Patterns of Cytokine Expression in Community-Acquired Pneumonia*

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Background: Pneumonia continues to be a major cause of disease and death among patients worldwide. Aspects of the host response to infection, such as the release of cytokines, may be contributing to the persistent morbidity and mortality.

Methods: Plasma levels of cytokines interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha (TNF-α) were measured in critically ill patients with pneumonia (ICUP; n=12) and less severely ill patients with pneumonia (NONICUP; n=8), and in 2 additional control groups of patients, viz, severely ill postoperative patients without evidence of infection (POSTOP; n=11) and less severely ill patients with nonpneumonia infections (NONP; n=9). All four groups of patients were studied in a multivariate one-way analysis of variance using the parameter vector: plasma IL-1β, IL-6, TNF-α, systolic blood pressure, diastolic blood pressure, plasma urea, creatinine, and temperature. Thereafter the significance of individual parameters were assessed by univariate analysis and pairwise comparisons.

Results: All cytokine concentrations were highest in the ICUP group. In the case of IL-1β, levels were significantly higher in the ICUP group when compared with the noninfected POSTOP group. The acute physiology and chronic health evaluation (APACHE) II scores were identical in these two groups (17 ± 3 [SD] and 10 ± 1, respectively, not significantly different). Intermediate levels were found in those groups with intermediate levels of infection. The IL-6 levels were not significantly different between the groups and in particular, the levels in the ICUP and POSTOP groups were similar. The TNF-α levels tended to mimic those of IL-1β, although the significant difference found was between the ICUP and NONICUP groups which had significantly different APACHE II scores (17 ± 3 vs 4.4 ± 1, respectively). No association between cytokine levels and patient mortality was demonstrated.

Conclusion: Among the cytokines, IL-1β appeared to be associated with the severity of infection, IL-6 appears to reflect severity of stress whether of infection or noninfective origin, and TNF-α may be a marker of severity of pneumonia.

APACHE=acute physiology and chronic health evaluation; ICUP=critically ill patients with pneumonia; IL=interleukin; NONICUP=less severely ill patients with pneumonia; NONP=less severely ill patients with nonpneumonia infections; POSTOP=severely ill postoperative patients without evidence of infection; TNF=tumor necrosis factor

Key words: cytokine; interleukin-1; interleukin-6; pneumonia; tumor necrosis factor

Pneumonia is an ongoing cause of morbidity and mortality among patients worldwide, despite the availability of potent antimicrobial agents and the advanced technology used in many ICU facilities. The mortality is particularly high among critically ill patients, and not all factors associated with the ongoing mortality have been fully elucidated. It is recognized, however, that there are a number of clinical and laboratory parameters which when present in patients with pneumonia on admission to the hospital are associated with a poorer prognosis.

More recently, it has become apparent that aspects of the host response to infection may be contributing to tissue injury. One component of the host response to infection is the release of monocyte and macrophage-derived cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha (TNF-α) to sepsis syndrome is under intense scrutiny both experimentally and in humans. The cytokines display pleiotropism and have several overlapping and antagonistic effects with respect to immunoinflammatory responses to infection. Under in vitro conditions of endotoxemia, there appears to be a hierarchy of cytokine expression. The first cytokine to appear under experimental conditions is TNF-α followed by IL-1β and IL-6. The presence of circulating cytokines such as IL-1, IL-6, and TNF-α in sepsis may represent either excessive production or saturation of receptor sites or both. In general, the degree of expression of cytokines in several studies appears to correlate with the degree of sepsis. However,
the individual cytokines are unable to reproduce the septic syndrome in full, with the exception of TNF-α and IL-1.17

Cytokines, in general, play an important role in host defense mechanisms,5,18 and it is only under certain conditions that they may mediate deleterious results and contribute to the manifestations of septic shock, such as multiple organ failure and death.5 The concept that cytokines may be associated with deleterious effects in the infected host is strengthened by the recognition that many of the so-called negative prognostic factors in patients with pneumonia, including leukopenia, thrombocytopenia, and hypalbuminemia,1-3 are all effects specifically mediated by individual cytokines.10,19,20

The aim of the present study was to determine the pattern of cytokine expression in patients with pneumonia. We compared plasma cytokine concentrations of such patients requiring admission to an ICU with less severely ill patients. In particular, we wished to determine whether specific profiles of IL-1, IL-6, and TNF were predictors of severity of pneumonia. This was not simply to create a new severity of illness scoring index for pneumonia patients but because modern approaches to decreasing mortality in patients with various infections have focused on the manipulation of cytokines in such patients. It would seem that a rational approach would be to define accurately patterns of cytokines in specific disease states before such studies.

**Patients and Methods**

This study was undertaken at the Hillbrow Hospital in Johannes-

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**Table 1—Clinical and Laboratory Data of Patients With Community-Acquired Pneumonia Admitted to an ICU**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Duration of Illness, days</th>
<th>Tmax</th>
<th>Pulmonary Consolidation</th>
<th>Treatment</th>
<th>WBC Count</th>
<th>Renal Dysfunction</th>
<th>Microorganisms Isolated**</th>
<th>Site of Isolation</th>
<th>Course, days</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>M</td>
<td>4</td>
<td>37.0°C</td>
<td>M/Lobar (5)</td>
<td>Yes</td>
<td>Yes</td>
<td>2.1</td>
<td>Yes</td>
<td>Klebsiella pneumoniae</td>
<td>Blood</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>M</td>
<td>&gt;30</td>
<td>38.5°C</td>
<td>M/Lobar (2)</td>
<td>Yes</td>
<td>Yes</td>
<td>10.0</td>
<td>Yes</td>
<td>NIL</td>
<td>NIL</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>M</td>
<td>&lt;2</td>
<td>37.5°C</td>
<td>U/Lobar (1)</td>
<td>Yes</td>
<td>Yes</td>
<td>11.5</td>
<td>Yes</td>
<td>NIL</td>
<td>NIL</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>M</td>
<td>4</td>
<td>39.0°C</td>
<td>M/Lobar (2)</td>
<td>Yes</td>
<td>Yes</td>
<td>9.7</td>
<td>Yes</td>
<td>NIL</td>
<td>NIL</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>M</td>
<td>Uncertain</td>
<td>37.0°C</td>
<td>M/Lobar (2)</td>
<td>Yes</td>
<td>Yes</td>
<td>11.8</td>
<td>Yes</td>
<td>NIL</td>
<td>NIL</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>M</td>
<td>1</td>
<td>40.0°C</td>
<td>M/Lobar (2)</td>
<td>No</td>
<td>No</td>
<td>8.9</td>
<td>No</td>
<td>Staphylococcus aureus</td>
<td>Sputum</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>M</td>
<td>2</td>
<td>38.8°C</td>
<td>U/Lobar (1)</td>
<td>No</td>
<td>Yes</td>
<td>15.9</td>
<td>No</td>
<td>NIL</td>
<td>NIL</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>38</td>
<td>F</td>
<td>3</td>
<td>37.5°C</td>
<td>M/Lobar (5)</td>
<td>Yes</td>
<td>Yes</td>
<td>20.6</td>
<td>No</td>
<td>NIL</td>
<td>NIL</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>M</td>
<td>30</td>
<td>39.7°C</td>
<td>M/Lobar (5)</td>
<td>Yes</td>
<td>Yes</td>
<td>4.3</td>
<td>Yes</td>
<td>Streptococcus pneumoniae</td>
<td>Blood</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>45</td>
<td>M</td>
<td>3</td>
<td>38.8°C</td>
<td>U/Lobar (1)</td>
<td>Yes</td>
<td>Yes</td>
<td>0.8</td>
<td>Yes</td>
<td>K pneumoniae</td>
<td>Sputum</td>
<td>7</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>F</td>
<td>Uncertain</td>
<td>37.5°C</td>
<td>M/Lobar (5)</td>
<td>Yes</td>
<td>Yes</td>
<td>14.9</td>
<td>Yes</td>
<td>S pneumoniae</td>
<td>Blood</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>F</td>
<td>3</td>
<td>39.4°C</td>
<td>U/Lobar (1)</td>
<td>Yes</td>
<td>Yes</td>
<td>10.2</td>
<td>Yes</td>
<td>Strep Viridans</td>
<td>Blood</td>
<td>4</td>
</tr>
</tbody>
</table>

*Tmax=maximum temperature during the past 24 h.

1M=multi; U=uni.

1V=ventilation; I=ionotropes; D=dialysis.

1Initial WBC count ×10⁹/L.

1Renal dysfunction as defined as a urea >7 mmol/L+an elevated creatinine level.

1L=lived; D=died.

**NIL=no organisms isolated from any site.
**Nil**-no

**PN**-pyelonephritis; **PID**-pelvic inflammatory disease.

Four groups of patients were studied: survivors in the ICU group alone, nonsurvivors in the ICU group alone, survivors in the NONICUP group, and nonsurvivors in the NONICUP group. The four groups were compared using the Student's t test for continuous variables and Fisher's exact (two-tailed) test for categorical variables. The latter tests were used to compare the ICUP and NONICUP groups with respect to all parameters. Thereafter, all groups of patients were studied in a multivariate one-way analysis of variance using the following parameter vector: plasma IL-1β, IL-6, TNF-α, systolic blood pressure, diastolic blood pressure, plasma urea, creatinine, and temperature. The significance of individual parameters was then assessed by means of univariate one-way analysis and pairwise comparisons at the Bonferroni adjusted level of significance. The possible association of the individual cytokines and clinical and laboratory features of fever, systolic and diastolic pressure, and urea and creatinine values were studied using the linear regression curve and correlation coefficient. The possible association between the plasma levels of IL-1β and TNF-α and IL-6 were studied using linear regression equation and correlation coefficient. The association between severity of disease (APACHE II scores) and the individual cytokines was assessed by means of the linear regression equation and correlation coefficient. To determine any relationship between cytokine levels and mortality, plasma concentrations of IL-1β, IL-6, and TNF-α were compared in survivors and nonsurvivors first, in the ICU group alone, second, among all the patients with pneumonia, and last, for the entire group of patients, using the Student's t test.

**RESULTS**

A total of 40 patients in the four groups were studied. The clinical diagnosis, data, and outcome of the four groups of patients are presented in Tables 1 to 4. Table 5 shows the initial data with significant differences between the ICUP and NONICUP groups. In addition to a significant difference in APACHE II scores (17±3 compared with 4.4±1, respectively; p=0.002), confirming the greater severity of illness, a higher age (p=0.001); greater degree of tachycardia (p=0.013); lower WBC count (p=0.045), platelet count (p=0.035), and serum albumin level (p=0.027); and higher urea (p=0.028) and creatinine (p=0.011) values characterized the ICUP group.

The APACHE II score for the POSTOP group also

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**Table 3—Clinical and Laboratory Data of Patients With Infections Other Than Pneumonia and not Requiring Admission to an ICU**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Tmax*</th>
<th>Diagnosis†</th>
<th>WBC¹</th>
<th>Renal Dysfunction‡</th>
<th>Microorganisms Isolated**</th>
<th>Source</th>
<th>Course, Days§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>F</td>
<td>38.6°C</td>
<td>PN</td>
<td>9.9</td>
<td>No</td>
<td><em>Escherichia coli</em></td>
<td>Urine</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>F</td>
<td>39.0°C</td>
<td>PN</td>
<td>10.0</td>
<td>No</td>
<td><em>E coli</em></td>
<td>Urine</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>F</td>
<td>40.0°C</td>
<td>PN</td>
<td>10.2</td>
<td>No</td>
<td><em>E coli</em></td>
<td>Urine</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>M</td>
<td>36.8°C</td>
<td>PN</td>
<td>4.9</td>
<td>No</td>
<td><em>E coli</em></td>
<td>Urine</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>F</td>
<td>38.0°C</td>
<td>PID</td>
<td>9.5</td>
<td>No</td>
<td>NIL</td>
<td>NIL</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>F</td>
<td>38.0°C</td>
<td>PID</td>
<td>11.5</td>
<td>No</td>
<td>NIL</td>
<td>NIL</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>19</td>
<td>M</td>
<td>40.0°C</td>
<td>Typhoid fever</td>
<td>4.7</td>
<td>No</td>
<td><em>Salmonella typhi</em></td>
<td>Blood</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>F</td>
<td>38.0°C</td>
<td>PN</td>
<td>20.4</td>
<td>No</td>
<td><em>Streptococcus pyogenes</em></td>
<td>Blood</td>
<td>28</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>F</td>
<td>38.0°C</td>
<td>PN</td>
<td>17.0</td>
<td>No</td>
<td><em>E coli</em></td>
<td>Blood</td>
<td>5</td>
</tr>
</tbody>
</table>

* Tmax=maximum temperature in the first 24 h.
† PN=pyelonephritis; PID=pelvic inflammatory disease.
‡ Initial WBC count×10⁹/L.
§ Renal dysfunction defined as urea >7 mmol/L + elevated creatinine level.
|| All patients survived duration of hospitalization.
** NIL=no organisms isolated from any site.
was significantly higher than in the NONICUP group (10 ± 1 vs. 4.4 ± 1, respectively; p < 0.004) but was not significantly different from the ICUP group.

The microbiologic data are shown in Tables 1 to 3. No single organism predominated in the ICUP group, and blood cultures were negative in 50% of cases. In the NONICUP group, all had negative blood cultures. In five patients, Gram-positive diploccoci thought to be Streptococcus pneumoniae were detected on sputum Gram's stain, but subsequent cultures were negative. Escherichia coli was the predominant organism isolated from urine or blood culture in the NONP group (56%).

The plasma concentrations of the individual cytokines are shown in Tables 5 and 6. Table 5 shows the initial comparison of cytokine levels between the ICUP and NONICUP groups. The plasma concentrations for IL-1β and IL-6 were not significantly different, although the values for TNF-α were significantly higher in the ICUP group of patients in comparison with the NONICUP patients (61 ± 17.5 vs. 9.5 ± 1.5 pg/mL, respectively; p < 0.029).

With respect to the parameter vector, multivariate analysis using all four patient groups showed significant differences between these groups (p < 0.003), in particular with respect to levels of IL-1β (p < 0.016), TNF-α (p < 0.017), urea (p < 0.014), and creatinine (p < 0.0002). Differences in IL-6 concentrations did not reach statistical significance between the groups at the 5% level (p = 0.056). Significant differences in cytokine concentrations in the case of IL-1β were between the ICUP and POSTOP groups (Table 6; p < 0.05), and in the case of TNF-α between the ICUP and NONICUP groups (Table 6; p < 0.05). The IL-1β, IL-6, and TNF-α plasma concentrations were significantly different in the ICUP vs the normal control group at the following levels of significance, respectively: p < 0.001, p < 0.05, and p < 0.01. With regard to IL-1β concentrations, the highest concentrations were found in the ICUP group (659 ± 67.5 pg/mL) and the lowest levels in the POSTOP group (443 ± 18.5 pg/mL).

### Table 4—Clinical and Laboratory Data of Noninfected Postsurgical Patients Admitted to an ICU

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Tmax*</th>
<th>Diagnosis</th>
<th>Surgical Procedure</th>
<th>Treatment</th>
<th>Course, Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>M</td>
<td>37.0°C</td>
<td>Carcinoma of the esophagus</td>
<td>Esophagectomy</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>M</td>
<td>38.0°C</td>
<td>Obstructive jaundice</td>
<td>Choledochoduodenectomy</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>F</td>
<td>36.6°C</td>
<td>Spinal fracture</td>
<td>Spinal fusion</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>M</td>
<td>36.6°C</td>
<td>Stabbed chest</td>
<td>Thoracotomy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>M</td>
<td>37.5°C</td>
<td>Carcinoma of the esophagus</td>
<td>Esophagectomy</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>M</td>
<td>38.4°C</td>
<td>Multiple fractures and abdominal injury</td>
<td>Laparotomy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>F</td>
<td>37.8°C</td>
<td>Carcinoma of the esophagus</td>
<td>Esophagectomy</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>36</td>
<td>F</td>
<td>37.0°C</td>
<td>Multiple fractures and abdominal injury</td>
<td>Laparotomy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>M</td>
<td>38.0°C</td>
<td>Carcinoma of the esophagus</td>
<td>Esophagectomy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>F</td>
<td>38.4°C</td>
<td>Carcinoma of the larynx</td>
<td>Laryngectomy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>M</td>
<td>38.4°C</td>
<td>Gunshot abdomen</td>
<td>Laparotomy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Tmax = maximum temperature during the first 24 h.
1 V = ventilation; I = ionotropes.
2 All patients survived duration of hospitalization.

### Table 5—Clinical and Laboratory Data Showing Significant Differences Between Patients With Community-Acquired Pneumonia Admitted and Not Admitted to an ICU*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ICU</th>
<th>NON-ICU</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II</td>
<td>17 ± 3.0</td>
<td>4.4 ± 1.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Age, yr</td>
<td>44.5 ± 2.2</td>
<td>32.2 ± 2.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Pulse rate, BPM</td>
<td>124 ± 5.4</td>
<td>100 ± 6.5</td>
<td>0.013</td>
</tr>
<tr>
<td>WBC count, X10⁶/L</td>
<td>9.9 ± 1.6</td>
<td>16.4 ± 2.9</td>
<td>0.045</td>
</tr>
<tr>
<td>Platelet count, X10⁶/L</td>
<td>149 ± 51</td>
<td>312 ± 79</td>
<td>0.035</td>
</tr>
<tr>
<td>Urea level, mmol/L</td>
<td>13.5 ± 5.3</td>
<td>5.1 ± 0.8</td>
<td>0.028</td>
</tr>
<tr>
<td>Creatinine level, μmol/L</td>
<td>197 ± 28</td>
<td>95 ± 14</td>
<td>0.011</td>
</tr>
<tr>
<td>Alburnin value, g/L</td>
<td>33 ± 5</td>
<td>42 ± 1.5</td>
<td>0.027</td>
</tr>
<tr>
<td>IL-1β, pg/mL</td>
<td>659 ± 67.5*</td>
<td>496 ± 34.3*</td>
<td>0.014*</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>1,733 ± 447.7</td>
<td>855 ± 423.9</td>
<td>0.007*</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>61 ± 17.5</td>
<td>9.5 ± 1.5*</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

*Results presented as mean ± SEM.
1 NS = not significant.

### Table 6—Plasma Concentrations of the Cytokines IL-1β, IL-6, and TNF-α in the Four Study Groups

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>ICU</th>
<th>NON-ICU</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>659 ± 67.5</td>
<td>500 ± 35.5</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-6</td>
<td>1,773 ± 447.7</td>
<td>855 ± 423.9</td>
<td>0.007*</td>
</tr>
<tr>
<td>TNF-α</td>
<td>61 ± 17.5</td>
<td>27 ± 6.7</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*(p < 0.05 of ICUP).
mL). The two groups of patients with intermediate severity of infection had intermediate concentrations of IL-1β as shown in Table 6. There were no significant differences in the IL-6 concentrations between the groups on multivariate analysis. In particular, there was no significant difference between the ICUP and POSTOP groups, the two groups with the highest APACHE II scores, which were found to have the highest values of IL-6 among all the groups (1.773 ± 447.7 and 1.676 ± 502.8 pg/mL, respectively; Table 6). The TNF-α concentrations tended to mimic those of the IL-1β group. However, while the highest concentration was found in the ICUP group (61 ± 17.5 pg/mL), the lowest level was in the NONICUP group (9.5 ± 1.5 pg/mL), this difference being significant (Table 6; p<0.05). The urea concentration was found to be significantly higher in the ICUP group than the POSTOP group (p<0.05). Creatinine concentrations were confirmed to be significantly higher in the ICUP group when compared with any of the other groups of patients, vs NONICUP—p<0.01, and vs NONP and POSTOP—p<0.001, respectively.

The only association between the individual cytokines and parameters of fever, systolic and diastolic pressure, urea and creatinine levels was between IL-1β and temperature (r=0.4, p<0.05). There was a significant association between plasma IL-6 and TNF-α concentrations and between IL-1β and TNF-α (p<0.05 in both cases) for both pneumonia groups and for all groups (p<0.05 and p<0.005, respectively) as determined by the linear regression equation and correlation coefficient. However, the correlation was poor as reflected by the very low coefficients of determination. There was a significant association between the APACHE II scores of all patients and the individual cytokines. The weakest association was with IL-1β (r=0.392; p<0.03) and the strongest association was with IL-6 (r=0.554; p<0.0012) and TNF-α (r=0.626; p<0.0002; Fig 1).

Five patients in the ICUP group died. However, there was no association noted between the individual cytokine levels and patient mortality, irrespective of how the data were analyzed.

**DISCUSSION**

The present study determined the cytokine profile of patients with acute community-acquired pneumonia, ICUP with NONICUP. The primary aim was to determine the specific pattern of cytokines in the ICUP group. Such knowledge may lead to rational approaches to the manipulation of cytokine levels in severely ill patients with pneumonia in an attempt to decrease the ongoing high mortality in such cases. A single measurement of the plasma cytokines on admission to the hospital, before therapy, was chosen to determine the cytokine profile. Although this represents a measurement at only one point, it is acknowledged that there is chronicity of expression of cytokines in patients, which differs from the estab-
lished experimental models where there is the rapid appearance and disappearance of the cytokines.\textsuperscript{23} The duration of illness, where this could be determined, varied and this factor could influence cytokine patterns. Limited evidence indicates that the expression of at least TNF-\(\alpha\) is stable over time in patients with sepsis.\textsuperscript{23}

The APACHE II score was significantly higher in the ICUP vs the NONICUP group (\(p=0.002\)), in keeping with their more severe illness. In addition, a number of other parameters, which previously have been described as negative prognostic factors or factors predicting the need for ICU admission in patients with pneumonia,\textsuperscript{2,3} were noted to be significantly different between the two groups. These included a higher age, greater tachycardia, lower WBC and platelet counts, higher serum urea and creatinine values, and a lower serum albumin level in the more seriously ill patients. Although IL-1\(\beta\) and IL-6 levels were not significantly different between these two groups; TNF-\(\alpha\) levels were significantly higher in the ICUP cases. Multivariate analysis allowed better definition of the possible associations of these cytokine levels in patients with pneumonia.

The IL-1\(\beta\) detection in plasma/serum under conditions of experimental endotoxemia and sepsis is controversial.\textsuperscript{9,24-26} In several studies, it has not been possible to detect significant concentrations of IL-1.\textsuperscript{10,24} Other studies have found elevated concentrations of IL-1\(\beta\) in patients who survived septic shock,\textsuperscript{25} which may suggest a protective role for IL-1\(\beta\). In the present study, we were able to measure elevated IL-1\(\beta\) concentrations in the plasma of our patients. The highest concentrations of IL-1\(\beta\) were found in the ICUP group, and significantly lower levels in the non-septic POSTOP patients (\(p<0.05\)). The two groups of patients with intermediate levels of infection had intermediate levels of this cytokine. Our results suggest that IL-1\(\beta\) concentrations appear to be related to the severity of infection of patients on admission.

The IL-6 has been identified as an important mediator of the synthesis of the acute phase reactants and this cytokine also has a possible role in the mediation of IL-1\(\beta\) and TNF actions.\textsuperscript{14,16,27} An alternative view is that IL-6 is a counter-regulatory/anti-inflammatory cytokine of the proinflammatory cytokines IL-1\(\beta\) and TNF-\(\alpha\). For example, IL-6 is known to downregulate the synthesis of monocyte-produced cytokines.\textsuperscript{12} Several studies have reported the detection of IL-6 in the plasma of patients under conditions of sepsis.\textsuperscript{16,28} In some cases, IL-6 concentrations have appeared to be related to the outcome in patients with sepsis,\textsuperscript{16,29} although this has not always been confirmed.\textsuperscript{29} In the present study, multivariate analysis failed to confirm any significant differences in the IL-6 concentrations among the four groups. In contrast to the IL-1\(\beta\) results, the levels of IL-6 were highest, and almost equal, in the ICUP and noninfected POSTOP groups, the groups with the highest APACHE II scores. The analyses suggest that IL-6 may be more closely associated with the severity of illness and that raised plasma levels may more accurately relate to severity of stress, whether of an infective or noninfective nature rather than severity of infection per se.

The TNF-\(\alpha\) has been identified as an important mediator of septic shock in both experimental models and in patients.\textsuperscript{6,10,24,25,30-33} The effects of TNF-\(\alpha\) in septic shock are thought to be mediated through the action of TNF-\(\alpha\) on endothelial cells, the myocardium, and through paracrine and autocrine loops.\textsuperscript{34,35} Studies have suggested that there may be synergy between TNF-\(\alpha\) and IL-1\(\beta\) in the induction of shock.\textsuperscript{17} In some reports, the concentrations of TNF-\(\alpha\) have been found to be related to the degree of sepsis.\textsuperscript{25,29,31} In our study, the levels of TNF-\(\alpha\), like that of the other cytokines, were highest in the ICUP group. The pattern of TNF-\(\alpha\) expression among the groups was similar to that found with IL-1\(\beta\), the only difference being that TNF-\(\alpha\) concentrations were significantly lower in the NONICUP group. It is tempting to suggest, therefore, that differences in TNF-\(\alpha\) levels in our study reflect differences in the severity of pneumonia in our patients. However, it should be borne in mind that there were a number of significant differences noted between the ICUP and NONICUP groups as shown in Table 1, which in themselves may have accounted for differences noted in the TNF-\(\alpha\) levels.

An additional finding from the multivariate analysis was the significantly higher concentration of urea in the ICUP group compared with the POSTOP group and of creatinine in the ICUP group compared with any of the other groups. This almost certainly reflects the importance of renal dysfunction as an indicator of poorer prognosis or need for ICU admission in patients with pneumonia, factors that have been regularly described before.\textsuperscript{1-3} Using the correlation coefficient, we found that the only association between the individual cytokines and the various clinical and laboratory features was with IL-1\(\beta\) and temperature (\(p<0.05\)).

Our study suggests that measurement of plasma levels of cytokines IL-1\(\beta\), IL-6, and TNF in patients with pneumonia may reflect various clinical scenarios; IL-1\(\beta\) may reflect severity of infection; IL-6, severity of illness (whether of an infective or noninfective nature); and TNF-\(\alpha\) concentrations, the severity of pneumonia. A weak correlation was found between the concentrations of IL-1\(\beta\) and TNF-\(\alpha\), which does not necessarily exclude the possibility of additive or synergistic interactions between the two
cytokines as previously described. Although the individual data are not shown, we were unable to show any association between cytokine concentrations and outcome. This is almost certainly due to the relatively small number of patients studied. In addition, although TNF-α appeared to correlate with the severity of pneumonia, it did not correlate with outcome. Previous studies showing a correlation of TNF-α with outcome were in cases with serum concentrations greater than 140 pg/mL, concentrations much higher than reported in the present study. The APACHE II scores of all patients studied were associated with the concentrations of the individual cytokines; the strongest association was with TNF-α stressing the possible centrality of the cytokine under various conditions of stress. Our study and another recently reported study are one of the few that have attempted to profile cytokine expression in various clinical scenarios. The present results and those from the reported study emphasize that different cytokine patterns are possible despite the differences in clinical pathologic findings and insignificant differences in severity as assessed by the APACHE II scores. The reported study shows an association between IL-1β, IL-6, and TNF-α under conditions of infection in comparison to patients without infection but with equivalent APACHE II scores. By contrast, our control group (POSTOP) had indistinguishable plasma IL-6 concentrations from the ICU pneumonia group but was distinct from the latter group when comparing IL-1β and TNF-α concentrations.

The current study, like that of others, does not allow the elucidation of whether greater elevations of cytokine levels occurred in some patients as a consequence of more severe illness or infection, or whether they actually contributed to the degree of illness. However, it is possible that in the future, measurement of absolute levels of cytokines may be of use in identifying more seriously ill patients, and cases likely to die, who could be singled out for more intensive therapy at an earlier phase of illness. In addition, manipulation of cytokine levels by reduction of cytokine production, or the use of agents inhibiting end-organ sites of action, such as the recently described IL-1β receptor antagonist, may be found to have additional benefit in infections such as pneumonia, a disease that continues to have significant morbidity and mortality.

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