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ORIGINAL REPORT

Early Hospital Discharge Followed by Outpatient Management Versus Continued Hospitalization of Children With Cancer, Fever, and Neutropenia at Low Risk for Invasive Bacterial Infection

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ABSTRACT

Purpose
To compare outcome and cost of ambulatory versus hospitalized management among febrile neutropenic children at low risk for invasive bacterial infection (IBI).

Patients and Methods
Children presenting with febrile neutropenia at six hospitals in Santiago, Chile, were categorized as high or low risk for IBI. Low-risk children were randomly assigned after 24 to 36 hours of hospitalization to receive ambulatory or hospitalized treatment and monitored until episode resolution. Outcome and cost were determined for each episode and compared between both groups using predefined definitions and questionnaires.

Results
A total of 161 (41%) of 390 febrile neutropenic episodes evaluated from June 2000 to February 2003 were classified as low risk, of which 149 were randomly assigned to ambulatory (n = 78) or hospital-based (n = 71) treatment. In both groups, mean age (ambulatory management, 55 months; hospital-based management, 66 months), sex, and type of cancer were similar. Outcome was favorable in 74 (95%) of 78 ambulatory-treated children and 67 (94%) of 71 hospital-treated children (P = NS). Mean cost of an episode was US $638 (95% CI, $572 to $703) and US $903 (95% CI, $781 to $1,025) for the ambulatory and hospital-based groups, respectively (P = .003).

Conclusion
For children with febrile neutropenia at low risk for IBI, ambulatory management is safe and significantly cost saving compared with standard hospitalized therapy.

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INTRODUCTION

During the past decade, nearly all children with cancer who suffered an episode of febrile neutropenia (FN) were hospitalized and managed with broad spectrum antimicrobials irrespective of their clinical condition.[1] More recently, an increasing body of evidence is supporting more selective approaches aimed to avoid unnecessary hospitalizations and prolonged broad spectrum antimicrobial therapies for children at low risk for an invasive bacterial infection (IBI).[2,3] These selective strategies have included short antimicrobial treatments,[4,5] short hospital stays,[6-8] use of oral antimicrobial therapy,[9-12] and ambulatory management.[13-16] The key requirement for success of a less aggressive approach is the accurate identification of children at low risk for IBI.[17-20]

During 1996 to 1997, we performed a collaborative, prospective, multicenter study

aimed at identifying clinical and laboratory variables present at the time of a first consult that could help identify children at high or low risk of an IBI. The following five independent risk variables (ranked by order of significance) were identified: serum C-reactive protein (CRP) levels of 90 mg/L or greater, presence of hypotension, relapse of leukemia as cancer type, platelet count of 50,000/μL or less, and recent ($\leq$ 7 days) chemotherapy.[19] IBI occurred in 2%, 17%, 48%, 75%, and 100% of episodes presenting with none, one, two, three, or four or more risk factors, respectively. During 1999 to 2000, we prospectively validated a model of risk prediction of IBI that considered a combination of these five risk factors. Sensitivity, specificity, and positive and negative predictive values for this model were 92%, 76%, 82%, and 90%, respectively.[21]

Provided with a reliable risk prediction model, our current hypothesis is that children at low risk for IBI can be treated as outpatients and have a comparable outcome to children treated in the hospital. In addition, we postulate that ambulatory management can be significantly cost saving for the health care system. Our aim is to compare outcomes of ambulatory versus hospitalized management of febrile neutropenic children at low risk for IBI and to determine whether ambulatory management is cost saving.

PATIENTS AND METHODS

Patient Selection

Children who were 18 years of age or younger with cancer, fever, and severe neutropenia and who were admitted to any of six participating hospitals located in Santiago, Chile, between June 1, 2000, and February 28, 2003, were evaluated at enrollment by a study physician who classified the episode as low or high risk for IBI according to a previously validated risk prediction model.[19,21] These hospitals participate in a national network, the National Child Program of Antineoplastic Drugs, responsible for the standardization of treatment protocols for different cancers. High-risk patients were managed with hospital-based, intravenous (IV), broad spectrum antimicrobials for a minimum of 7 days and excluded from further study. Individuals at low risk for IBI were invited to participate in this prospective, collaborative, randomized, multicenter study. Informed consent was obtained for all patients, and the study was approved by the ethical committee of each hospital.

Initial Evaluation and Treatment

Initial evaluation included medical history, clinical examination, and laboratory examinations were aimed at identifying possible sites of infection and assessing risk variables included in the prediction model. Laboratory evaluation included a CBC, serum CRP, central- and peripheral-blood cultures, urine examination and culture, chest radiograph, nasopharyngeal aspirate for respiratory viruses, and cultures from other sites (skin lesions and stools) if focal signs and/or symptoms were present.

Children at low risk for IBI were admitted to the hospital during a 24- to 36-hour period and were then re-evaluated to determine whether they continued in the low-risk category. Children who remained at low risk were randomly assigned to receive ambulatory or hospital management. Empirical antimicrobial treatment used for both groups was IV ceftriaxone (Acantex; Roche, Basel, Switzerland), 100 mg/kg/d every 24 hours, and IV teicoplanin (Targocid; Aventis Pharma, Bridgewater, NJ), 20 mg/kg/d every 12 hours for the first day followed by 10 mg/kg/d every 24 hours. After completing a minimum of 3 days of IV therapy, a decision to switch therapy to oral cefuroxime axetil (Curocef; GlaxoSmithKline Biologicals, Research Triangle Park, NC), 50 mg/kg/d every 12 hours, was decided on an individual basis, based on predefined criteria of favorable or unfavorable evolution as described later in this article.

Follow-Up Treatment and Evaluation

After 24 to 36 hours in the hospital, children randomly assigned to ambulatory management were discharged with precise instructions to return to the oncology clinic of the corresponding hospital on a daily basis for evaluation and antimicrobial treatment and to the emergency room at any time if a significant new symptom occurred. The duration for clinic visits was estimated to last 90 to 120 minutes considering 30 minutes for medical and laboratory evaluation, 30 minutes for the IV infusion (less if on oral antimicrobial), and a 1-hour observation period after infusion. Children managed in the hospital received treatment according to routine hospital guidelines.

Children from both treatment groups were evaluated daily until fever resolved and the absolute neutrophil count (ANC) reached 500/μL. Monitoring included physical examination directed to detect possible sites of infection and laboratory evaluation with daily determinations of CRP level and every-other-day measurement of ANC. Monocyte and platelet counts were measured until the counts reached 100 and 50,000/μL, respectively. For children with a positive culture obtained at admission (blood, urine, CSF, or other site), a repeat culture was obtained on day 3.

Outcome Evaluation

Outcome was considered unfavorable if one or more of the following situations indicative of a possible IBI occurred: (1) hemodynamic instability not attributable to volume loss; (2) axillary temperature more than 38°C in two or more daily recordings after day 4; (3) increase in temperature after a 48-hour afebrile period persisting for at least 24 hours; (4) an ascending CRP curve or a nondescending curve over normal limits (a value $>$ 40 mg/L and $<$ 30% decrease from a previous recording) after day 3 persisting for at least 2 consecutive days; (5) isolation of a bacterial pathogen from a significant sample obtained on day 3; and (6) death occurring during the febrile episode attributable to infection. An unfavorable outcome determined an adjustment of antimicrobial treatment and readmission to the hospital if the child was in the ambulatory treatment group. The outcome was considered favorable if none of the situations indicative of an IBI occurred and the child completed follow-up without requiring either antimicrobial adjustments or readmission.

IV ceftriaxone and teicoplanin were switched to oral cefuroxime after 72 hours if the clinical evolution was favorable. Criteria for ending antimicrobial treatment were two consecutive CRP values of 40 mg/L or less and 1 full day without fever.

Cost Evaluation

The following items were considered for cost analysis: (1) Hospital bed per day, transitory hospitalization, and medical visits; (2) medical supplies including IV lines, IV fluids, gloves, syringes, and masks; (3) laboratory exams including hematology, serum biochemistry, bacteriology, and imaging studies; (4)

medications including ceftriaxone, teicoplanin, cefuroxime, analgesics, and others; and (5) transportation (net costs incurred by the family). Costs for items 1 to 4 were obtained from the Chilean National Health Fund when indexed.[22] Values established by the Chilean National Health Fund represent the cost assigned for public institutions and, in most cases, are subsidized. On a daily basis, a study nurse filled in a standard data capture form with all medical procedures and items used for each study patient. A second evaluator reviewed the information, assigned the standard value for each item, and obtained a total cost per episode. Results are presented in US dollars using 2003 official exchange values.

Definitions

Severe neutropenia was defined as ANC less than 500/μL, and fever was defined as one axillary recording of 38.5°C or greater or two recordings of 38°C or greater separated by at least 1 hour. IBI was defined as demonstrated if one or both of the following criteria were met: (1) occurrence of bacteremia ($\geq$ one blood culture positive for bacterial pathogens, with the exception of coagulase-negative *Staphylococcus*, which required $\geq$ two positive blood cultures) and/or (2) a positive bacterial culture for a specimen obtained from a usually sterile site (eg, indwelling catheter, urine, or CSF). IBI was considered probable if, in the absence of a positive culture result, one or both of the following criteria were met: (1) clinical and laboratory findings strongly suggestive of a sepsis syndrome[23] and/or (2) focal organ involvement in a child with hemodynamic instability and severe malaise.

Statistical Analysis

Sample size was calculated based on the hypothesis that the frequency of occurrence of an unfavorable outcome was the same for both groups. Considering an unfavorable outcome of 10% as previously reported for this population,[19,21] a maximum acceptable difference between groups of 15%, a type I error of 0.05, and a potency of 0.90, we determined that 69 patients per groups were required (*n*-Query software package, Advisor 4 , Copyright 1995-2000; Janet D. Elashoff, PhD, Los Angeles, CA). Continuous variables were compared using the Student's *t* test and Mann-Whitney *U* test, and noncontinuous variables were compared using the χ^2 and Fisher's exact tests when appropriate.

RESULTS

Overall Description of Febrile Neutropenic Episodes

A total of 390 episodes occurring in 313 children were admitted to the participating hospitals during the 28-month study period. Of them, 222 and 168 were classified as high and low risk at enrollment, respectively. Children with high-risk episodes received aggressive antimicrobial treatment, and children with low-risk episodes were managed in the hospital for 24 to 36 hours according to protocol. After the second evaluation, five additional episodes were reclassified as high risk and excluded from the study, and two additional episodes were deemed misclassified at enrollment, for a total of 229 episodes (59%) classified as high risk for IBI. Overall mortality was 5% (16 of 313 patients), and all but one death occurred during an episode classified as high risk.

Of the 161 episodes classified as low risk for IBI after the 24- to 36-hour inpatient management period, 149 were randomly assigned to ambulatory (n = 78) or hospital-based (n = 71) treatment. Twelve patients could not be randomized because of lack of informed consent (n = 2), rural origin (n = 2), lack of notification (n = 2), diagnosis coinciding with the debut of an acute lymphocytic leukemia (n = 2), clinical suspicion of an anaerobic infection requiring broader antimicrobial coverage (n = 2), seizure (n = 1), and intestinal subocclusion at admission (n = 1). The overall characteristics of the children and episodes in both treatment groups were similar (Table 1). All participating children were receiving chemotherapy, and none was a recipient of a stem-cell transplantation.

The clinical and, when available, microbiologic diagnoses of the 149 episodes that were randomized are listed in Table 2. One hundred thirty-eight episodes cataloged as low risk had a final diagnosis of absence of IBI (eg, fever of

Table 1. Overall Characteristics by Treatment Group of the 149 Low-Risk Febrile Episodes Occurring in 107 Children With Cancer and Neutropenia

Characteristics	Treatment Strategy (N = 107)*	
	Ambulatory Treatment	Hospital-Based Treatment
Age, months		
Mean	55	66
95% CI	45 to 66	57 to 74
Male, %	43	49
Cancer type, %		
Leukemia/lymphoma	40	51
Solid tumor	60	49
At the time of admission (n = 149 episodes)		
Permanent catheter in place, %	37	44
Hours of fever, No.		
Mean	10.1	9.4
95% CI	7.6 to 12.6	7.7 to 11.1
ANC, /μL		
Mean	146	137
95% CI	111 to 182	98 to 180
AMC, /μL		
Mean	149	145
95% CI	103 to 246	96 to 194
After admission (n = 149 episodes)		
Days of fever, No.		
Mean	2.3	2.8
95% CI	1.7 to 2.6	2.3 to 3.0
Days of ANC < 500/μL		
Mean	3.5	3.9
95% CI	3.3 to 4.9	3.3 to 4.7
Days of AMC < 100/μL		
Mean	1.6	1.8
95% CI	1.1 to 2.2	1.3 to 2.3

Abbreviations: ANC, absolute neutrophil count; AMC, absolute monocyte count.
*None of the differences are significant.

Table 2. Clinical and Microbiologic Diagnoses Associated With 149 Low-Risk Febrile Neutropenic Episodes

Final Diagnosis	No. of Episodes by Treatment Strategy*	
	Ambulatory Treatment	Hospital-Based Treatment
Fever of unknown origin	31	25
Upper respiratory infection	23	22
Lower respiratory infection	10	8†
Noninvasive diarrhea	6	8
Localized skin/soft tissue infection	2	3
Urinary tract infection	2	2‡
Bacteremia	1	2§
Septic syndrome	1	1
Pneumonia	1	0
Central catheter infection	1	0‖
Total	78	71

*Distribution of clinical and microbiologic diagnoses did not differ between groups.
†Isolates from eight of 18 episodes included respiratory syncytial virus (n = 4), influenzae virus (n = 2), parainfluenzae virus (n = 1), and adenovirus (n = 1).
‡Isolates included *Escherichia coli* (n = 4).
§Isolates included *Pseudomonas aeruginosa* (n = 1), *E coli* (n = 1), and coagulase-negative *Staphylococcus* (n = 1).
‖Isolates included coagulase-negative *Staphylococcus*.

unknown origin, upper respiratory infection, lower respiratory infection, noninvasive diarrhea, and localized infection of skin and/or soft tissues). Eleven episodes cataloged as low risk had a final diagnosis of IBI (eg, urinary tract infection, bacteremia, septic syndrome, pneumonia, and central catheter infection). The distribution of diagnoses did not differ between the treatment groups.

Outcome of Febrile Neutropenic Episodes by Treatment Groups

Seventy-four (95%) of 78 ambulatory and 67 (94%) of 71 hospital-based episodes had a favorable outcome according to our predefined criteria (P = NS). Mean duration of antimicrobial treatment was 6.1 days (95% CI, 5.4 to 6.8 days) for the ambulatory-treated children and 6.4 days (95% CI, 5.9 to 7.0 days) for the hospital-treated children. Divided by therapy, with IV therapy, the mean duration was 4.3 days (95% CI, 3.7 to 5.0 days) and 4.8 days (95% CI, 4.4 to 5.3 days), and with oral therapy, it was 1.8 days (95% CI, 1.2 to 2.3 days) and 1.6 days (95% CI, 1.1 to 2.1 days) for the ambulatory- and hospital-treated children, respectively. (P = NS for the three comparisons).

Eight patients had an unfavorable outcome, four in each treatment group (Table 3). Seven children recovered completely after therapy modifications. The child that died was a 1-year old child with a stage III neuroblastoma receiving induction chemotherapy who had low-risk parameters at admission and at 24 to 36 hours and a negative admission blood culture. He deteriorated on day 3 and was immediately transferred to the intensive care unit; new cultures were obtained, and antimicrobials were changed to include *Pseudomonas aeruginosa* coverage. The child had a fulminate course and died on the same day; day 3 blood culture was later reported as positive for *P aeruginosa*.

Cost of Ambulatory and Hospital-Based Treatment Strategies

The mean cost for ambulatory treatment was significantly less than for hospital-based treatment (US $638; 95% CI, $572 to $703; *v* US $903; 95% CI, $781 to $1,025, respectively; P = .003; Table 4). The main item accounting for this difference was hospital bed per day. The additional cost for transportation in the ambulatory group had a small impact in increasing overall cost. The number of medical supplies, laboratory evaluations, and medications was similar between both groups (P = NS).

DISCUSSION

In this prospective, randomized study of Chilean children with cancer, fever, and neutropenia at low risk of IBI

Table 3. Description of the Eight Children Classified As Low Risk at Enrollment Who Had an Unfavorable Outcome

Treatment Group	Age (years)	Cancer Type	Criteria for Unfavorable Outcome				Microbiology Result	Death
			Hemodynamic Instability	Fever > 3 Days	Reappearance of Fever	CRP > 40 mg/L		
Ambulatory	8	ST	+*	+	−	−	−	−
Ambulatory	11	ST	−	−	+	+	−	−
Ambulatory	2	ALL	−	+	−	−	−	−
Ambulatory	8	ST	+	−	−	−	−	−
Hospitalized	10	ST	−	−	−	+	Influenzae A	−
Hospitalized	1	ST	+	+	NE	+	*Pseudomonas aeruginosa*	+
Hospitalized	4	ALL	−	−	+	−	−	−
Hospitalized	5	ALL	−	+	−	+	−	−

Abbreviations: ST, solid tumor; ALL, acute lymphocytic leukemia; CRP, C-reactive protein; NE, not evaluated.
*+ means criteria is present, and − means it is absent or negative.

Table 4. Quantification of Actions and Supplies and Mean Costs (US $) for Ambulatory and Hospital-Based Management of Low-Risk Febrile Neutropenic Episodes in Chile

Item	Quantification and Cost of Items by Treatment Groups			
	Ambulatory Treatment		Hospital-Based Treatment	
	Mean	Range	Mean	Range
Medical care				
Hospital bed/d	1.0	1-2	5.3	3-9*
Transitory bed/d	2.8	2-6	0*	0
Medical visits, No.	4.5	3-22	5.3	3-9
Cost, $				
Mean	198		477	
95% CI	164-231		402-551*	
Medical supplies, No.				
IV lines	7.4	3-14	7.2	4-15
IV fluids, L	3.1	2-15	2.6	2-9
Gloves	5.0	2-12	3.6	2-6
Masks	7.9	2-27	8.0	2-64
Syringes	20.2	4-37	23.8	8-54
Cost, $				
Mean	17		14	
95% CI	12-22		11-17	
Laboratory evaluations, No.				
Hematology	6.6	4-10	6.0	2-11
Serum biochemistry	11.4	2-16	11.0	2-22
Microbiology	4.2	2-7	4.1	2-11
Imaging studies	1.3	1-3	1.5	1-4
Cost, $				
Mean	151		137	
95% CI	137-165		114-161	
Medications, No. of days				
IV antibiotics	4.3	2-22†	4.8	2-10
Oral antibiotics	1.8	0-7	1.6	0-7
Cost, $				
Mean	259		271	
95% CI	218-302		237-320	
Transportation cost, $				
Mean	13		4	
95% CI	0.6-27		3.2-4.4‡	
Total mean cost, $				
Mean	638		903	
95% CI	572-703		781-1,025‡	

Abbreviation: IV, intravenous.
*$P < .001$ for the difference between ambulatory and hospital-based management.
†One child with an unfavorable outcome who was randomly assigned to the ambulatory group required prolonged antimicrobial treatment and readmission to the hospital.
‡$P = .003$ for the difference between ambulatory and hospital-based management.

according to previously validated criteria, ambulatory management was as effective and safe as hospital-based management and also significantly cost saving compared with hospital-based management.

During the 1990s, Kaplinsky et al[24] and Mustafa et al[25] paved the way to a more selective, less aggressive approach for children with cancer and FN by showing in two nonrandomized studies that outpatient management of children who met low-risk criteria was possible.[24,25] Successful outcomes of ambulatory management strategies were further reported in two small series, one including children at low risk according to nonstandardized criteria, using ceftriaxone monotherapy or ceftriaxone in combination with teicoplanin,[26] and another using ceftazidime followed by oral ciprofloxacin.[13] In a more recent, larger series, Petrilli et al[15] demonstrated that oral ciprofloxacin was comparable to IV ceftriaxone in 116 episodes of low-risk FN defined by oncologic criteria (presence of a solid tumor or stage I or II lymphoma); therapy was successful in 83% and 75% of patients, respectively.[15] In the most recent trial, from Argentina, Paganini et al[16] treated 175 episodes of low-risk FN (defined by oncologic, clinical, and laboratory criteria) with one dose of ceftriaxone and amikacin followed by randomization to ambulatory management using either oral ciprofloxacin or IV ceftriaxone; the outcome was favorable in 95% and 93% of episodes, respectively.[16] The high rates of favorable outcome, over 94% in our study, which was comparable to the study of Paganini et al, strongly support our selection criteria for children at low risk, based on a model of risk prediction that was rigorously constructed,[19,21] and our selective management strategy. In addition, we have demonstrated that hospitalization provides no additional benefit to these children.

Antimicrobial selection for ambulatory therapy has included parenteral antibiotics with a long half-life, such as ceftriaxone and/or teicoplanin, and oral antimicrobials. We selected IV ceftriaxone and teicoplanin as initial therapy for this study in lieu of previous microbiologic data reporting that *Escherichia coli*, *Klebseiella pneumoniae*, *S aureus*, and coagulase-negative *Staphylococcus* represented 65% of isolates in this population.[27] Considering that the great majority of positive cultures are obtained from children at high risk and that most bacterial cultures are negative in children at low risk (141 of 149 episodes in this study), we currently believe that broad-spectrum combinations as selected for this study are recommendable for high-risk children but not for low-risk children, in whom ceftriaxone or an oral fluorquinolone monotherapy represent a more rationale alternative. Patients with coagulase-negative *Staphylococcus* catheter-associated infections or bacteremia that can mimic low-risk episodes will not have appropriate coverage; albeit in the current study, only two of 149 low-risk episodes involved this situation.

Mean cost for the ambulatory management strategy was approximately two thirds of the cost of the hospital-based strategy. Even though these costs cannot be extrapolated to other areas that have different socioeconomic realities and where prices are not necessarily subsidized as in Chile, the significant cost savings of the ambulatory management strategy is probably universal.

Results from this study have been used to support a recent change in national recommendations for children with cancer, fever, and neutropenia. We currently recommend a 24- to 48-hour hospitalization period aimed to assess the child's risk category using our validated model,[19,21] followed by outpatient management if children are at low risk for IBI. Implementation of this policy nationwide and possibly at a regional level will require work to convince physicians that this strategy is as safe as hospital-based management; after 10 years of a stepwise evidence-based approach, sufficient information has been generated to strongly support this recommendation. A prerequisite before recommending implementation of an outpatient management program in different settings is to have an experienced medical team that can assure close follow-up of patients and a rapid response for those patients who are not doing well at home.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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