

## ORIGINAL ARTICLE

## Relation between lymphopenia and bacteraemia in UK adults with medical emergencies

D H Wyllie, I C J W Bowler, T E A Peto

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See end of article for authors' affiliations

Correspondence to: D H Wyllie, Nuffield Department of Clinical Laboratory Sciences, John Radcliffe Hospital, Oxford OX3 9DU; david.wyllie@ndcls.ox.ac.uk

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**Aims:** To determine the relevance of lymphopenia to the diagnosis of bacteraemia in patients admitted with medical emergencies, relative to peripheral blood white cell count and neutrophilia.**Patients/Methods:** A two year cohort study carried out in a teaching hospital in Oxford, UK of 21 495 consecutive adult emergency admissions to general medical or infectious disease wards. Full blood data were available in 21 372 cases; 41 cases with extreme full blood count results (neutrophil count,  $> 75 \times 10^9/\text{litre}$ ; lymphocyte count,  $> 10 \times 10^9/\text{litre}$ ) were excluded, leaving 21 331 cases for analysis. The association between the admission lymphocyte and neutrophil counts and the risk of bacteraemia was assessed.**Results:** Neutrophilia and lymphopenia were both associated with bacteraemia. Lymphopenia was the better predictor in this cohort. Both neutrophilia and lymphopenia were more predictive of bacteraemia than the total white blood cell count.**Conclusions:** Both lymphocyte and neutrophil counts, rather than total white blood cell count, should be considered in adult medical admissions with suspected bacteraemia.

Alterations of white blood cell count (WBC) are well recognised features of sepsis,<sup>1</sup> and raised WBC and neutrophilia are associated with bacteraemia in both adults<sup>2</sup> and children.<sup>3-4</sup> A rapid, profound lymphopenia occurs in primates with experimental bacteraemia.<sup>5-7</sup> Recent clinical studies, performed on groups at low human immunodeficiency virus (HIV) risk, suggest that lymphopenia may define patients at high risk of adverse outcome. For example, lymphopenia is a risk factor for intensive care in unwell infants,<sup>8</sup> and for death in nursing home residents with pneumonia.<sup>9</sup>

"The existing literature on the relation between lymphopenia and bacteraemia is difficult to evaluate"

In view of this, we investigated whether lymphopenia was useful for predicting bacteraemia clinically, an activity that remains imprecise even after detailed study.<sup>2-10</sup> The existing literature on the relation between lymphopenia and bacteraemia is difficult to evaluate: two observational studies, involving a total of about 750 elderly patients, have noted lymphopenia in some patients with bacteraemia, but specificity varied between the studies, and the distributions of the counts were not reported.<sup>11-12</sup> Generalisation of the published data to other populations is further complicated by the gradual decline in lymphocyte counts that occurs as normal adults age.<sup>13-14</sup> We sought to clarify the relation between age, lymphocyte count, neutrophil count, and bacteraemia by the study of a large cohort of adults with medical emergencies in a region, which, at the time of study, had a low prevalence of HIV.

## METHODS

## Study design and setting

The cohort studied comprised consecutive patients, aged at least 18 years, admitted from the community as emergencies to general medical or infectious diseases services of the Oxford Radcliffe Hospital, UK, from 1 February 1999 to 31 January 2001. Patients admitted to haematology or

cardiology wards did not form part of the cohort because admission to these wards usually implies either known haematological disease or an acute coronary syndrome.

## Microbiology and haematology

Blood cultures were taken by medical staff if thought to be clinically indicated, using pairs of anaerobic and aerobic Bactec F+ bottles (Becton-Dickinson, Oxford, UK). Bottles were incubated for five days, unless endocarditis was suspected, when 21 day incubations were used. Isolates were speciated by routine methods. Admission cultures were defined as those taken in the first two days of admission. Full blood counts were performed using a Technicon H3 analyser (Bayer, Newbury, UK). The clinical laboratories involved in specimen processing were accredited by the UK Clinical Pathology Accreditation scheme.

For the purposes of our study, we considered "significant isolates" as any blood culture yielding an organism other than a coagulase negative staphylococcus or *Corynebacterium* spp. These isolates are unlikely to reflect genuine bacteraemia in the population studied, in which line related sepsis is very rare. Mixed cultures were considered significant if organisms other than coagulase negative staphylococcus or *Corynebacterium* spp were isolated.

## Data collection and analysis

Data used in the study were recorded during the patients' admissions on the hospital's information systems, and abstracted in an anonymous form. Analysis was performed at the end of the study period.

## Statistical methods

SPSS version 11 was used for logistic regression and receiver operating characteristic (ROC) plotting. ROC plots displayed sensitivity versus 1-specificity, such that the areas under the curve (AUCs) generated varied from 0.5 to 1.0, with higher

**Abbreviations:** AUC, area under the curve; HIV, human immunodeficiency virus; ROC, receiver operating characteristic; WBC, white blood cell count

**Table 1** Blood culture isolates obtained

	Age (years)								Total
	18–29	30–39	40–49	50–59	60–69	70–79	80–89	≥90	
Not cultured	1369	1238	1270	1575	2030	3051	2869	766	14168
No significant isolates	639	586	552	595	815	1468	1553	460	6668
Coagulase negative staphylococci	29	28	35	57	79	124	132	36	520
Diphtheroids	2	1	4	2	2	12	11	5	39
All significant isolates	38	35	27	38	57	151	157	33	536
<i>Escherichia coli</i>	7	4	5	5	15	50	49	11	146
Other Enterobacteriaceae and <i>Pseudomonas</i> spp	5	3	2	6	11	12	28	6	73
<i>Staphylococcus aureus</i>	5	7	6	11	7	18	22	1	77
<i>Streptococcus pneumoniae</i>	3	6	1	3	12	16	10	3	54
β Haemolytic streptococci	1	3	2	3	1	11	11	1	33
Anaerobes		1				1	2		4
Fungi		1				1	2		4

The numbers of cases cultured and the culture results are shown, stratified by age.

values indicating increased discriminatory ability. Confidence intervals on AUCs of ROC plots were calculated using non-parametric assumptions. The odds of significant bacteraemia for a given group of patients were calculated as: cases of significant bacteraemia/cases without significant bacteraemia. For univariate and multivariate logistic regression analysis, a variable was calculated to represent the distance between the observed lymphocyte and neutrophil counts and a count in the normal range ( $7 \times 10^9/\text{litre}$  and  $2 \times 10^9/\text{litre}$ , respectively). This variable, calculated as  $((\text{neutrophils}) - 7 \times 10^9/\text{litre}) \times (2 \times 10^9/\text{litre} - (\text{lymphocytes}))/1 \times 10^9/\text{litre}$ , increases as lymphocytes fall and neutrophils rise.

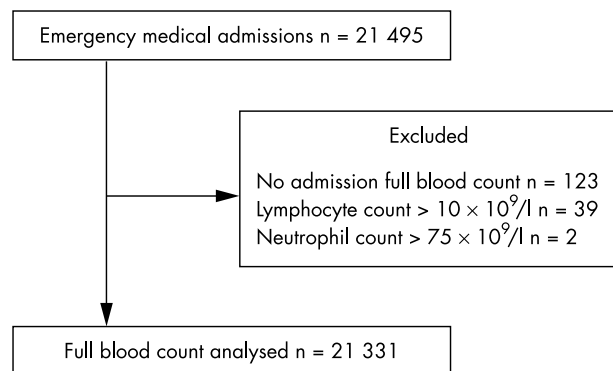
## RESULTS

### Composition of the cohort

There were 21 495 patients and 21 331 were analysed further. Figure 1 shows the reasons for exclusion. Ages ranged from 18 years to 106 years; the average inpatient stay was 6.4 days. Admission cultures were obtained from 7182 (33.6%) patients. Of these, in 5964 cases (83.0%), a single pair (aerobic and anaerobic) was used. Significant isolates were isolated from 530 patients. There were 520 cases of coagulase negative staphylococcus and 39 cases of *Corynebacterium* spp; these were considered contaminants. Table 1 shows the numbers of patients, their ages, and the blood culture isolates obtained.

### Association between age, bacteraemia, and cell counts

In our cohort, the peripheral lymphocyte count declined with age (fig 2), as described previously.<sup>13 14</sup> However, at all ages,



**Figure 1** Cases analysed. The reasons for exclusion of cases, and the distribution of lymphocyte and neutrophil counts within the cohort are shown.

the lymphocyte count was highest in those in whom cultures were not performed, intermediate in those in whom cultures were taken but no significant isolate obtained, and lowest in the patients with bacteraemia (fig 2A).

### Change in lymphocyte count during admission

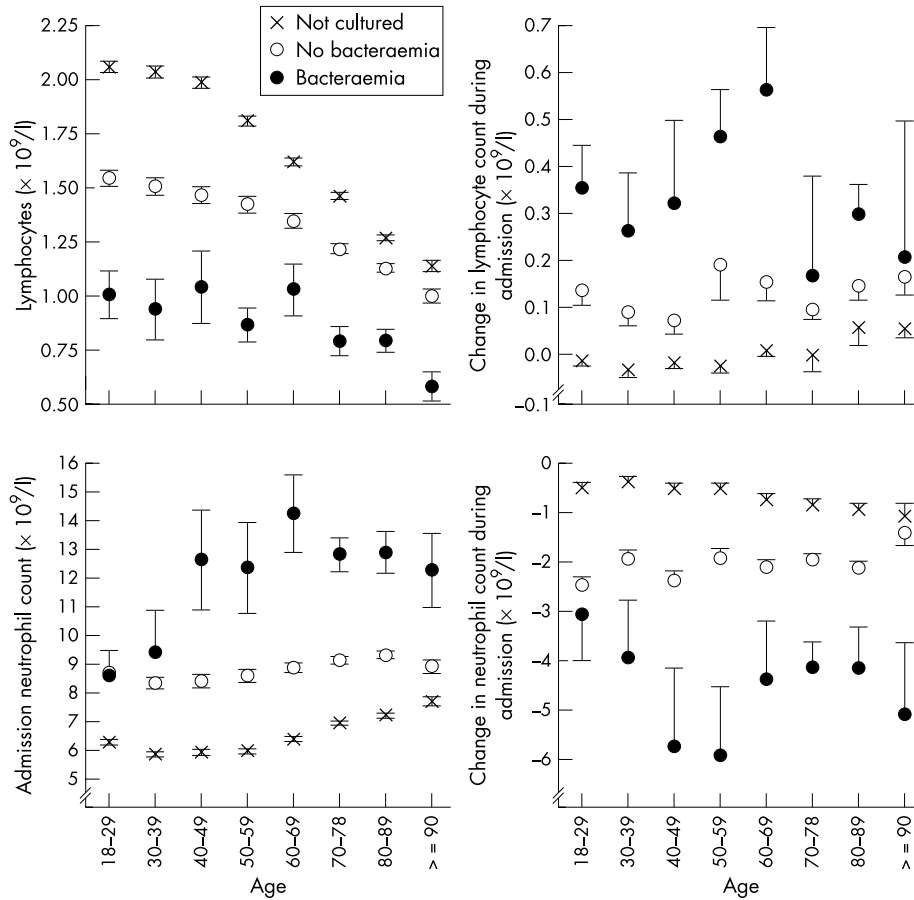
We considered whether the lymphopenia that we observed was, as predicted by experimental data,<sup>5 6</sup> a transient phenomenon, or whether it represented a pre-existing condition predisposing to bacteraemia. Admission blood counts were compared with the last count taken during the admission. Figure 2 shows that, during admission, both the admission neutrophilia and lymphopenia seen in the patients with bacteraemia declined, compatible with both changes being a response to bacteraemia.

### Lymphocyte and neutrophil counts and bacteraemia risk

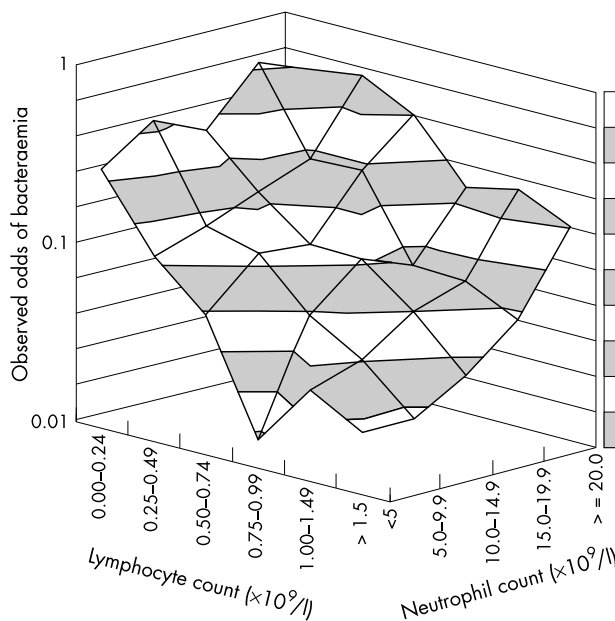
The observed odds of bacteraemia (the number of patients with bacteraemia/number without bacteraemia) were calculated for the 7182 patients whose blood had been cultured, stratified by lymphocyte and neutrophil count. Table 2 shows the absolute numbers of patients in each stratum. In fig 3, a surface is drawn through the observed bacteraemia odds. As expected, odds of bacteraemia increased with increasing neutrophil count. However, there was also a pronounced increase in bacteraemia odds as the lymphocyte count declined below  $1.5 \times 10^9/\text{litre}$ , an effect evident at all neutrophil counts. This suggests that neutrophilia and lymphopenia independently predict bacteraemia.

Lymphocyte counts less than  $0.25 \times 10^9/\text{litre}$ , referred to here as extreme lymphopenia, identified the group with the highest risk of bacteraemia. This is evident from fig 4, which shows an alternative representation of the data in fig 3. Extreme lymphopenia was found in 12% (63 of 530) of the patients with bacteraemia, but only 2.4% (162 of 6652) of the patients without significant isolates. Extreme lymphopenia, similar to less severe lymphopenia, appears to recover during hospital stay: the mean difference between admission and predischarge lymphocyte counts was  $0.62 \times 10^9/\text{litre}$  (95% confidence interval, 0.48 to 0.76) with extreme lymphopenia, and  $0.36 \times 10^9/\text{litre}$  (95% confidence interval, 0.29 to 0.43) without extreme lymphopenia.

Interestingly, in the extreme lymphopenic group, the strength of the association of bacteraemia with the neutrophil count appears to be less than that at higher lymphocyte counts. Mathematically, this would represent an interaction between neutrophil and lymphocyte counts. To investigate this further, and to examine the effect of age, logistic regression was performed. Univariate logistic regression



**Figure 2** Neutrophil and lymphocyte counts by age. Age stratified lymphocyte and neutrophil counts among non-cultured, culture negative, and culture positive patients are shown. Symbols indicate the admission value; errors are standard errors of the mean. Table 1 shows the numbers of cases at each point.



**Figure 3** Odds of bacteraemia by cell count. The odds of bacteraemia (number of patients with bacteraemia/number without bacteraemia) among the patients whose blood was cultured, stratified by neutrophil and lymphocyte counts.

showed that the neutrophil count, the lymphocyte count, and their interaction were strongly associated, and age and WBC were weakly associated with bacteraemia (table 3). WBC was not used in multivariate modelling because of a strong correlation with neutrophil count. Of the other variables, neutrophil count, lymphocyte count, their interaction, but not age, remained significant on multivariate analysis (table 3).

**Comparison of counts in bacteraemia prediction**

Single variables associated with disease are simple to use clinically, and are potentially of diagnostic value. The 7182 blood cultured cases were examined, both as a whole, and in age stratified bands, and a comparison was made of the ability of raised WBC, depressed lymphocyte count, and raised neutrophil count to predict bacteraemia using ROC plotting. A significantly higher AUC, a parameter reflecting discriminatory ability, was found for lymphocyte count compared with either WBC or neutrophil count (fig 5). This effect was also evident in age stratified analysis; the lymphocyte count performed significantly better than the WBC or neutrophil count in all but one of the strata examined (table 4).

**DISCUSSION**

Our study describes the quantitative association between lymphopenia and the risk of bacteraemia in a large cohort of patients admitted to a UK hospital with medical emergencies. Both lymphopenia and neutrophilia are independently associated with bacteraemia, and there is a group of patients

**Table 2** Distribution of lymphocytes and neutrophils in patients with medical emergencies

Culture status	Neutrophils ( $\times 10^9/l$ )	Index test: lymphocytes ( $\times 10^9/l$ )							Total
		0.00–0.24	0.25–0.49	0.50–0.74	0.75–0.99	1.00–1.49	1.50–1.99	$\geq 2.00$	
Not cultured	0.0–4.9	33	111	290	503	1431	1269	1766	5403
	5.0–9.9	32	213	581	860	1916	1463	1742	6807
	10.0–14.9	14	129	203	246	423	227	267	1509
	15.0–19.9	7	26	63	68	62	43	44	313
	$\geq 20.0$	5	11	20	24	17	16	24	117
	Total	91	490	1157	1701	3849	3018	3843	14149
No significant bacteraemia	0.0–4.9	56	118	181	206	368	260	231	1420
	5.0–9.9	56	265	415	512	821	528	501	3098
	10.0–14.9	24	161	217	246	378	174	154	1354
	15.0–19.9	12	69	97	86	138	48	57	507
	$\geq 20.0$	14	30	52	48	55	38	36	273
	Total	162	643	962	1098	1760	1048	979	6652
Significant bacteraemia	0.0–4.9	16	13	11	3	12	6	5	66
	5.0–9.9	25	36	47	31	33	12	11	195
	10.0–14.9	8	29	23	26	24	8	3	121
	15.0–19.9	8	16	23	7	11	3	3	71
	$\geq 20.0$	6	17	21	9	12	2	10	77
	Total	63	111	125	76	92	31	32	530

The numbers of patients in each stratum of lymphocytes and neutrophils examined are shown.

who are lymphopenic, and at very high risk of bacteraemia, whose total WBC and neutrophil counts lie within the normal range. The lymphopenia–bacteraemia association was seen in patients at all ages studied.

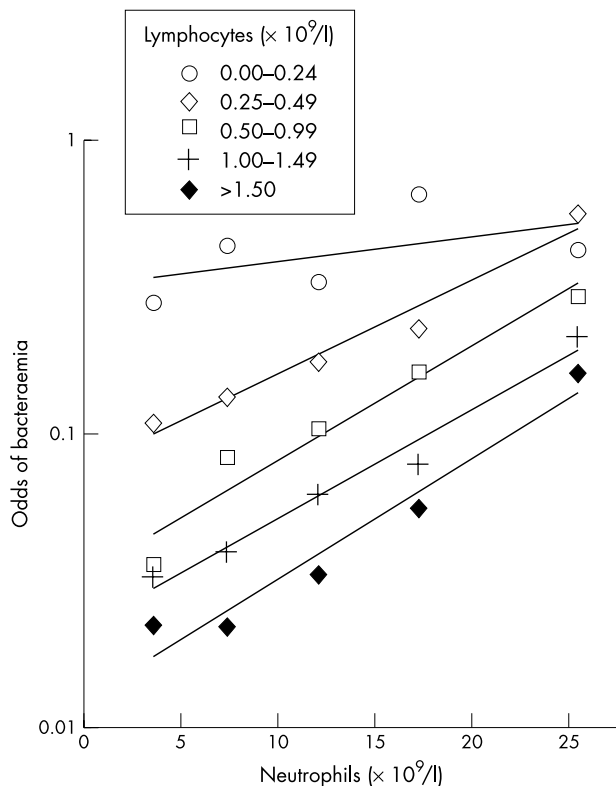
Our observations are compatible with reports from smaller series of elderly patients describing lymphocyte counts less than  $1 \times 10^9/litre$  as being associated with bacteraemia.<sup>11 12</sup> An association of bacteraemia and lymphopenia may also explain the associations between lymphopenia and disease severity in nursing home residents with pneumonia,<sup>9</sup> and

surgical patients after emergency laparotomy.<sup>15</sup> Our observations are also compatible with the rapid decline in blood lymphocyte count occurring in animal and human models of sepsis.<sup>5–7</sup> Bacterial sepsis was an important cause of lymphopenia in the population studied, but lymphopenia is not specific for sepsis of bacterial origin, because it also occurs in severe viral infections.<sup>16–18</sup>

Although the hospital in which the study was performed is a tertiary referral centre, the study cohort comprised individuals admitted from the community as an emergency. As such, they are likely to be representative of emergency medical admissions in the UK. Their microbiological investigation was probably typical of that widely practiced, because the proportion of patients cultured in this cohort was similar to that reported from a comparable cohort in another European hospital.<sup>12</sup>

HIV associated lymphopenia might complicate the observed association between lymphopenia and bacteraemia. However, HIV prevalence, determined by an unlinked seroprevalence study,<sup>19</sup> was about 1/1000 during the study, and the lymphopenia–bacteraemia association was seen at all ages, including the elderly, in whom HIV is extremely rare in Oxfordshire,<sup>19</sup> so HIV related changes in WBC are unlikely to be an important confounder.

We used a stringent definition of significant bacteraemia, regarding all isolates except *Corynebacterium* spp or coagulase negative staphylococci as significant for the purpose of our study. Therefore, our definition will classify many organisms, including  $\alpha$  haemolytic streptococci and enterococci, as significant. Although such organisms are sometimes associated with serious pathology, their isolation may also be of little importance, especially when only isolated from a single culture. A chart review could have been used to determine the probable relevance of individual cases. However, this process is often subjective, so we persisted with a stringent definition, which probably led to an underestimation of the true lymphopenia–bacteraemia association.



**Figure 4** Odds of bacteraemia by cell count. The odds of bacteraemia (number of patients with bacteraemia/number without bacteraemia) among the patients whose blood was cultured, stratified by neutrophil and lymphocyte counts. An alternative representation of the data in fig 3.

“The clinical usefulness of lymphopenia as a diagnostic and prognostic marker merits further investigation in other centres and populations”

The induction of tumour necrosis factor family members occurs early in the inflammatory response; these engage receptors expressed on lymphocytes and cause lymphocyte

**Table 3** Logistic regression relating significant bacteraemia to full blood count

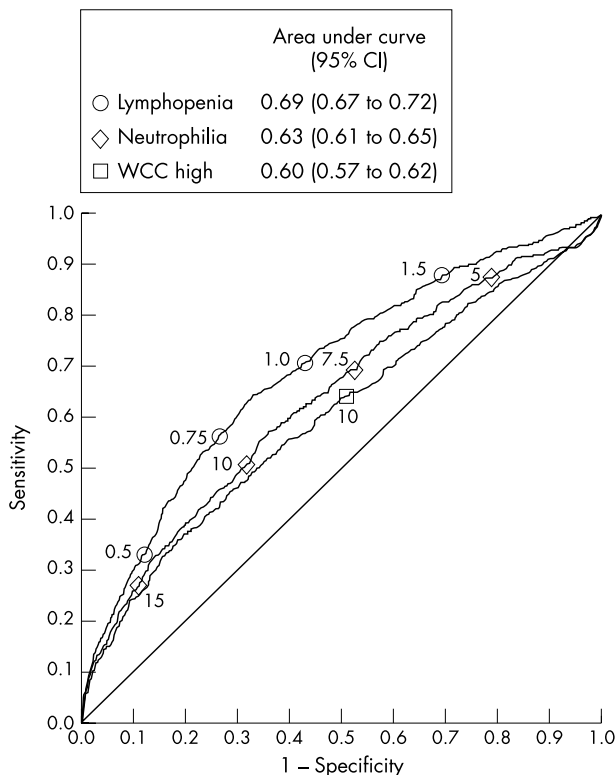
	Culture negative (n=6652)		Culture positive (n=530)		Univariate			Multivariate				
	Mean	SD	Mean	SD	OR	95% CI	Wald	p Value	OR	95% CI	Wald	p Value
Age	64.3	21.5	68.4	19.8	1.01	(1.01 to 1.01)	18	<0.001	1.00	(1.00 to 1.01)	1.8	0.17
WBC ( $\times 10^9/l$ )	11.3	7.4	14.2	8.9	1.04	(1.02 to 1.05)	39	<0.001	Not entered			
Lymphocytes ( $\times 10^9/l$ )	1.30	0.90	0.85	0.72	0.35	(0.29 to 0.41)	140	<0.001	0.3	(0.24 to 0.37)	114	<0.001
Neutrophils ( $\times 10^9/l$ )	8.9	5.2	12.4	8.4	1.09	(1.07 to 1.10)	165	<0.001	1.12	(1.06 to 1.15)	95	<0.001
Neutrophil-lymphocyte interaction	2.4	6.9	6.9	12.5	1.07	(1.06 to 1.08)	165	<0.001	0.97	(0.95 to 0.98)	15	<0.001

Univariate and multivariate logistic regression of admission peripheral blood count with blood culture positivity. Wald refers to the Wald statistic. CI, confidence interval; OR, odds ratio; WBC, white blood cell count.

**Table 4** AUCs (95% CI) for the discrimination of patients with bacteraemia from those without bacteraemia

Age	Lymphocytopenia	Neutrophilia	Raised total WBC
<50	0.69 (0.66 to 0.72)	0.56 (0.53 to 0.59)**	0.52 (0.49 to 0.55)**
50-69	0.67 (0.64 to 0.70)	0.63 (0.60 to 0.68)*	0.59 (0.56 to 0.63)*
70-79	0.69 (0.67 to 0.71)	0.67 (0.65 to 0.70)	0.65 (0.62 to 0.67)*
>80	0.68 (0.66 to 0.70)	0.63 (0.61 to 0.66)**	0.62 (0.60 to 0.64)**
All cases	0.69 (0.67 to 0.72)	0.63 (0.61 to 0.66)**	0.60 (0.57 to 0.62)**

WBC components predicting bacteraemia stratified by age. AUCs were calculated for different age groups, comparing the ability of lymphocytopenia, neutrophilia, and raised total WBC to discriminate patients with bacteraemia from those without. Higher AUCs indicate better discrimination. Comparisons were made between the lymphocytopenia AUCs and neutrophilia or WBC AUCs. \*p<0.05; \*\*p<0.01 (comparisons made by Z testing). AUC, area under the receiver operator characteristic plot; CI, confidence interval; WBC, white blood cell count.



**Figure 5** White cell count (WCC) components predicting bacteraemia. A receiver operator characteristic plot is shown, illustrating the ability of admission WCC, neutrophil count, and lymphocyte count to predict bacteraemia among all 7182 patients in whom blood cultures were taken. The symbols on the curve indicate the positions of particular counts; for example, the circle 1.0 indicates the performance of a lymphocyte count of  $1.0 \times 10^9/l$  litre. Areas under the curve, and their confidence intervals (CI), are shown in the box for each variable. Higher areas under the curve indicate better discrimination.

apoptosis, as reviewed previously.<sup>20</sup> The decline in lymphocyte numbers seen in our study is probably the result of large scale lymphocyte apoptosis, which has been seen in several animal models of sepsis,<sup>21-22</sup> in the spleens of humans who have died of sepsis,<sup>23</sup> and in the peripheral blood of patients with sepsis.<sup>6, 23-25</sup> Interestingly, CD4 T helper type 1 and 2 cells may be differentially susceptible.<sup>25, 26</sup> The study of mice with genetic abnormalities of the apoptotic machinery, and of mice treated with apoptosis inhibitors,<sup>27, 28</sup> shows that lymphocyte apoptosis influences mortality in sepsis. This is probably because protective lymphocyte dependent immune responses<sup>24</sup> are decreased by the widespread death of lymphocytes. These studies imply that the decline in peripheral blood lymphocyte numbers seen in our study is the result of a key pathogenic mechanism in sepsis.

The data presented in our paper show that, in populations with a high prevalence of bacterial infections, lymphopenia may reflect bacteraemia. Importantly, in our large cohort, lymphopenia performed significantly better than either neutrophil count or WBC in bacteraemia prediction, although these last two markers are very widely used in the assessment of infected patients. Therefore, the clinical usefulness of lymphopenia as a diagnostic and prognostic marker merits further investigation in other centres and populations, both

**Take home messages**

- In a cohort of adult medical admissions with suspected bacteraemia, neutrophilia and lymphopenia were both associated with bacteraemia, although lymphopenia was the better predictor
- Both neutrophilia and lymphopenia were more predictive of bacteraemia than the total white blood cell count

alone and in combination with other laboratory measures of the acute phase response.<sup>29 30</sup>

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## Authors' affiliations

**T E A Peto**, Nuffield Departments of Medicine, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK

**D H Wyllie, I C J W Bowler**, Nuffield Department of Clinical Laboratory Sciences, University of Oxford, John Radcliffe Hospital

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