Bacteraemic infection represents the severe end of the spectrum of community acquired infectious disease,\textsuperscript{5} and is associated with a high mortality.\textsuperscript{1,2} Mortality is improved with appropriate treatment,\textsuperscript{3,4} suggesting that early recognition is a relevant clinical objective.

``We attempted to predict bacteraemia based on C reactive protein, lymphocyte count, and neutrophil count, using a large database of UK emergency admissions''

Experimental data show that the lymphopenia that occurs in sepsis is partly responsible for the outcome of infection.\textsuperscript{5,7} We have recently reported that lymphopenia, and the well known rise in the neutrophil count occurring in sepsis,\textsuperscript{8,9} are independently associated with bacteraemia in UK adults with medical emergencies.\textsuperscript{10} In our institution, estimation of the C reactive protein (CRP) concentration has become very prevalent. Increases in CRP concentration are associated with bacteraemia in patients admitted from the community,\textsuperscript{11,12} and in series of hospitalised patients comprising both community acquired and nosocomial infections.\textsuperscript{13,14} We thought that the clinical estimation of bacteraemia risk in the individual patients admitted as an emergency would be aided by an understanding of both the quantitative relation between CRP and bacteraemia, and of how CRP adds to the inferences made from the neutrophil and lymphocyte counts. Because existing data do not address this question, we have attempted to predict bacteraemia based on CRP, lymphocyte count, and neutrophil count, using a large database of UK emergency admissions, derived from a region of low human immunodeficiency virus prevalence.

METHODS

Study design and setting
This cohort has been described previously\textsuperscript{10}; it comprises consecutive emergency adult medical admissions, aged at least 18 years, admitted from the community to general medical or infectious diseases services of Oxford Radcliffe Hospitals, UK, from 1 February 1999 to 31 January 2001. Patients admitted to haematology or cardiology wards did not form part of the cohort. Because this represented a retrospective observational study of routinely collected anonymous healthcare records, we did not seek ethical approval for the analysis.

Microbiology, haematology, and CRP estimation
Blood cultures and full blood counts were processed as described previously.\textsuperscript{10} CRP measurements were performed with a Biostat kit on an Aeroset analyser (Abbott, Maidenhead, Berkshire, UK). This has limits of linearity at 8 and 285 mg/litre; results outside these limits are reported as < 8 and > 285 mg/litre. 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 \textit{Corynebacterium} spp, as described previously.\textsuperscript{10}

Data collection and analysis
Data used in our study were recorded during the patients’ admissions on the hospital’s information systems, and

Abbreviations: AUC, area under the curve; CRP, C reactive protein; ROC, receiver operator characteristic

ORIGINAL ARTICLE

Bacteraemia prediction in emergency medical admissions: role of C reactive protein

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

RESULTS
Characteristics of the cohort
There were 21 495 cases in the cohort. Of these, 164 cases had characteristics of significant bacteraemia for a given group of patients were calculated as (cases of significant bacteraemia)/(cases without significant bacteraemia).

To examine the quantitative associations between bacteraemia and neutrophil, lymphocyte, and CRP results, cases were analysed in strata. There was no overlap between the strata. For neutrophils, strata were 0.5 × 10^9/litre wide; for lymphocytes, 0.25 × 10^9/litre; and for CRP, 10 mg/litre. The odds of bacteraemia were then plotted for each stratum. For CRP, results of < 8 or > 285 mg/litre were coded as 8 and 285, respectively.

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 areas under the curve (AUC) generated varied from 0.5 to 1.0, with higher 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).

Using the derivation set, we constructed logistic regression models predicting bacteraemia. Neutropenic patients (neutrophil counts less than 1 × 10^9/litre); as expected, their bacteraemia risk was high. For counts above 1 × 10^9/litre, the data are compatible with a linear increase in log odds of bacteraemia with rising neutrophil count. This is also the case for CRP concentrations. We coded results as being outside the limit of the assay at the assay limits of 8 and 285 mg/litre; however, deviation of these points from the relation seen within the linearity of the assay is not evident, justifying this approach. For lymphocyte count, the log of the odds of bacteraemia is proportional to the log of the lymphocyte count.

Models of bacteraemia risk
Using the derivation set, we constructed logistic regression models predicting bacteraemia. Neutropenic patients (neutrophil counts, < 1 × 10^9/litre) represent a special case, as described above, and are rare in this cohort; we excluded them from further analysis (fig S1; http://www.jclinpath.com/supplemental). Because of the linear relation between log odds of bacteraemia and log lymphocyte count, in our models we used log lymphocyte count, rather than lymphocyte count, as a predictor. By univariate analysis, patient age, neutrophil count, lymphocyte count, CRP concentration, and all interactions between neutrophil count, lymphocyte count, and CRP concentration were significant by forward and backward logistic regression analysis. Table 2 shows the results for backward analysis. We then constructed two logistic regression models: one included all the above terms, and the other omitted terms involving CRP. Age, lymphocyte count, neutrophil count, CRP concentration (when entered), and the lymphocyte–neutrophil interaction were significant by multivariate analysis (table 3).

Performance of two models and single variables
We examined the performance of neutrophil count, lymphocyte count, and CRP concentration, and of the probabilities of bacteraemia calculated using the two models derived from them, in the validation set. ROC curves for each of the five methods in differentiating bacteraemia from non-bacteraemia are presented. Figure 1A shows the curves, fig 1B shows

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Blood cultured cases by C reactive protein (CRP) measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRP present</strong> (n = 6234)</td>
<td><strong>CRP missing</strong> (n = 948)</td>
</tr>
<tr>
<td>Age/years</td>
<td>64.5</td>
</tr>
<tr>
<td>Duration of stay/days</td>
<td>8.89</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>127</td>
</tr>
<tr>
<td>Lymphocytes (×10^9/l)</td>
<td>1.27</td>
</tr>
<tr>
<td>Neutrophils (×10^9/l)</td>
<td>9.13</td>
</tr>
<tr>
<td>Platelets (×10^9/l)</td>
<td>279</td>
</tr>
<tr>
<td>Died as inpatient</td>
<td>0.0993</td>
</tr>
</tbody>
</table>
Table 2 Logistic regression models predicting bacteraemia in derivation set

<table>
<thead>
<tr>
<th>Term</th>
<th>No bacteraemia (n = 324)</th>
<th>Bacteraemia (n = 324)</th>
<th>Univariate analysis (n = 4145)</th>
<th>Multivariate model, CRP not included (n = 4145)</th>
<th>Multivariate model, CRP included (n = 4145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean, SD</td>
<td>76, 81</td>
<td>81, 87</td>
<td>1.08, 1.01</td>
<td>1.08, 1.01</td>
<td>1.08, 1.01</td>
</tr>
<tr>
<td>log CRP (mg/l)</td>
<td>0.28, 0.28</td>
<td>0.28, 0.28</td>
<td>0.20, 0.20</td>
<td>0.20, 0.20</td>
<td>0.20, 0.20</td>
</tr>
<tr>
<td>log lymphocytes</td>
<td>0.51, 0.51</td>
<td>0.51, 0.51</td>
<td>-0.21, 0.62</td>
<td>-0.21, 0.62</td>
<td>-0.21, 0.62</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>8.9, 5.1</td>
<td>12.1, 7.4</td>
<td>8.9, 7.4</td>
<td>8.9, 7.4</td>
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</tr>
<tr>
<td>log lymphocytes CRP</td>
<td>-0.12, 0.10</td>
<td>-0.12, 0.10</td>
<td>0.09, 0.13</td>
<td>0.09, 0.13</td>
<td>0.09, 0.13</td>
</tr>
<tr>
<td>log log lymphocytes</td>
<td>-0.04, 0.02</td>
<td>-0.04, 0.02</td>
<td>0.01, 0.01</td>
<td>0.01, 0.01</td>
<td>0.01, 0.01</td>
</tr>
<tr>
<td>CRP</td>
<td>76, 81</td>
<td>147, 95</td>
<td>1.008, 1.009</td>
<td>1.008, 1.009</td>
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</tr>
<tr>
<td>CRP Neutrophils</td>
<td>7.4, 7.4</td>
<td>10.7, 10.7</td>
<td>1.032, 1.076</td>
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<td>8.9, 7.4</td>
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<tr>
<td>CRP log CRP</td>
<td>0.28, 0.28</td>
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<td>0.01, 0.01</td>
<td>0.01, 0.01</td>
<td>0.01, 0.01</td>
</tr>
</tbody>
</table>

**Likelihood ratios for bacteraemia**

An alternative method of looking at these data, and one that is more useful when faced with an individual patient, is to examine the likelihood ratio for bacteraemia associated with the models and variables studied. The likelihood ratio is the factor relating the pre-test to the post-test odds; we calculated the observed likelihood ratios for a range of parameter values within the derivation set (fig 2). Neutrophil count, lymphocyte count, and both the models derived can generate likelihood ratios of greater than 10 for bacteraemia, although the number of cases in which this occurs is small (table 3).

The peak likelihood ratio achieved by CRP concentrations is less, at 4.0, and occurs with concentrations of 285 mg/litre.

**DISCUSSION**

To our knowledge, this is the first study to assess the quantitative association between bacteraemia, white blood cell components, and CRP, even though alterations in white blood cell distribution and CRP are regarded as classic markers of inflammation. We show that CRP, lymphopenia, and neutrophilia independently predict bacteraemia, and we describe the associations between the values of these parameters and the risk for bacteraemia. Models are derived and validated that further increase the predictive value of these tests. Evidence based medicine theory suggests that tests with likelihood ratios of 10 or over are those most helpful clinically; likelihood ratios over 10 are only achieved in about 2.7%, 2%, and 1% of cases using our bacteraemia models, neutrophilia, or lymphopenia respectively; they are never achieved using CRP as an infection marker, the peak likelihood ratio achievable with which is 4.0. Thus, although the models we present may be of substantial use to clinicians in some cases, in others their clinical usefulness is uncertain. The information added by CRP to the examination of neutrophil and lymphocyte counts is small.

"In the early detection of the most severe, bacteraemic forms of community acquired infection, the role of C reactive protein may be limited"
be indications for measuring CRP in acute medical patients, such as monitoring the progression of illness.\textsuperscript{20–22} However, in the early detection of the most severe, bacteraemic forms of community acquired infection, the data presented here suggest that its role is limited. If the detection of severe infectious illness is the aim of using an acute inflammatory marker, and a full blood count is available, one needs to consider whether expending resources on CRP estimation is worthwhile. Other markers may offer better performance. In particular, a substantial literature is emerging on the use of procalcitonin. Studies in emergency departments in Taiwan,\textsuperscript{23} France,\textsuperscript{24} and Turkey\textsuperscript{25} were performed on populations that are probably similar to our blood cultured cohort. Inclusion criteria included having symptoms or signs compatible with infection,\textsuperscript{23} systemic inflammatory respiratory syndrome,\textsuperscript{23} or having a CRP done.\textsuperscript{23} The outcome measures in these studies also varied, but included clinical definitions of infection,\textsuperscript{23–24} systemic infection,\textsuperscript{23} and septic shock.\textsuperscript{23} All three studies showed that in the diagnosis of systemic infection\textsuperscript{23} and sepsis,\textsuperscript{23–25} procalcitonin performed better than CRP. These studies are compatible with studies showing better performance of procalcitonin than CRP in the prediction of bacteraemia,\textsuperscript{11} and of pneumonia severity,\textsuperscript{26} and with studies from intensive care units showing that procalcitonin is more closely correlated with the severity of infection than is CRP.\textsuperscript{27–29}

This work emphasises the need for clinical studies that document the performance of existing and novel markers of infection in clearly defined populations, so that severe forms of community acquired infection may be recognised and treated rapidly.

**ACKNOWLEDGEMENTS**

We thank members of our department for helpful comments.

<table>
<thead>
<tr>
<th>Analysis of derivation set (n = 2049)</th>
<th>Cutoff value for (LR &gt; 5)</th>
<th>Cutoff value for (LR &gt; 10)</th>
<th>(LR &gt; 5) n = %</th>
<th>(LR &gt; 5) n = %</th>
<th>(LR &gt; 10) n = %</th>
<th>(LR &lt; 10) n = %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modelled probability, CRP included</td>
<td>0.197</td>
<td>0.304</td>
<td>168</td>
<td>8.2%</td>
<td>57</td>
<td>2.8%</td>
</tr>
<tr>
<td>Modelled probability, CRP excluded</td>
<td>0.181</td>
<td>0.250</td>
<td>156</td>
<td>7.6%</td>
<td>53</td>
<td>2.6%</td>
</tr>
<tr>
<td>Neutrophil count (\times 10^9/l)</td>
<td>20.7</td>
<td>26.2</td>
<td>92</td>
<td>4.5%</td>
<td>39</td>
<td>1.9%</td>
</tr>
<tr>
<td>Lymphocyte count (\times 10^9/l)</td>
<td>0.263</td>
<td>0.149</td>
<td>70</td>
<td>3.4%</td>
<td>23</td>
<td>1.1%</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>0.0%</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

This table shows the proportion of blood cultured cases in the validation set in which likelihood ratios of 5 and 10 for bacteraemia are predicted by the two models derived here, and by neutrophil count, lymphocyte count, and CRP protein when used as single variables.

**Take home messages**

- In patients with acute medical emergencies who are suspected of bacteraemia clinically, C reactive protein (CRP) concentrations, although associated with bacteraemia, have a limited role in bacteraemia prediction.
- The measurement of CRP concentrations in these patients adds little extra information to neutrophil and lymphocyte counts, and may be a waste of resources.
- Other markers, such as procalcitonin, may perform better.

Figure 1 This figure illustrates the performance, in the validation of models built using C reactive protein (CRP) concentration, lymphocyte count (LC), and neutrophil count (NP). (A) Receiver operator characteristic (ROC) curves for models built using CRP concentration, lymphocyte count, and neutrophil count (CRP, LC, NP), lymphocyte and neutrophil counts (NP, LC), or single variables. (B) Areas under the ROC curves. (C) The significance of pairwise comparisons between the areas.
Figure 2  The observed likelihood ratios for bacteremia associated with the parameters shown in fig 1. (A) The likelihood ratios associated with probabilities of bacteremia calculated by models without (plus symbols) or with (dots) C reactive protein (CRP). (B–D) Likelihood ratios produced by the range of neutrophil counts, CRP measurements, and lymphocyte counts, respectively.

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**REFERENCES**

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