Bacteraemic infection represents the severe end of the spectrum of community acquired infectious disease, and is associated with a high mortality. Mortality is improved with appropriate treatment, 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"
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) 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.

RESULTS

Characteristics of the cohort

There were 21 495 cases in the cohort. Of these, 164 cases had missing, or extreme (neutrophils, > 75 × 10^9/litre; or lymphocytes > 10 × 10^9/litre) blood count results, leaving 21 331 cases for further analysis. Of these, 14 149 cases were not blood cultured, whereas 7182 (33.6%) were, a proportion similar to that reported in another European centre. A breakdown of the cases is shown as a flow chart in the supplementary data shown online (fig S1; http://www.jclinpath.com/supplemental). The patients’ ages ranged from 18 to 106 years, and the average inpatient stay was 6.4 days. Of the cases that were blood cultured, 6668 cultures were negative, and 536 yielded significant pathogens, including *Escherichia coli* (146 cases), other enterobacteriaceae and *Pseudomonas* spp (73 cases), *Staphylococcus aureus* (77 cases), *Staphylococcus pneumoniae* (55 cases), and β haemolytic streptococci (33 cases). A more detailed breakdown of this cohort has been published. The distributions of CRP and white cell counts are shown, by blood culture result, in the supplementary data (table S1; http://www.jclinpath.com/supplemental).

In this article, we address the issue of the value of CRP in those patients in whom bacteraemia was suspected clinically, as judged by the taking of a blood culture. For this purpose, 7182 cases were available, and our further analyses concern these. CRP was measured on the day of admission in 6234 cases (86.8%). The patients in whom CRP was measured did not differ from those in whom it was not taken in age, proportion dying in hospital, haemoglobin, and neutrophil, lymphocyte, or platelet counts; however, they did stay one day longer in hospital (table 1). In view of the low proportion (13.2%) of missing CRP data and their comparable initial parameters, we thought that the 6234 cases were probably an unbiased sample of all blood cultured cases and analysed them further. To construct and validate bacteraemia prediction methods we split the 6234 cases into two, randomly assigning two thirds to a derivation set, and one third to a validation set. The characteristics of these two sets were comparable (table S2; http://www.jclinpath.com/supplemental).

Association between age, bacteraemia, and cell counts

Using the derivation set of 4185 cases, we analysed the quantitative association between CRP, neutrophil and lymphocyte counts, and bacteraemia. In a preliminary analysis, cases were divided into strata based on their count, and the odds of bacteraemia in each stratum plotted (fig S2; http://www.jclinpath.com/supplemental). Forty patients were neutropenic (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></td>
<td>CRP present (n = 6234)</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>
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:\(^2\); 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 >10 for bacteraemia, although the number of cases in which this occurs is small (table 3). The peak likelihood ratio achievable 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\(^17\) 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”

We chose to study bacteraemia as an outcome measure because it represents a dichotomous, objective outcome associated with mortality and with the most severe forms of community acquired sepsis. However, bacteraemia has several limitations as an outcome measure. First, it is not a sensitive measure of adverse outcome,\(^18\) and the prediction of non-bacteraemic infection may be as important as bacteraemic infection. Our data do not address the issue of whether our model would adequately predict severe non-bacteraemic infections. Neither do they address whether it adds to clinically discernable factors, such as the presence of shock, which are associated with the severity of infection and with outcome.\(^18\)\(^19\)

In our hospital, 86% of blood cultured patients had CRP estimations performed. They were also performed in 70% of those who were not blood cultured; overall, this suggests that CRP is now regarded as a routine test in this setting, into which considerable resources are being directed. There may
be indications for measuring CRP in acute medical patients, such as monitoring the progression of illness. 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, France, and Turkey were performed on populations that are probably similar to our blood cultured cohort. Inclusion criteria included having symptoms or signs compatible with infection, systemic inflammatory respiratory syndrome, or having a CRP done. The outcome measures in these studies also varied, but included clinical definitions of infection, systemic infection, and septic shock. All three studies showed that in the diagnosis of systemic infection and sepsis, procalcitonin performed better than CRP. These studies are compatible with studies showing better performance of procalcitonin than CRP in the prediction of bacteraemia, and of pneumonia severity, and with studies from intensive care units showing that procalcitonin is more closely correlated with the severity of infection than is CRP.

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.

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Table 3 Proportions of cases with high likelihood ratios

<table>
<thead>
<tr>
<th>Analysis of derivation set (n = 2049)</th>
<th>Cutoff value for LR &gt; 5</th>
<th>LR &gt; 5 n (%)</th>
<th>Cutoff value for LR &gt; 10</th>
<th>LR &gt; 10 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modelled probability, CRP included</td>
<td>0.197</td>
<td>168</td>
<td>0.304</td>
<td>57</td>
</tr>
<tr>
<td>Modelled probability, CRP excluded</td>
<td>0.181</td>
<td>156</td>
<td>0.250</td>
<td>53</td>
</tr>
<tr>
<td>Neutrophil count (x10⁹/l)</td>
<td>20.7</td>
<td>92</td>
<td>26.2</td>
<td>39</td>
</tr>
<tr>
<td>Lymphocyte count (x10⁹/l)</td>
<td>0.263</td>
<td>70</td>
<td>0.149</td>
<td>23</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>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.

CRP, C reactive protein; LR, likelihood ratio.

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.

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

A ROC curves

B Areas under ROC curves

C Differences in ROC areas

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

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