Conditions Associated with Leukocytosis in a Tertiary Care Hospital, with Particular Attention to the Role of Infection Caused by Clostridium difficile

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Few modern studies have enumerated the conditions associated with leukocytosis. Our clinical experience has implicated Clostridium difficile infection in a substantial proportion of patients with leukocytosis. In a prospective, observational study of 400 inpatients with WBC counts of ≥15,000 cells/mm³, we documented ≥1 infection in 207 patients (53%). Of these 207 patients, 97 (47%) had pneumonia, 60 (29%) had urinary tract infection, 34 (16%) had soft-tissue infection, and 34 (16%) had C. difficile infection. C. difficile infection was present in 25% of patients with WBC counts of >30,000 cells/mm³ who did not have hematological malignancy. Other causes of leukocytosis in the 400 patients included physiological stress, in 152 patients (38%); medications or drugs, in 42 (11%); hematological disease, in 22 (6%); and necrosis or inflammation, in 22 (6%). C. difficile infection is a prominent cause of leukocytosis and this diagnosis should be considered for patients with WBC counts of ≥15,000 cells/mm³, even in the absence of diarrheal symptoms.

The WBC count is one of the most widely used laboratory tests; at Texas Medical Center alone, >1,000,000 such determinations are done each year (authors’ unpublished observation). One might imagine that there have continued to be articles in the modern era to help clinicians evaluate the finding of an elevated WBC count. However, although the National Library of Medicine cites 7600 articles on the general subject of leukocytosis published since 1965, and Index Medicus lists hundreds of articles published between 1955 and 1964, only a small number have dealt with the specific causes of this condition [1–11], and even fewer have actually enumerated them [3, 6, 8, 9, 11].

Clostridium difficile is a well-recognized etiologic agent of nosocomial infection that causes diarrhea, fever, and inflammation of the colonic mucosa with pseudomembrane formation [12–14]. Recent studies have emphasized the importance of leukocytosis as a manifestation of C. difficile infection [13–16], but the frequency with which this agent contributes to leukocytosis in hospital-based practice has not been reported.

We believed that it would be useful for clinicians to have data on the medical conditions associated with leukocytosis, especially in light of modern diagnostic techniques and therapeutic modalities. As we became more interested in the clinical factors associated with leukocytosis, our clinical experience suggested that a substantial proportion of patients, especially those with WBC counts of ≥30,000 cells/mm³, have C. difficile infection. Accordingly, at our tertiary care hospital, we...
undertook a prospective, observational study of inpatients and outpatients with WBC counts of >15,000 cells/mm³, with a dual purpose: (1) to determine conditions associated with leukocytosis, and (2) to define the role of infection caused by *C. difficile*.

**PATIENTS AND METHODS**

**Clinical setting.** The Houston Veterans Affairs Medical Center is a large, tertiary care medical center with 520 active beds that provides primary medical care for ∼55,000 adults. There were an average of 1920 admissions and 56,652 outpatient clinic and urgent care visits per month during the time of the study. The complete medical record for every case patient is available electronically, including all progress, consultation, and discharge notes and all results of laboratory, radiographic, and pathologic studies, as these results are obtained.

**Identification of patients with leukocytosis.** In a prospective observational study that began on 1 January 2001, we reviewed laboratory records each day to identify patients with WBC counts of ≥15,000 cells/mm³. Each patient was included only once and was stratified on the basis of the highest WBC count recorded. As patients were identified, an investigator studied the complete medical record of each, with attention paid to the date of admission; any and all condition(s) that might cause fever and/or leukocytosis; findings of physical examination, laboratory tests, and imaging studies; daily progress notes; diagnoses by the primary care team; and opinions of consultants. Medical records were reviewed again every few days until the patient was discharged from the hospital. Patients were assigned diagnoses on the basis of all available information in the medical record through the time of discharge (and after, if results of essential studies were outstanding).

We originally intended to study 200 inpatients with WBC counts of 15,000–19,999 cells/mm³ and 200 with WBC counts of ≥20,000 cells/mm³. Once the study had begun, we discovered that approximately one-third of patients with WBC counts of ≥15,000 cells/mm³ at our hospital were outpatients, and we decided to collect data from these individuals as well but to tabulate the results separately. We examined their medical records for the period preceding the relevant clinic visit and at the time of the visit and the records of other outpatient visits and/or hospital admissions for the subsequent 4 months. The study protocol was approved by the Institutional Review Board, Baylor College of Medicine (Houston).

**Classification of potential causes of leukocytosis.** Patients were assigned to ≥1 of 6 groups corresponding to potential causes of leukocytosis, which were categorized according to the general classification of Holland and Gallin [17] (however, in reporting results, we changed the order of the categories of causes to reflect the actual frequency with which they were implicated). These causes were as follows: (1) infection, (2) physiological stress, (3) medications or drugs (including illicit drugs), (4) disease of the hematopoietic system, (5) necrosis or inflammation, and (6) unknown. The greatest care was used in categorizing patients. For example, patients with acute myocardial infarction were assigned to category 5 (necrosis/inflammation), whereas those with unstable angina were assigned to category 2 (physiological stress). Patients with acute pancreatitis (with or without a pseudocyst) were included in category 5, unless infection was also thought to be present, in which case the patient was listed in both categories 1 and 5. Multiple potential causes were recorded, when present; however, because 400 patients were inpatients, we did not include hospitalization itself as a form of physiological stress, even though it may well be one.

**Laboratory tests for *C. difficile* infection.** Fecal samples were analyzed for *C. difficile* toxin by use of Premier A (Meridian Diagnostics), an EIA that detects toxin A. Fecal samples were refrigerated at 8°C overnight or at −80°C over the weekend; assays were performed 3 times weekly. The US Food and Drug Administration has approved an EIA kit for detection of *C. difficile* toxins A and B (Premier Toxins A and B; Meridian Diagnostics), but that kit was unavailable from the manufacturer for use in the United States throughout the time of our study.

**Statistical analysis.** The χ² test was used to compare the prevalence of conditions for various groups of subjects. To determine whether there was a difference in the mean values between 3 groups, we used analysis of variance [18]. P values ≤.05 were considered significant.

**RESULTS**

**Hospitalized patients.** In accord with our intention, we accrued 200 patients with WBC counts of 15,000–19,999 cells/mm³ and 200 with WBC counts of ≥20,000 cells/mm³. For the purpose of presenting our results, we stratified patients on the basis of WBC counts of 15,000–19,999 cells/mm³, 20,000–29,999 cells/mm³, and ≥30,000 cells/mm³ (table 1). Because multiple factors that might cause leukocytosis were present, the total number of conditions exceeds the number of patients. Overall, the majority of patients (207 [52%]) had ≥1 infections. Physiological stress was next-most common causal factor; it was identified in 152 patients (38%). Medications or drugs were implicated in 42 patients (11%), and hematological disease and necrosis or inflammation were each found in 22 patients (6%). Leukocytosis of unknown cause was present in only 16 (4%) of all 400 patients; for most of these patients, acute leukocytosis developed in the hospital, the patient died without a diagnosis, and no autopsy was
performed; it is likely that most of these patients had infections.

**Infection.** Among inpatients with WBC counts of \(\geq 15,000\) cells/mm\(^3\), infection was the most frequently implicated cause of leukocytosis (range, 48%–60% of patients; table 1). The percentage of patients with infection increased slightly but not significantly \( (P = .23)\) with the degree of leukocytosis. As shown in table 2, nearly all of these patients had acute infection attributable to bacterial disease, including 97 patients with pneumonia (47% of all patients), 60 (29%) with urinary tract infection, 34 (16%) with soft-tissue infection, 17 (8%) with intra-abdominal infection, 9 (4%) with vascular infection, and 7 (3%) with osteomyelitis. The highest proportion of patients with WBC counts of \(\geq 30,000\) cells/mm\(^3\) were in the intravascular infection group (5 [56%] of 9 patients), and the lowest proportion was in the osteomyelitis group (0 [0%] of 7).

**C. difficile colitis.** A novel finding of this study was the importance of *C. difficile* colitis as a cause of leukocytosis, as demonstrated by documentation of the presence of *C. difficile* toxin A in the feces of 34 patients (9%) (table 2). On the basis of this unexpected finding, which required that the diagnosis be considered and an appropriate sample be sent for analysis, we undertook a more intensive study to determine whether additional patients might have clinical features suggesting this diagnosis. To do so, we reviewed the entire computerized record (which was available for the previous 4.5 years) for results of other studies for *C. difficile* toxin; for the admitting intern’s note; for the pharmacy record (also stored in the computer system) of antibiotics prescribed in the preceding 6 weeks; and for all recorded notes (especially those of the nurses) with any mention of diarrhea.

Forty-two patients with leukocytosis had a clinical picture consistent with *C. difficile* colitis, including all of the following features: a history of having received antibiotic(s) in the preceding 6 weeks; fever, leukocytosis, and diarrhea; or another major manifestation of colitis, such as ileus, severe abdominal pain, or toxic megacolon. These 42 patients were stratified to 1 of 5 subcategories according to EIA test status and/or other clinical findings; these subcategories are listed in table 3 in decreasing order of likelihood that *C. difficile* infection was present. For 4 patients, EIA for *C. difficile* toxin A yielded a borderline (“indeterminate”) result. Seven patients either had no test done or had an EIA result negative for *C. difficile* toxin at the time leukocytosis was detected (for 4 patients, this test was only done once), but review of the medical record revealed *C. difficile* infection(s) in the past that had been documented by EIA. Eleven patients were treated with metronidazole in the absence of a positive diagnostic test result and responded well. The remaining 20 patients either had no study done (5 patients) or had \(\geq 1\) EIA negative for *C. difficile* toxin (15 patients). Thus, of 400 patients with WBC counts of \(\geq 15,000\) cells/mm\(^3\), 76 (19%) had a clinical picture consistent with *C. difficile* infection, 56 (14%) had such a clinical picture with some laboratory or clinical support, and 34 (9%) had confirmed infection. The proportion of patients who had a clinical syndrome consistent with *C. difficile* colitis or who had proven *C. difficile* colitis increased significantly as the WBC count increased \( (P < .01)\). When individuals with leukemia were excluded from analysis, 25% of all patients with WBC counts of \(\geq 30,000\) cells/mm\(^3\) had proven *C. difficile* infection (figure 1).

**Physiological stress.** Acute physiological stress was present in 152 (38%) of 400 patients, including the following conditions: surgery with general anesthesia (in 57 [41%] of the 152 patients), acute respiratory distress syndrome (ARDS) (in 40 patients [29%]), hypovolemia due to hemorrhage or dehydration (in 34 patients [25%]), and diabetic ketoacidosis (in 8 patients [6%]). Physiological stress was generally more likely to be associated with an elevated WBC count of 15,000–19,999 cells/mm\(^3\) than with a count of \(\geq 30,000\) cells/mm\(^3\) \( (P = .04)\); for example, hemorrhage was associated with WBC counts of

<table>
<thead>
<tr>
<th>Causal factor</th>
<th>Stratum, by WBC count, cells/mm(^3)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15,000–19,999 ( (n = 200))</td>
<td>20,000–29,999 ( (n = 147))</td>
</tr>
<tr>
<td>Infection</td>
<td>96 (48)</td>
<td>79 (54)</td>
</tr>
<tr>
<td>Physiological stress</td>
<td>87 (44)</td>
<td>54 (37)</td>
</tr>
<tr>
<td>Medications or drugs</td>
<td>26 (13)</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Hematological condition</td>
<td>5 (3)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Necrosis or inflammation</td>
<td>10 (5)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Total</td>
<td>226 (113)</td>
<td>173 (118)</td>
</tr>
</tbody>
</table>

**NOTE.** The total number and percentage in each column may exceed the \(n\) value and 100%, respectively, because \(\geq 1\) factor was present in some patients.
15,000–19,999 cells/mm³ in 9 patients, 20,000–29,999 cells/mm³ in 3 patients, and ≥30,000 cells/mm³ in 0 patients. ARDS was significantly more likely to be associated with WBC counts of ≥30,000 cells/mm³ (P < .01) than with lower levels of leukocytosis, but many of the patients with ARDS were thought to have concurrent infection. In patients who had leukocytosis associated with physiological stress, when other factors were not also present, the leukocytosis promptly resolved after the stress was ended.

**Medications or drugs.** The great majority of patients (37 [88%] of 42) for whom medications or drugs were implicated as a cause of elevated WBC counts were receiving prednisone (≥40 mg/day) or its equivalent. This medication appeared to be more commonly responsible for WBC counts of 15,000–19,999 cells/mm³, whereas other drugs were implicated in patients with various levels of leukocytosis: granulocyte colony-stimulating factor (G-CSF; 2 patients), cocaine (2 patients), and lithium (1 patient). In no patients were medications or drugs solely responsible for WBC counts of ≥30,000 cells/mm³.

**Hematological condition.** The proportion of patients with an associated hematological condition increased with the WBC count (P < .01). Overall, 22 patients had a malignancy that involved the hematopoietic system: 15 patients had leukemia, 2 had lymphoma, and 3 had widespread metastatic cancer that involved the bone marrow. Two patients had stable elevations in WBC counts resulting from prior splenectomy.

**Necrosis or inflammation.** In 22 patients, necrosis or inflammation was associated with leukocytosis. This group included 7 patients with myocardial infarction (patients who had unstable angina were assigned to the category “physiological stress”), 3 with pulmonary infarction, 2 with pancreatitis, and 2 with incarcerated umbilical hernia without necrosis. Of these 22 subjects, 4 had WBC counts of ≥30,000 cells/mm³; only 1 patient (who had myocardial infarction) had no associated condition other than necrosis or inflammation.

**Unknown.** The majority of patients for whom no cause for leukocytosis was determined were in extremis and died shortly after the high WBC count was documented. Infection was probably responsible in most instances, but its presence was not documented, and autopsies were not performed.

**Outpatients.** A total of 133 outpatients were found to have WBC counts of ≥15,000 cells/mm³. Because the total numbers were smaller, these patients were stratified into 2 categories: those with WBC counts of 15,000–19,999 cells/mm³ (n = 74) and those with WBC counts of ≥20,000 cells/mm³ (n = 59) (table 4). As might have been predicted, infection was implicated as a cause of leukocytosis in a smaller proportion of outpatients than inpatients (24 [18%] of 133 vs. 207 [52%] of 400; P < .001). Only 1 (1%) of 133 outpatients was proven to have *Clostridium difficile* colitis, compared with 34 (9%) of 400 hospitalized patients (P < .001). In contrast, 60 (45%) of 133 outpatients had a hematological condition (vs. 22 [11%] of 400 inpatients; P < .001). Three patients had WBC counts of ≥20,000 cells/mm³ that were attributable to medications; 2 were receiving G-CSF, and the other was receiving risperidone.
proportion of outpatients with no identified cause for leukocytosis (33 [25%] of 133 patients) was much greater than the proportion of inpatients (16 [4%] of 200; \( P < .01 \)).

**Presence of band forms.** Among inpatients with infection, \( \geq 3\% \) band forms (a “left shift”) were detected in 20% of patients with WBC counts of 15,000–19,999 cells/mm\(^3\), 37\% of patients with counts of 20,000–29,999 cells/mm\(^3\), and 53\% of patients with counts of \( \geq 30,000 \) cells/mm\(^3\); the proportion of infected patients with a left shift was significantly greater for higher WBC counts (\( P = .01 \)), although the mean percentage of bands was not necessarily greater for patients with higher WBC counts (7.0\% for patients with WBC counts of 15,000–19,999 cells/mm\(^3\) vs. 9.3\% for patients with WBC counts of \( \geq 30,000 \) cells/mm\(^3\); \( P = .45 \)). An elevated percentage of band forms (\( \geq 3\% \)) was also observed in 12\% of patients with physiological stress, 19\% of patients with medication- or drug-associated leukocytosis, and 5\% of patients with necrosis or inflammation. Band form percentages of \( \geq 12\% \) were seen exclusively in patients with infection (19 patients) and those receiving G-CSF (2 patients).

**DISCUSSION**

At its inception, our study had 2 related goals: (1) to elucidate causes of leukocytosis in hospitalized patients and (2) to determine the role of *C. difficile* infection as a contributing cause of leukocytosis. The justification for the first goal was clear. Although the complete blood count is the most commonly ordered laboratory test, and nearly every textbook has a table showing the causes of leukocytosis, there is a remarkable paucity of studies that have actually tabulated factors associated with elevated WBC counts. The justification for the second goal was our clinical experience, which had suggested that a substantial proportion of patients with leukocytosis, especially those without a clearly recognized cause and with very high WBC counts, are likely to have *C. difficile* infection.

Leukocytosis is well described in many specific infectious states—for example, appendicitis [4, 19], cellulitis [20], and pneumonia [21]. Elevated WBC counts have also been reported in noninfectious conditions such as myocardial infarction [22–24], acute pulmonary embolism [25], alcoholic hepatitis

**Table 3. Subcategories of patients with a clinical picture consistent with *Clostridium difficile* infection, according to results of EIA for *C. difficile* toxin A.**

<table>
<thead>
<tr>
<th>EIA result, other clinical finding</th>
<th>Stratum, by WBC count, cells/mm(^3)</th>
<th>Total (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15,000–19,999 (n = 32)</td>
<td>20,000–29,999 (n = 27)</td>
</tr>
<tr>
<td>Positive</td>
<td>11 (34)</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>0 (0)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Negative or test not done</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With positive result in past</td>
<td>3 (9)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>With response to medication</td>
<td>5 (16)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Test not done</td>
<td>3 (9)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Negative</td>
<td>10 (31)</td>
<td>4 (15)</td>
</tr>
</tbody>
</table>

**NOTE.** Patients with a clinical picture that suggested *C. difficile* colitis had all of the following clinical features: a history of having received antibiotic(s) within the preceding 6 weeks; fever; leukocytosis; and diarrhea or another major symptoms of colitis, such as ileus, severe abdominal pain, or toxic megacolon.
Documenting an association between *C. difficile* colitis and leukocytosis is not novel. For example, in a retrospective study of 35 patients with proven *C. difficile* infection, Bulusu et al. [15] found that the mean peak WBC count was 15,800 cells/mm³. Seven patients (20%) had WBC of 20,000–30,000 cells/mm³, and 2 (6%) had WBC counts of >30,000 cells/mm³. Other studies have noted leukocytosis (WBC counts of >30,000 cells/mm³) in patients with this condition [34–38]. An important finding of our study, however, is the frequency with which *C. difficile* infection was found among all patients with leukocytosis. Of 400 inpatients with WBC counts of >15,000 cells/mm³, 19% had a clinical picture consistent with *C. difficile* infection; 14% had such a clinical picture with some laboratory support, and 9% had confirmed infection. The proportion of cases attributable to *C. difficile* increased with higher WBC counts, such that nearly one-third of patients with WBC counts of >30,000 cells/mm³ had a consistent clinical picture and 21% had proven *C. difficile* infection. Our results, together with those of a prospective interventional study now in progress (authors’ unpublished data), confirm the observation [15] that an elevated WBC count may precede abdominal discomfort or diarrhea, which suggests that the diagnosis of *C. difficile* infection...
During the time of the present study, we assayed only for C. difficile but no laboratory confirmation of has studies [43, 44]; the package insert, which claims that the assay cases of together, these observations suggest that a single stool sample is to toxin A may miss additional diagnoses [41, 42]. Taken to-
Administration–approved kit that measures levels of toxins A and B was unavailable from the manufacturer; an assay confined to toxin A, in part because that is a generally accepted procedure [14] and in part because the only US Food and Drug Administration–approved kit that measures levels of toxins A and B was unavailable from the manufacturer; an assay confined to toxin A may miss additional diagnoses [41, 42]. Taken to-
Our documentation of C. difficile infection likely underestimates the magnitude of this problem. Manabe et al. [36] showed that 3 EIA tests detected C. difficile infection in 90% of patients who had evidence from tissue culture or EIA for the presence of C. difficile toxin, whereas a study confined to the first stool sample would have yielded the diagnosis for only 72% of patients. Gerding et al. [39] found that 10% of patients who had negative results of toxin assays but who had stool cultures positive for C. difficile had pseudomembranous colitis. False-negative assay results for C. difficile toxin may be due, in part, to the instability of the toxin in stored samples [16, 40].

Our hospital laboratory performs assays for C. difficile toxin only 3 times weekly, storing specimens at 4°C–8°C overnight and at ∼80°C over the weekend; the manufacturers of the EIA kit state that storage should be at 4°C–8°C but that samples should be stored frozen if >72 h will elapse before testing. During the time of the present study, we assayed only for C. difficile toxin A, in part because that is a generally accepted procedure [14] and in part because the only US Food and Drug Administration–approved kit that measures levels of toxins A and B was unavailable from the manufacturer; an assay confined to toxin A may miss additional diagnoses [41, 42]. Taken to-

Table 5. Causal factors associated with leukocytosis in hospitalized pa-

<table>
<thead>
<tr>
<th>Causal factor</th>
<th>Chang et al. [6] (n = 75)</th>
<th>Reding et al. [9] (n = 100)</th>
<th>Present study (n = 400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>27 (38)</td>
<td>48 (48)</td>
<td>224 (56)</td>
</tr>
<tr>
<td>Hematological</td>
<td>20 (28)</td>
<td>15 (15)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Necrosis or inflammation</td>
<td>16 (22)</td>
<td>6 (6)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Physiological stress</td>
<td>46 (64)</td>
<td>17 (17)</td>
<td>152 (38)</td>
</tr>
<tr>
<td>Medication or drugs</td>
<td>16 (22)</td>
<td>12 (12)</td>
<td>42 (11)</td>
</tr>
<tr>
<td>Unknown</td>
<td>—</td>
<td>2 (2)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>141 (196)</td>
<td>100 (100)</td>
<td>478 (120)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless indicated otherwise. The total number and percentage in each column may exceed the n value and 100%, respectively, because >1 factor was present in some patients. The WBC counts used to define leukocytosis in the 3 studies were as follows: in Chang et al. [6] and Reding et al. [9], ≥25,000 cells/mm³, and in the present study, ≥15,000 cells/mm³.

should be considered for all patients with leukocytosis, especially if some other cause is not immediately apparent.

Our documentation of C. difficile infection likely underestimates the magnitude of this problem. Manabe et al. [36] showed that 3 EIA tests detected C. difficile infection in 90% of patients who had evidence from tissue culture or EIA for the presence of C. difficile toxin, whereas a study confined to the first stool sample would have yielded the diagnosis for only 72% of patients. Gerding et al. [39] found that 10% of patients who had negative results of toxin assays but who had stool cultures positive for C. difficile had pseudomembranous colitis. False-negative assay results for C. difficile toxin may be due, in part, to the instability of the toxin in stored samples [16, 40].

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In summary, in the course of an observational study to ex-
amine all causes of leukocytosis in a tertiary care hospital, we discovered a surprisingly great contribution by C. difficile infection, especially among patients with WBC counts of ≥30,000 cells/mm³. Accordingly, we have initiated a prospective inter-

valent study to look at all patients with leukocytosis. Pre-
liminary results suggest that, at our facility, if EIA for C. difficile toxin is done for every hospitalized patient who has leukocytosis without an apparent explanation, ~50% of patients will have a positive assay result (authors’ unpublished observations).

References

13. Manabe YC, Vinetz JM, Moore RD, Merz C, Charache P, Bartlett JG.