Discontinuation of Antimicrobial Therapy for Febrile, Neutropenic Children with Cancer: A Prospective Study

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During a 2-year period, all children with cancer, neutropenia, and fever who were admitted to Hospital de Niños Luis Calvo Mackenna (Santiago, Chile) were enrolled in a study of the safety of stopping antibiotic therapy on day 3 of treatment. Children who met predefined criteria for nonbacterial fever were randomized on day 3 to stop (group A) or continue (group B) antibiotic therapy. A total of 220 children with cancer had 238 episodes of fever and neutropenia; 68 children with 75 episodes met entry criteria for nonbacterial fever (group A, 36; group B, 39). Both groups were comparable in terms of age, gender, oncological disease, chemotherapy status, and initial neutrophil count. Resolution of symptoms occurred in 34 of 36 episodes in group A and 36 of 39 episodes in group B (P > .05). No deaths occurred, and bacterial superinfections were uncommon. For children with cancer as well as episodes of fever and neutropenia without an identifiable bacterial etiology at admission, stopping antibiotic therapy on day 3 was safe and not associated with a higher risk of bacterial superinfections.

In children with cancer, infections represent a major cause of morbidity and mortality. Infections are favored by the impairment of host defense mechanisms induced by the cancer and the use of chemotherapy [1–3]. Neutropenia is an expected side effect of chemotherapy, and the relationship between the severity and duration of neutropenia and infection has been well established [4]. The risk of infection increases significantly when the absolute neutrophil count (ANC) falls to <500/mm³ [5], and infection occurs almost invariably when the ANC decreases to 100/mm³ [6].

The high impact of infections in children with cancer and neutropenia on morbidity and mortality has led to aggressive management of these children when a febrile episode occurs. With the aim of reducing the impact of infections on the prognosis of oncological disease, different strategies have been developed: e.g., prevention of episodes of fever by means of antimicrobial therapy [7]; reduction of the frequency of or shortening the duration of episodes of neutropenia after chemotherapy by using colony-stimulating factors [8]; or better discrimination of which episodes of fever may be occurring with a bacterial infection and thus benefit from antimicrobial treatment [9, 10]. To accomplish the last objective, researchers have studied endotoxins, interleukin 6, tumor necrosis factor, and C-reactive protein (CRP) as markers for bacterial infection [11–13].

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Informed consent was obtained from the patients, and this study was approved by the ethical committee of Hospital de Niños Luis Calvo Mackenna, Santiago, Chile.

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During the past 5 years, we have developed strategies for selective antibiotic management of fever and neutropenia in children with cancer. We have focused on the use of serum CRP as a marker for bacterial infection because it is inexpensive to determine and because we have experience with this laboratory parameter in immunocompetent and immunodeficient children [14–17].

We [17] previously reported that children with leukemia, lymphoma, or solid tumors have baseline serum CRP levels comparable with those in healthy children, variations in CRP levels are sensible and specific markers for bacterial infections in the presence of fever and neutropenia, and serial determinations of CRP levels aid in determining the group of children for whom treatment fails or who have bacterial superinfections during their clinical course. In our experience, etiologic workup of febrile episodes in Chilean children with cancer and neutropenia shows that 30%–35% of patients have demonstrated bacterial infection; 30%–35% have probable, albeit not documented, bacterial infection; 30% have demonstrated viral infection or fever of unknown origin without clinical and laboratory evidence of bacterial and/or viral infections; and 10% have fungal infection (unpublished data, M. E. Santolaya).

According to statistics from Programa Infantil Nacional de Drogas Antineoplásicas, which is supported by the Chilean Ministry of Health, there were >1,500 pediatric patients with cancer in Chile during the past 5 years (1989–1993). This circumstance resulted in an explosive increase in the number of children receiving chemotherapy and consequently an increase in the number of episodes of fever and neutropenia. In Chile, current recommendations for patients with severe neutropenia and fever include hospitalization for intravenous therapy with broad-spectrum antibiotics until the episode of fever and neutropenia resolves [18]. The potential drawbacks
of this policy include overuse of antibiotics, prolonged hospitalization with a psychological burden for the patient and the patient’s family, the risk of colonization and emergence of multidrug-resistant bacterial strains, and a significant increase in the cost of patient management [19–21].

These observations led us to design a prospective, randomized study of the safety of stopping antibiotic therapy during day 3 of antimicrobial treatment of children with cancer and episodes of fever and severe neutropenia; these children did not have evidence of bacterial infection on the basis of clinical and laboratory findings and serial CRP measurements during the first 2 days of illness. We also evaluated the usefulness of serial CRP levels for early detection of bacterial superinfections during the course of the neutropenic episode.

Materials and Methods

Population selection. All children hospitalized at Hospital de Niños Luis Calvo Mackenna (Santiago, Chile) because of cancer, fever, and severe neutropenia (ANC, ≤500/mm³) from 1 January 1994 to 31 January 1996 were eligible for enrollment. This center is a public hospital affiliated with the Universidad de Chile; it provides health care to 400,000 children in the low to average income population.

Initial evaluation. All children underwent a thorough clinical evaluation performed by one of the authors (M.E.S. or M.V.), and the following standard laboratory tests were carried out: determination of complete blood cell count, liver and renal function tests, chest roentgenography, urine sediment and urine cultures, and blood cultures (including quantitative cultures if an indwelling central venous catheter was present). Quantitative serum CRP levels were determined at admission and on day 2. The following examinations were performed according to clinical findings: serial stool cultures, rotavirus detection, ova and parasite detection, bacterial and fungal cultures of pharyngeal and skin specimens, indirect immunofluorescence of nasopharyngeal aspirates for detection of respiratory syncytial virus, adenovirus, parainfluenza virus types 1, 2, and 3, and influenza virus types A and B, and adenovirus culture.

Therapy with an antistaphylococcal penicillin and a third-generation cephalosporin or an aminoglycoside was started at admission for all children; all children were monitored daily by one of the authors (M. E. S or M. V.). All children who had clinical and/or laboratory evidence of bacterial infection and/or a serum CRP level of >40 mg/L on day 1 or 2 were considered potentially bacteremic and were excluded from the study. Children with no identifiable focus of bacterial infection, hemodynamic stability, negative admission cultures, and serum CRP levels of ≤40 mg/L on days 1 and 2 were considered at low risk for bacterial infection. These children continued in the study. They were randomized on day 3 to one of the following two treatment groups after informed consent was obtained from their parents or guardians: group A, all antibiotic therapy stopped; and group B, antibiotic therapy continued until the episode of fever and neutropenia was resolved. Trimethoprim-sulfamethoxazole prophylaxis is not routinely administered to children with cancer and neutropenia in our hospital, and this therapy was not given to any of the study patients.

Patient follow-up. Children from both groups were monitored daily in the hospital until the fever resolved and the ANC was >500/mm³. Monitoring included determination of temperature and blood pressure, evaluation of consciousness level and hemodynamic stability, and complete physical examination for identification of potential bacterial complications. Blood was obtained daily for determination of CRP level and every 2 days for measurement of complete blood cell count. Additional laboratory evaluations were done on the basis of individual clinical findings.

Outcome variables. The following variables were considered indicative of an unfavorable outcome determining restarting antibiotic therapy for children in group A and adjusting antibiotic therapy for children in group B: detection of a clinical focus suggestive of a bacterial infection, a positive bacterial culture after day 3, reappearance of fever, deterioration of hemodynamic stability that was not attributable to blood loss, or progressive increase in serum CRP levels to >40 mg/L during at least two consecutive measurements. Outcome was defined as favorable when none of the above-mentioned variables occurred.

Determination of CRP level. Blood for determination of CRP level was obtained by thumb prick and processed as previously described [15]. Briefly, 20 μL of serum was incubated out: determination of complete blood cell count, liver and renal function tests, chest roentgenography, urine sediment and urine cultures, and blood cultures (including quantitative cultures if an indwelling central venous catheter was present). Quantitative serum CRP levels were determined at admission and on day 2. The following examinations were performed according to clinical findings: serial stool cultures, rotavirus detection, ova and parasite detection, bacterial and fungal cultures of pharyngeal and skin specimens, indirect immunofluorescence of nasopharyngeal aspirates for detection of respiratory syncytial virus, adenovirus, parainfluenza virus types 1, 2, and 3, and influenza virus types A and B, and adenovirus culture.

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of $\leq 40$ mg/L; probable viral infection, clinical findings suggestive of acute viral infection (skin rash and upper respiratory tract infection transmitted by a household contact) in the absence of any positive bacterial culture and all serum CRP levels of $\leq 40$ mg/L; mixed infection, acute viral infection and bacterial infection during the same neutropenic episode; and fever of unknown origin (FUO), negative bacterial and viral cultures, no clinical or laboratory evidence suggestive of a bacterial and/or viral infection, and serum CRP levels of $\leq 40$ mg/L. 

Statistical analysis. Results of univariate analyses for both groups were compared by the $\chi^2$ test. The Student's $t$ test and the Mann-Whitney $U$ test were used to compare means. The Student's $t$ test was used for parameters that displayed a normal distribution, while the Mann-Whitney $U$ test was used for parameters that did not display a normal distribution. A $P$ value of $\leq 0.05$ was considered significant.

Results

Population. During the 25-month study period, 220 patients with cancer who had 238 episodes of fever and neutropenia were admitted to our hospital. All patients received antibiotic therapy and were evaluated daily according to the study protocol. On day 3, 149 febrile episodes were excluded from the study because they were associated with clinical signs of bacterial infection, positive bacterial cultures, and serum CRP levels of $>40$ mg/L. For this group of patients with 149 febrile episodes, the mean CRP value $\pm$ SD was $101 \pm 48.7$ mg/L and the discharge diagnoses included demonstrated bacterial infection (46%), probable bacterial infection (38%), bacterial and fungal infections (8%), fungal infection (5%), viral infection (2%), and mixed infection (1%). For this group of children, the mean duration of neutropenia $\pm$ SD was $9 \pm 5.38$ days, which did not differ from those for the study groups (Student’s $t$ test).

Of the 89 febrile episodes associated with low serum CRP levels and the absence of clinical and laboratory evidence of bacterial infection, 14 were excluded from the study because antimicrobial treatment was administered during the 7 days before admission. The remaining 68 patients with 75 febrile episodes (seven children had two episodes) were randomized to group A ($n = 36$) or group B ($n = 39$) (figure 1).

Characteristics of study groups. Groups A and B were comparable in terms of age, gender, oncological disease, chemotherapy status, use of indwelling catheters, and initial ANC (table 1). No child received treatment with colony-stimulating factors. Discharge diagnoses were also comparable between both groups (table 2); they included 35 cases of acute respiratory viral infection (23 diagnosed by culture and/or immunofluorescence and 12 diagnosed by clinical criteria), 14 cases of varicella diagnosed clinically on the basis of characteristic skin lesions, 2 probable cases of enterovirus infection diagnosed on the basis of characteristic mouth vesicular lesions, and 1 case of hepatitis A diagnosed by the presence of serum IgM.

Mixed viral and bacterial infections occurred in three children: one child admitted with varicella, one with an upper respiratory tract infection, and one with an enterovirus infection who acquired *Enterobacter aerogenes* bacteremia, pneumonia (indicated by radiological findings), and periodontal abscesses, respectively. Two children developed indwelling central venous catheter-associated infection due to coagulase-negative staphylococcus. Eighteen episodes were classified as FUO.

Clinical outcome by study groups. The mean duration of fever $\pm$ SD was $2.7 \pm 1.82$ days in group A and $3.5 \pm 3.62$ days in group B (NS, Mann-Whitney $U$ test). In group A, antibiotic therapy was stopped in 29 febrile episodes that resolved and in seven febrile episodes despite continuous fever. The mean duration of severe neutropenia $\pm$ SD was $8.3 \pm 5.42$ days in group A and $9.0 \pm 5.83$ days in group B (NS, Student’s $t$ test). Hospital stay was determined by the duration of neutropenia according to the protocol; the mean hospital stay $\pm$ SD was similar in both groups ($8 \pm 5.22$ days for group A vs. $9 \pm 5.87$ days for group B; NS, Student’s $t$ test). The mean duration of antibiotic treatment $\pm$ SD in group B was $7 \pm 3.98$ days. A favorable outcome occurred in 34 (94%) of 36 episodes in group A and in 36 (92%) of 39 episodes in group B (table 3). None of the children died during the 75 febrile episodes.

Treatment failed in five episodes, two in group A and three in group B. In group A, antibiotic therapy for a 14-year-old girl with rhabdomyosarcoma who enrolled in the study with a clinical diagnosis of upper respiratory tract infection in the absence of clinical and laboratory evidence of bacterial infection and a CRP level of 15 mg/L was stopped. Fever resolved...
Table 1. Baseline characteristics of 68 children with cancer who had 75 episodes of severe neutropenia and fever.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A: antibiotic therapy stopped (n = 36)</th>
<th>Group B: antibiotic therapy continued (n = 39)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y) ± SD</td>
<td>6.8 ± 4.3</td>
<td>5.6 ± 3.8</td>
<td>.2</td>
</tr>
<tr>
<td>Male to female ratio</td>
<td>20:16</td>
<td>21:18</td>
<td>.3</td>
</tr>
<tr>
<td>No. with oncological disease</td>
<td></td>
<td></td>
<td>.3</td>
</tr>
<tr>
<td>Leukemia</td>
<td>15</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td>19</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>No. with chemotherapy status</td>
<td></td>
<td></td>
<td>.3</td>
</tr>
<tr>
<td>Induction</td>
<td>27</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>No. with indwelling catheter</td>
<td>13</td>
<td>17</td>
<td>.2</td>
</tr>
<tr>
<td>Mean ANC (/mm³) ± SD on day 1</td>
<td>297 ± 181</td>
<td>246 ± 167</td>
<td>.2</td>
</tr>
</tbody>
</table>

NOTE. ANC = absolute neutrophil count.
* χ² and Student’s t tests.

Fever reappeared on day 5, the CRP level increased to a maximum of 98 mg/L on day 5, and two repeated blood cultures were positive for *E. aerogenes* resistant to third-generation cephalosporins. Antibiotic therapy (imipenem) was started; the patient had an uneventful course and recovered after 7 days.

In group B, treatment failed in three episodes. Two boys (a 3-year-old and a 7-year-old) with acute lymphoblastic leukemia and a history of use of indwelling central venous catheters developed catheter infection due to coagulase-negative staphylococcus despite the fact that antibiotic treatment was continued; therapy was changed from cloxacillin to vancomycin. The serum CRP levels increased to >40 mg/L in the 3-year-old boy, while repeated CRP levels in the 7-year-old boy remained at <40 mg/L. The third child, a 9-year-old boy with a relapse of acute nonlymphoblastic leukemia who was enrolled in the study with oral vesicular lesions suggestive of an enterovirus infection, developed a periodontal abscess with reappearance

Table 2. Discharge diagnoses for 68 children with cancer who had 75 episodes of severe neutropenia and fever.

<table>
<thead>
<tr>
<th>Diagnosis*</th>
<th>Group A: antibiotic therapy stopped (n = 36)</th>
<th>Group B: antibiotic therapy continued (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus infection</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory syncytial virus infection</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Parainfluenza virus infection</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Influenza virus infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Clinical upper respiratory tract infection</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Varicella</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Enterovirus infection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mixed infection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Coagulase-negative staphylococcus infection</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>39</td>
</tr>
</tbody>
</table>

NOTE. The differences between groups A and B were not statistically significant by the χ² test.
* See text for diagnosis criteria.

Table 3. Outcome of 75 episodes of severe neutropenia and fever in 68 children with cancer according to study group.

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Group A: antibiotic therapy stopped (n = 36)</th>
<th>Group B: antibiotic therapy continued (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td>Documented bacterial infection</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Probable bacterial infection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. The differences between groups A and B were not statistically significant by the χ² test.
* See text for definitions of outcome variables.
of fever and increasing CRP levels that reached a maximum of 153 mg/L. Antibiotic treatment was changed, and the child recovered after 3 days.

Discussion

In most pediatric cancer centers worldwide, children with cancer and neutropenia who develop a febrile episode receive in-hospital treatment that includes broad-spectrum antibiotics. More recently, a less aggressive, more selective approach aimed at determining relevant risk factors that could help identify patients with fever and concomitant bacterial infection has been proposed [24].

Previous studies [17, 18] have reported that 30% of children with cancer, fever, and neutropenia lack clinical or laboratory evidence of a bacterial infection, an observation that was confirmed in our study where 26% of 220 patients had a viral infection. An additional 8% of patients lacked evidence of viral and bacterial infections and were classified as having FUO. Continuous enrollment of patients during a 2-year study period removes the possible influence of seasonality in the identification rate for viral infections. However, determining the true role of viruses in these febrile episodes will require performing a complete virological workup for all children with cancer, neutropenia, and fever (not only for those with clinical signs of a viral infection and a CRP level of <40 mg/L as in this study).

Our results strongly suggest that children with cancer and neutropenia who develop fever and lack clinical and laboratory evidence of a bacterial infection according to well-defined criteria (which in our study included at least two CRP levels of <40 mg/L) can be managed without antibiotic therapy after day 3 and not be at an increased risk for an unfavorable outcome. The findings of our initial study [17], which proved that a serum CRP level of <40 mg/L in children with cancer, neutropenia, and fever (not only for those with clinical signs of a viral infection and a CRP level of <40 mg/L as in this study).

Additional support for this selective approach comes from the analysis of the two cases in group A and the three cases in group B that had an unfavorable outcome. Organisms not covered by the empirical antibiotic therapy usually used at admission were recovered from one of the two children with bacterial superinfections in group A; therefore, it is probable that the superinfections would have occurred with or without antibiotic use.

On the other hand, adjustment of wide-spectrum antibiotic therapy for the three children in group B who had superinfections was required, which suggests that the antibiotic coverage was most probably not affording a specific benefit against the infectious process. Other investigators [25] have shown that stopping antibiotic therapy on day 3 of fever in adult patients with cancer and neutropenia who lack clinical and laboratory evidence of bacterial infection can be done safely.

The previous observation that the serum CRP level could be a sensitive marker for the occurrence of a bacterial superinfection during the clinical course of children admitted to the hospital with nonbacterial fever was also confirmed in this prospective study [18]. All 70 episodes with a favorable clinical course were associated with serial CRP levels of <40 mg/L, while four of five episodes in children who presented with a bacterial superinfection were associated with increasing serum CRP levels that were greater than the cutoff value. It is notable that serum CRP levels remained below the cutoff value in one of the two children who had an indwelling central venous catheter–associated infection due to coagulase-negative staphylococcus. This finding has been reported by other investigators [26] and suggests that patients with cancer, neutropenia, and fever who have an indwelling catheter may be infected with a coagulase-negative staphylococcus despite persistently low serum CRP levels. The appropriate antibiotic management for this particular group of children will require additional study.

In summary, we propose that children with cancer, fever, and neutropenia who are at low risk for bacterial infection according to predefined criteria can be safely managed without antibiotic therapy after day 3. We strongly believe that this selective approach can benefit many patients who will be at lower risk for antibiotic-associated complications. The adoption of this strategy must be closely evaluated by each institution because of the possibility of local differences in patient populations and in clinical and laboratory monitoring. A carefully designed protocol or strict criteria must be used to avoid the occurrence of serious complications. The duration of in-hospital observation will also have to be carefully determined.

Although the relatively small size of our groups could be seen as a limitation of our study, the results highly favored the hypothesis that stopping antibiotic therapy for children at low risk for bacterial infection is safe. In Santiago, our observations have prompted the development of a multicenter protocol for the management of these children. In this protocol, we consider stopping antibiotic therapy for children with cancer, fever, and neutropenia according to the same clinical and laboratory criteria described in this article.

Until further experience is obtained, we recommend in-hospital follow-up for these children up to the time that the ANC is >500/mm³; follow-up should include daily clinical evaluation and determination of serum CRP levels. Close monitoring of this protocol will allow us to evaluate our observations on a wide-scale basis in the future, extend our recommendations, critically analyze potential pitfalls of this approach, and determine the potential economic benefit of these recommendations for the Chilean National Health Care System.

References


