognostic significance of neutrophilia in human tuberculosis remains elusive. We therefore aimed to analyse this phenomenon in a study powered to detect an independent relationship with mortality.

Tuberculosis patients were identified by database/case-note review at Newham University Hospital Trust and King's College Hospital, London, UK. All patients diagnosed between 1999 and 2006 were eligible for inclusion in an analysis of neutrophilia at baseline; those with a recorded outcome of successfully completing treatment or death were included in an analysis of determinants of mortality. Healthy contacts of tuberculosis cases were recruited from the same hospitals.

Data were extracted on patient age, sex, ethnicity, comorbidity, use of immunosuppressive medication, HIV status and site of disease. Laboratory data were collected from samples taken on the date of tuberculosis diagnosis: serum sodium, bilirubin and albumin concentrations; peripheral blood haemoglobin concentration; and peripheral blood neutrophil, monocyte, lymphocyte and platelet counts. Blood culture results were recorded where performed. Protocols were approved by the Barking and Havering NHS Research Ethics Committee (REC 08/H0702/25) and North East London Research Ethics Committee (REC P/02/146).

We calculated that 584 patients (34 deaths and 550 survivors) would be required to detect a three-fold difference in mortality in the presence of neutrophilia with 80% power (5% significance level), assuming a 15% prevalence of neutrophilia and a death/survival ratio of 1/16 (parameters derived from preliminary analysis). We aimed to include twice this number to allow for missing data.

Comparisons of proportions used Chi-squared tests. Comparisons of non-Gaussian continuous data (neutrophil counts and age) used Mann–Whitney tests. To investigate demographic or clinical associations with neutrophilia in tuberculosis patients, neutrophil counts were treated as a categorical dependent variable for binary logistic regression: $\geqslant 7.5 \times 10^9$ or $<7.5 \times 10^9$ cells per litre. Analysis of predictors of mortality used death/survival as the binary dependent variable. Multivariate regression was performed using all significant ($p<0.05$) predictors from univariate analysis. Age was divided into strata pre-analysis. Laboratory parameters were also assigned pre-analysis into categorical predictors, as relationships were not anticipated to be linear, and both high and low values are usually pathological. A distinction was made between pathological neutropenia ($<1 \times 10^9$ cells per litre) and mild, usually benign ethnic neutropenia. Predictors with >25% missing values (HIV status and comorbidity) were assigned a separate group (''unknown'') to enable inclusion of patients with missing data in multivariate analyses. Bootstrapping analysis used simple (nonstratified) sample selection. Analyses were performed using SPSS versions 18–21 (IBM, Armonk, NY, USA).

1236 tuberculosis patients were identified; 855 had recorded neutrophil counts and data for all demographic variables except HIV status and comorbidity (see earlier). There was no difference in age ($p=0.29$), sex distribution ($p=0.80$), ethnic distribution ($p=0.07$) or neutrophil count ($p=0.55$) between included patients and excluded patients for whom this information was available. 49 patients were transferred or lost to follow-up and 88 patients lacked data for one or more laboratory parameters, resulting in 718 patients entering case fatality analysis.

Pulmonary tuberculosis was the commonest disease site (49.4%), and HIV infection was known to be present in 13.5% of the 855 patients. 214 contacts were also analysed. Cases and contacts did not differ in sex distribution (57.3% *versus* 50.5% male, respectively; $p=0.07$) but did differ in age (median age 33 *versus* 30 years, respectively; $p=0.002$) and ethnic distribution (11.6% *versus* 16.4%, respectively, were white; 19.3% *versus* 33.6% South Asian; 59.8% *versus* 40.7% black; and 9.4% *versus* 9.3% other ethnic origin; $p<0.001$).

Neutrophilia (peripheral blood neutrophil count $\geqslant 7.5 \times 10^9$ cells per litre) was commoner in patients with active tuberculosis disease than in healthy contacts (158 (18.5%) or of 855 *versus* eight (3.7%) out of 214). The adjusted odds ratio (aOR) for neutrophilia among cases *versus* contacts, controlling for age and ethnicity, was 6.13 (95% CI 2.94–12.82; $p<0.001$). Median (interquartile range) neutrophil count was also higher in cases than contacts (4.65 (3.17–6.75) *versus* 3.66 (2.78–4.78) $\times 10^9$ cells per litre; $p<0.0001$).

Analysis of 297 blood cultures performed on tuberculosis patients revealed three pathogenic bacteria other than *Mycobacterium tuberculosis* (one culture of methicillin-resistant *Staphylococcus aureus*, one of *Proteus vulgaris* and one of an unidentified coliform). Only the patient with *P. vulgaris* had concomitant neutrophilia.

We next sought to identify any associations with neutrophilia at tuberculosis diagnosis (table 1). In multivariate analysis, white ethnicity increased the odds of neutrophilia compared to black ethnicity (aOR 1.75, 95% CI 1.03–3.03; $p=0.036$). Pulmonary disease was associated with increased the odds of neutrophilia compared to peripheral lymph node tuberculosis (aOR 2.56, 95% CI 1.25–5.26; $p=0.011$). HIV infection reduced the odds of neutrophilia compared to HIV-uninfected subjects (aOR 0.50, 95% CI 0.26–0.97; $p=0.039$); however, this result is confounded by pathological neutropenia (five (38.5%) out of 13 patients with neutrophil count $<1 \times 10^9$ cells per litre were HIV infected, and removing all pathologically neutropenic patients from the analysis negates the association between HIV positivity and the absence of neutrophilia).

TABLE 1 Associations with neutrophilia and mortality in tuberculosis patients

	Analysis of neutrophilia[#]						Analysis of mortality[¶]					
	Subjects n	Univariate analysis			Multivariate analysis		Subjects n	Univariate analysis			Multivariate analysis	
		Neutrophilia n (%)	OR	p-value	OR (95% CI)	p-value		Deaths n (%)	OR	p-value	OR (95% CI)	p-value
Sex												
Male	490	99 (20.2)	1				408	29 (7.1)	1			
Female	365	59 (16.2)	0.76	0.133			310	13 (4.2)	0.57	0.103		
Age years												
<20	102	16 (15.7)	0.95	0.869	0.98 (0.53–1.80)	0.951	82	0 (0)	NA		NA	
20–39	471	77 (16.3)	1		1		390	6 (1.5)	1		1	
40–59	196	40 (20.4)	1.31	0.210	1.28 (0.83–1.97)	0.274	165	26 (12.7)	**9.33**	**<0.001**	**8.73 (2.88–26.44)**	**<0.001**
⩾60	86	25 (29.1)	**2.10**	**0.006**	1.75 (0.99–3.10)	0.055	81	15 (18.5)	**14.55**	**<0.001**	**8.68 (2.30–32.71)**	**0.001**
Ethnicity												
White	99	30 (30.3)	1		1		88	13 (14.8)	1		1	
South Asian[+]	165	33 (20.0)	0.58	0.059	0.71 (0.39–1.30)	0.272	120	6 (5.0)	**0.30**	**0.021**	0.57 (0.16–2.05)	0.385
Black[§]	511	81 (15.9)	**0.43**	**0.001**	**0.57 (0.33–0.97)**	**0.036**	439	20 (4.6)	**0.28**	**0.001**	0.52 (0.18–1.52)	0.233
Other	80	14 (17.5)	0.49	0.050	0.59 (0.28–1.23)	0.157	71	3 (4.2)	**0.26**	**0.039**	0.45 (0.09–2.34)	0.344
Site of disease												
Pulmonary	422	92 (21.8)	1		1		362	27 (7.5)	1			
Peripheral LN only	99	9 (9.1)	**0.36**	**0.005**	**0.39 (0.19–0.80)**	**0.011**	84	2 (2.4)	0.30	0.108		
CNS	39	8 (20.5)	0.93	0.852	0.86 (0.38–1.98)	0.863	31	2 (6.5)	0.86	0.837		
Miliary	23	5 (21.7)	1.00	0.994	1.04 (0.36–2.96)	0.948	18	1 (5.6)	0.73	0.764		
Other extrapulmonary	272	44 (16.2)	0.69	0.069	0.69 (0.46–1.03)	0.071	223	10 (4.5)	0.58	0.155		
Immunosuppressive therapy[f]												
No	804	148 (18.4)	1				679	41 (6.0)	1			
Yes	51	10 (19.6)	1.08	0.831			39	1 (2.6)	0.41	0.384		
Comorbidity[##]												
No	564	103 (18.3)	1				468	20 (4.3)	1		1	
Yes	53	11 (20.8)	1.17	0.655			42	7 (16.7)	**4.48**	**0.002**	**5.94 (1.65–21.37)**	**0.006**
Unknown	238	44 (18.5)	1.02	0.940			208	15 (7.2)	1.74	0.116	1.18 (0.45–3.10)	0.732
HIV status												
Uninfected	280	58 (20.7)	1		1		243	9 (3.7)	1		1	
Infected	115	13 (11.3)	**0.49**	**0.029**	**0.50 (0.26–0.97)**	**0.039**	105	11 (10.5)	**3.04**	**0.017**	1.46 (0.39–5.42)	0.575
Unknown	460	87 (18.9)	0.89	0.549	0.76 (0.50–1.14)	0.178	370	22 (5.9)	1.64	0.219	1.17 (0.37–3.76)	0.788
Serum sodium mmol·L^{-1}												
<130							60	10 (16.7)	**4.94**	**<0.001**	1.01 (0.37–2.74)	0.982
130–140							591	23 (3.9)	1		1	
>140							67	9 (13.4)	**3.83**	**0.001**	**4.59 (1.18–17.86)**	**0.028**
Serum bilirubin μmol·L^{-1}												
⩽17							614	29 (4.7)	1		1	
>17							104	13 (12.5)	**2.88**	**0.003**	1.52 (0.57–4.05)	0.398
Serum albumin g·L^{-1}												
⩾30							584	14 (2.4)	1		1	
<30							134	28 (20.9)	**10.76**	**<0.001**	**4.43 (1.79–11.00)**	**0.001**

TABLE 1 Continued

	Analysis of neutrophilia[#]					Analysis of mortality[¶]					
	Subjects n	Univariate analysis			Multivariate analysis		Subjects n	Univariate analysis			Multivariate analysis	
		Neutrophilia n (%)	OR	p-value	OR (95% CI)	p-value		Deaths n (%)	OR	p-value	OR (95% CI)	p-value
Peripheral blood haemoglobin g·dL^{-1}												
⩾11.5							346	9 (2.6)	1			
<11.5							372	33 (8.9)	**3.65**	**0.001**	2.34 (0.81–6.76)	0.116
Peripheral blood cell counts												
Platelets × 10^9 cells per L												
<150							52	16 (30.8)	**10.43**	**<0.001**	**3.75 (1.25–11.22)**	**0.018**
150–400							465	19 (4.1)	1		1	
>400							201	7 (3.5)	0.85	0.712	0.47 (0.15–1.47)	0.192
Neutrophils × 10^9 cells per L												
<1							13	3 (23.1)	**7.11**	**0.005**	0.73 (0.05–9.80)	0.813
1–1.99							50	2 (4.0)	0.99	0.987	0.54 (0.08–3.71)	0.528
2–7.49							519	21 (4.0)	1		1	
⩾7.5							136	16 (11.8)	**3.16**	**0.001**	**2.93 (1.17–7.34)**	**0.022**
Lymphocytes × 10^9 cells per L												
<1							252	33 (13.1)	**7.35**	**<0.001**	**3.24 (1.24–8.44)**	**0.016**
1–4							448	9 (2.0)	1		1	
>4							18	0 (0)	NA		NA	
Monocytes × 10^9 cells per L												
<0.2							38	11 (28.9)	**7.91**	**<0.001**	1.51 (0.43–5.35)	0.524
0.2–0.8							490	24 (4.9)	1		1	
>0.8							190	7 (3.7)	0.74	0.497	0.92 (0.31–2.69)	0.876

Bold represents statistical significance. NA: not applicable; LN: lymph nodes; CNS: central nervous system. [#]: n=855; [¶]: n=718; [+]: Indian, Sri Lankan, Pakistani and Bangladeshi; [§]: black African, black Caribbean and other black ethnicities; [f]: corticosteroids, azathioprine or cyclosporin; [##]: renal failure, hepatic failure, previous ischaemic cardiovascular events, diabetes mellitus, hypertension, sickle cell disease, respiratory failure, arthritis (unspecified), inflammatory bowel disease, celiac disease or ankylosing spondylitis.

Table 1 also summarises results from a logistic regression analysis of predictors of mortality (n=718). Neutrophilia was present in 16 (38.1%) out of 42 patients who died and 120 (17.8%) out of 676 survivors, and was an independent risk for case fatality in multivariate analysis (aOR 2.93, 95% CI 1.17–7.34; p=0.022). Bootstrapping analysis (1000 samples) confirmed the result's robustness (aOR 2.93, 95% CI 1.16–12.03; p=0.018). Further laboratory parameters predicting fatality were hypernatraemia, hypoalbuminaemia, thrombocytopenia and lymphopenia. Increased age and the presence of comorbidity other than HIV were also associated with increased risk of death, but receiving immunosuppressive medication was not.

Our study yielded some important new findings. A modest neutrophilic response was common in tuberculosis: even survivors with active tuberculosis had higher median neutrophil counts than healthy contacts. Others have reported that higher blood neutrophil counts correlate with sputum *M. tuberculosis* PCR positivity and, especially, smear positivity [7], while separate studies discovered higher neutrophil counts associated with slower conversion of sputum culture to negative [5, 6]. Together with the higher prevalence of neutrophilia in patients who die (reported here), these results suggest that, broadly speaking, the neutrophil count in tuberculosis positively correlates with bacillary load.

It is therefore important to know which other factors associate with neutrophilia in human tuberculosis. We found no convincing evidence that nontuberculous bacteraemia explained this phenomenon, as only one out of 158 instances of neutrophilia was associated with a pathogenic nonmycobacterial species in blood culture. Lower risk of neutrophilia with isolated peripheral lymph node disease probably reflects lower mycobacterial load and less systemic inflammation. The finding that white ethnicity independently predicts neutrophilia may be biologically important in tuberculosis and help to explain the previous finding that European ethnic origin is a risk factor for death independently of age [8]. Indeed, the lowest case fatality in our study was seen with neutrophil counts in the range $1–1.99 \times 10^9$ cells per litre, which is likely to largely reflect benign ethnic neutropenia. The apparent effect of HIV in reducing risk of neutrophilia is explained by pathological neutropenia, a well-described complication of HIV [9]. Indeed, pathological neutropenia ($<1 \times 10^9$ cells per litre) was associated with higher case fatality as compared to a normal-range neutrophil count. In addition to the association with HIV infection, this can be seen in the context of severe, disseminated tuberculosis [10].

Our study has some limitations. 381 potentially eligible patients were excluded, but their demographics and neutrophil counts were similar to included patients. Comorbidity and HIV status were poorly documented, necessitating an ''unknown'' coding category. Tuberculosis cases and contacts were not formally matched; in particular, they differed in age and ethnic distribution, but the odds of neutrophilia were much higher in the former even after adjustment for these factors.

In summary, we have demonstrated that neutrophilia in tuberculosis independently associates with increased risk of mortality. Interestingly, abrogating the immunopathological neutrophil response in some animal models improves outcome in acute infection [4]. Similar strategies might therefore have therapeutic application in humans with severe tuberculosis.

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Neutrophilia is common in tuberculosis and independently predicts case fatality
http://ow.ly/pgHoa

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Pulmonary fibrosis in dyskeratosis congenita with *TINF2* gene mutation

To the Editor:

Dyskeratosis congenita is a rare inherited disorder of ectodermal dysplasia characterised by the classical mucocutaneous triad of abnormal skin pigmentation, nail dystrophy and leukoplakia [1–3], at least one of which is present in around 80–90% of dyskeratosis congenita cases. Bone marrow failure is another common feature, and a variety of other abnormalities (*e.g.* dental, gastrointestinal, neurological, ophthalmic, pulmonary and skeletal) have been also described [1–3]. The main causes of mortality in dyskeratosis congenita are bone marrow failure, pulmonary disease and malignancy [1]. Three modes of inheritance have been recognised: X-linked recessive, autosomal dominant and autosomal recessive [1, 3]. Eight dyskeratosis congenita genes (*DKC1* (dyskeratosis congenita 1), *TERC* (telomerase RNA component), *TERT* (telomerase reverse transcriptase), *NOP10* (nucleolar protein 10), *NHP2*, *TINF2* (TERF1-interacting nuclear factor 2), *TCAB1* and *RTEL1* (regulation of telomere elongation helicase 1)) have already been identified, and their mutations account for ~60% of all dyskeratosis congenita cases [1]. Among the dyskeratosis congenita genes, mutations in *TERC*, *TERT* and *DKC1* have recently been reported to be associated with familial pulmonary fibrosis and idiopathic pulmonary fibrosis, and pulmonary fibrosis is recognised as one of the features of dyskeratosis congenita. However, the relationship between mutations in the other dyskeratosis congenita genes and pulmonary fibrosis has not yet been clarified. To the best of our knowledge, this is the first case report describing a dyskeratosis congenita patient with pulmonary fibrosis who had a *TINF2* mutation.

A 43-year-old female visited our hospital with cough and progressive dyspnoea. She had never smoked, and had a history of aplastic anaemia, ocular pemphigoid, erythroplasia of Queyrat and infertility. Her father had been diagnosed as having aplastic anaemia and his whole body was pigmented. About 2 years ago, she complained of cough and consulted her personal doctor. Her chest radiographs showed diffuse reticular shadows in the bilateral lung fields. She was referred to a general hospital and was diagnosed with idiopathic interstitial pneumonia. Because her general condition was stable at that time, she was followed up without any specific therapy for 1 year. She was referred to our hospital due to gradual worsening of dyspnoea and admitted for further examinations. Her physical examination was remarkable for skin pigmentation on her whole body, ocular pemphigoid in the left eye and fine crackles in both lung fields. Her fingertip skin was rough but her nails were not dystrophic. Although no leukoplakia was found in the oral mucosa, she had erythroplasia of Queyrat of the vulva. Laboratory data showed elevated lactate dehydrogenase, transaminases, erythrocyte sedimentation rate and sialylated carbohydrate antigen KL-6 with thrombocytopenia. Chest radiographs demonstrated consolidation and reticular shadows in the bilateral lung fields. Furthermore, chest computed tomography revealed consolidation and reticular shadows in both lung fields, as well as bronchiectasis and cystic shadows in the left lung.