Infections in Hospitalized Children and Young Adults With Acute Leukemia in Morocco

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Background. Overall survival from leukemia is less in low and middle-income countries than in high-income countries. Our purpose was to describe the incidence, clinical features, and mortality of febrile illness with or without documented infection in children and young adults treated for AML and ALL in two centers in Rabat and Casablanca during 2011. ***Methods.*** This retrospective cohort study included patients <30 years of age who were newly diagnosed with AML and ALL in 2011 in Casablanca and Rabat. Each patient's chart was evaluated for patient demographics, febrile episodes, chemotherapy regimen, and clinical or microbiological evidence of infection, neutropenia, antibiotics, and mortality. ***Results.*** One hundred sixty-six evaluable patients had 228 inpatient febrile episodes. The median number of febrile episodes in AML was three per patient, and for ALL, one per patient. Clinically identified infections mainly included pneumonitis and mucositis. Coagulase negative staphylococcus was the most commonly isolated bacterium, followed by gram-negative bacteria. Fifty-three percent of febrile episodes were classified as fever of undetermined origin. Broad-spectrum antibiotics were routinely used, with the addition of antifungals in 62 episodes and vancomycin in 83 episodes. The rate of deaths per febrile illness was 11.3% (16/141) in patients with AML, and 9.2% (8/87) in patients with ALL. ***Conclusion.*** The higher rate of infectious deaths in leukemia compared to that reported in high-income countries, suggests that improvements in infection care and prevention, including consistent access to rapid hospitalization, diagnostics and antibiotics; and standardizing quality of patient care are necessary to improve as well as survival in patients with leukemia in Morocco. Pediatr Blood Cancer © 2013 Wiley Periodicals, Inc.

Key words: ALL; AML; infections; leukemia; low-income countries; support care

INTRODUCTION

In high-income countries (HIC), pediatric cancer is the leading cause of death from illness in children and young adults [1] and the third most common cause of potential years of life lost after breast and lung cancer [2]. Clinical trials over the last few decades have improved survival rates in HICs to 80%, and decreased death rates from toxicity to below 5% [3].

In contrast, less is known about the epidemiology of pediatric cancer in middle-income countries (MIC) and low-income countries (LIC). Studies have shown a lower incidence of cancer in LIC as compared to HIC, possibly due to under diagnosis and under registration [4]. It is estimated that approximately 160,000–200,000 children in MIC and LIC develop cancer each year [1]. Hematopoietic malignancies, including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) account for the largest proportion of childhood cancer.

In HICs, patients with acute leukemia have a high incidence of infection. Febrile neutropenia is assumed to be infection until proven otherwise, and is the second most common reason for hospital admission among children with cancer. It is a cause of significant morbidity in children and young adults with cancer [5]. According to the Infectious Diseases Society of America, greater than 80% of patients in the US with hematologic malignancies will develop fever during at least one chemotherapy cycle. In HICs, mortality from febrile neutropenia has decreased from 30% in the 1970s to 1% in the late 1990s [5]. In MIC/LICs, febrile neutropenia and infection still pose a significant issue for the survival of patients with acute leukemia. Studies from India have documented infectious complications as being responsible for over 60% of deaths in children with ALL [6].

Morocco, considered a lower middle income country by the World Bank [7] and ranked 125th out of 178 countries on the human development index [8], has four pediatric cancer units with 64 total pediatric oncology beds and 53 day beds as of 2012. Access to medications, chemotherapy, and blood products are considered ''limited,'' defined as inconsistent access or a long wait for results. Postulated 5 years survival rates for all causes of childhood cancer in Morocco was 30%, as compared to 5–10% in low income countries such as Bangladesh and Tanzania, or 40–60% in other middle income countries such as Egypt or Venezuela, based on data from hospital cancer registries) [9].

Few studies have described the epidemiology and outcome of infections in pediatric cancer patients in LICs/MICs. Our primary objective was to describe the incidence of febrile illness with or without documented infection in children and young adults treated for AML and ALL in two centers in Rabat and Casablanca during 2011. We aimed to characterize the febrile illnesses by describing phase of leukemia treatment, evidence of neutropenia, number of hospitalized and febrile days, clinical and microbiologic characteristics of the infections, antibiotic therapy, and associated mortality from these infections in leukemia patients.

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Grant sponsor: University of California, San Francisco (UCSF) Global Health Pathway; Grant sponsor: Mildred V. Strouss Chair in Translational Oncology, the Campini Foundation and Conner Research Fund at UCSF.

Conflict of interest: Nothing to declare.

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Received 13 June 2012; Accepted 16 September 2012

DOI 10.1002/pbc.24365
Published online in Wiley Online Library (wileyonlinelibrary.com).

METHODS

Patients/Setting

The study period was January 1 though December 31, 2011, and the study population consisted of all children and young adults <30 years of age who were newly diagnosed with acute leukemia during this study period at the Hôpital 20 Aout in Casablanca and the Hôpital des Enfants in Rabat, Morocco. The two main pediatric oncology units in Rabat and Casablanca have a working partnership with researchers and clinicians from St. Jude Children's Research Hospital and UCSF. Though these sites do have AML and ALL rates that are consistent with the rest of the region, there have been an unusually high proportion (up to 27% in children) of the t(8;21) AML subtype. This subtype of AML has favorable survival outcomes as compared to other subtypes of AML; for this reason, the hospitals have adopted an aggressive treatment protocol with a curative intent for these patients [10].

Patients were excluded if they were lost to follow up before any treatment was initiated or if their chart was not retrievable from medical records. Requirement for informed consent was waived due to the retrospective nature of the study with de-identified subjects. This study was reviewed and approved by the institutional review board at UCSF and the Ethics Committee in Morocco.

Chemotherapy Protocol

Patients with ALL were stratified into high and standard risk treatment groups, determined by initial white blood cell count, age, central nervous system (CNS) involvement, and corticosteroid response. All patients started with 7 days of pre-phase steroids, followed by induction, consolidation, intensification, interphase, and second intensification, followed by standard maintenance. The high risk therapy was similar to the BFM regimen widely utilized in Europe and North America [11], using prednisone, vincristine, daunomycin, L-asparaginase, doxorubicin, cyclophosphamide, cytarabine, high-dose methotrexate, and 2 years of oral maintenance therapy with monthly vincristine and dexamethasone pulses the first year and daily oral 6-mercaptopuruine and weekly methotrexate. The patients with standard risk ALL received a less intensive version of this protocol, without cyclophosphamide in the initial consolidation and without any high-dose methotrexate. All patients received standard CNS prophylaxis with intrathecal therapy. Patients with AML were stratified by age and cytogenetics into favorable or standard risk and received two induction cycles and two or three consolidation cycles, using the following drugs: high-dose cytarabine, daunomycin, etoposide, mitoxantrone, and L-asparaginase. Patients with AML were typically admitted to the hospital for treatment, while patients with ALL were primarily treated at a day hospital. Growth factors were not used, and prophylactic antibiotics were not used except for trimethoprim-sulfa for patients with ALL at the Rabat facility.

Study Design

This was a retrospective cohort study. The collaborating institutions provided a list of eligible patients diagnosed with acute leukemia to the investigator. The subject's charts were retrieved from medical records. Each patient's handwritten chart was evaluated for patient demographics, leukemia therapy and febrile episodes. Fever was defined as an oral temperature of 38.0°C or higher on two or more occasions during a 12 hours period or an oral temperature of 38.3°C or higher on a single occasion. For each febrile episode, information was collected including absolute neutrophil count, antibiotic regimen, hospital days, and number of febrile days. Documentation of microbiologic and clinical etiology was recorded, including radiographic and symptomatic evidence of infection. When possible, blood culture results were verified with the microbiology laboratory. Adverse events were recorded, including intensive care unit (ICU) admission and death. Each death was reviewed with co-investigators and categorized into deaths possibly, probably or definitely related to infection and deaths related primarily to leukemia.

RESULTS

During the study period, 185 patients were diagnosed with leukemia (62 AML, 123 ALL). After excluding patients for abandonment prior to therapy or unobtainable records, there were a total of 166 patients included. Table I illustrates the characteristics

TABLE I. Characteristics of Evaluable Patients (n = 166) Diagnosed With Acute Leukemia in Casablanca and Rabat in 2011

	AML			ALL		
	Casablanca, N (range)	Rabat, N (range)	Total, N (range)	Casablanca, N (range)	Rabat, N (range)	Total, N (range)
Patients[a]	29	22	51	47	68	115
Median age (years)	19 (1–28)	8 (0–15)	13 (0–28)	13 (1–29)	4 (1–14)	5 (1–29)
Median WBC ($\times 10^6$/L)	36.5 (3.3–453)	32.9 (3.2–202)	36.5 (3.2–453)	17.3 (1.8–272)	17.1 (1.2–884)	17.1 (1.2–884)
AML with t(8;21)	8	1	9	—	—	—
Pre-B-ALL	—	—	—	31	47	78
T-ALL	—	—	—	18	13	31
Patients with insurance	5/18	7/19	12/37 (32%)	5/31	20/87	25/115 (21.7%)
Median BMI[b]	20.7	16.6	18.3	16.5	16.4	16.5
Total febrile episodes	87	54	141	32 ip, 2 op	55 ip, 18 op	87 ip, 20 op

AML, acute myeloid leukemia; WBC, white blood cell count at diagnosis; ALL, acute lymphoblastic leukemia; BMI, body mass index; ip, inpatient, op, outpatient. [a]Does not include patients who were excluded due to: chart irretrievable, patient lost to follow-up after diagnosis, patient died before any documentation made; [b]BMI does not include age-adjusted percentiles; after age adjustment, 17% had BMI at or below the tenth percentile.

TABLE II. Characteristics of Inpatient Febrile Episodes in Patients With AML*

	Casablanca	Rabat	Total
Total number of episodes	87	54	141
Median number per patient (range)	3 (0–7)	3 (0–7)	3 (0–7)
Fever onset by phase of therapy[a]			
Pre-induction	15	11	26
Induction	32	21	53
Post-induction	40	19	59
Lowest ANC at time of febrile episode[b]			
0–200	63	42	105
200–500	7	4	11
>500	12	8	20
Median febrile days (range)	6.5 (1–32)	5 (1–21)	6 (1–32)
Median hospital days (range)	28 (7–76)	13 (6–36)	25 (6–76)
Median days on antibiotics (range)	13 (1–37)	9 (2–34)	11 (2–34)
Clinically localized source only	22	18	40
Microbiological evidence only	1	3	4
Clinical and microbiologic evidence	15	8	23
Total infectious fevers	38	29	67
Fever of undetermined origin	49	25	74

AML, acute myeloid leukemia; ANC, absolute neutrophil count. [a]This refers to phase of therapy when patient developed initial fever. In three patients phase of therapy was not retrieved; [b]In five episodes, the ANC was not retrieved or documented; *All numbers in Tables II–IV refer to the number of febrile episodes.

of this population, both in aggregate and divided by institution. Since the hospital in Rabat is a children's hospital and the hospital in Casablanca treats both adults and children, the median age of patients in Casablanca was significantly older than in Rabat. Additionally, there were more patients with AML in Casablanca, and more patients with ALL in Rabat, presumably because of the age difference in the two populations. Only 37/152 (24%) patients had insurance, a proxy for socioeconomic status. Patients in almost all groups were underweight, with the median Body Mass Index (BMI) in most groups on admission less than 18.5 (normal range 18–25). After correction for age, 28 patients (17%) were at or below the 10th percentile. Other co-morbidities in this population included one case each of epilepsy, lupus, asthma, history of meningitis, and HBV. There were eight cases of consanguinity.

Febrile episodes in patients with AML (Table II) were more common than in ALL (Table III), both in absolute number and number per patient, with a median of three febrile episodes per patient for AML compared to one for ALL. For both groups of patients, fever was most common at diagnosis before therapy (pre-induction) and in the early phases of treatment, but in AML patients fever was associated with severe neutropenia (ANC < 200) in 74% of episodes, while in ALL patients the

TABLE III. Characteristics of Inpatient Febrile Episodes in 115 Patients With ALL (Inpatient Only)

	Casablanca	Rabat	Total
Total episodes	32	55	87
Median number per patient (range)	1 (0–3)	1 (0–3)	1 (0–3)
Fever onset by phase of therapy[a]			
Pre-induction	14	26	40
Induction	2	12	14
Consolidation/intensification	10	13	23
Interphase	4	3	7
Lowest ANC at time of febrile episode			
0–200	13	14	27
200–500	0	8	8
>500	17	28	45
Median febrile days (range)	4 (1–26)	2 (1–23)	3 (1–26)
Median hospital days (range)	9 (1–39)	8 (1–52)	9 (1–39)
Median days on antibiotics (range)	8 (0–33)	7 (1–25)	8 (0–33)
Clinically localized source only	7	21	28
Microbiologic evidence only	3	3	6
Clinical and microbiologic	0	3	3
Total infectious fevers	10	27	37

ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count. [a]Refers to phase of therapy when patient first noted to be febrile.

TABLE IV. Results of Microbial Cultures

	AML		ALL		
	Casablanca	Rabat	Casablanca	Rabat	Total
Blood cultures taken (positive/total)	15/52	10/24	3/14	2/10	30/100
Urine cultures taken (positive/total)	0/13	1/13	0/4	4/5	5/35
Wound cultures taken (positive/total)	0/0	0/2	0	0/3	0/5
Gram-positive[a]	10 CNS [9] *Enterococcus* [1]	5 CNS [4] MRSA [5]	2 CNS *Corynebacterium*	0	17
Gram-negative[a]	1 *E. coli* ESBL	5 *Enterobacter* [3] *Klebsiella*[c] [2]	0	4 *E. coli* *Enterobacter* *Klebsiella*[f] *Pseudamonas*	10
Yeast[a]	2 *C. albicans* *C. parapsilosis*	0	0	2[g]	4
Polymicrobial/other[a]	2[b]	1[d]	1[e]	1[h]	5

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MRSA, methicillin resistant *Stapholococcus aureus*; *E. coli*, *Escherichia coli*; ESBL, extended spectrum beta lactamase; CNS, coagulase negative *Staphylococcus*. [a]Refers to blood culture unless otherwise noted; [b]One culture had coagulase negative staph and *Acinetobacter*, one culture grew coagulase negative *Staphylococcus* and *Candida albicans*; [c]One *Klebsiella* sample was obtained from a urine culture; [d]*Staphylococcus epidermidis* and *Streptococcus pneumoniae*; [e]Malaria identified on blood smear, as well as *Streptococcus viridan*; [f]*Escherichia coli*, *Enterobacter cloaceae*, and *Klebsiella pneumoneae* all from urine cultures; [g]One patient had budding yeasts in stool, yeast in blood smear (not cultured); [h]Urinary catheter: *Staphylococcus hemolyticus*, urethral probe: *Candida albicans*.

majority of inpatient fevers (56%) occurred in the setting of ANC >500. There was also a higher median number of febrile days per episode for patients with AML versus ALL (median 6 vs. 3) and a higher number of antibiotic days per febrile episode for patients with AML than ALL (median 11 vs. 7.5). Antibiotic treatment was delayed more than 24 hours in 44/228 febrile episodes (19%).

Only limited data regarding the outpatient febrile illnesses were available. Twenty outpatient febrile illnesses were recorded, and only one of these illnesses had a microbiologically identified source of infection in the records (*Streptococcus* species not otherwise specified). Because of insufficient documentation, these data are coded separately in Table I, and not included in Tables II–IV, where all results refer to febrile episodes that were treated in the hospital.

Among patients with AML, 26 febrile episodes occurred before starting chemotherapy, 53 occurred during induction, and 59 occurred during consolidation. Among those patients with ALL, 40 episodes occurred before starting therapy, while 14 occurred during induction, 23 during consolidation, and seven during interphase (Tables II and III).

In all 228 inpatient febrile episodes, 107 episodes were associated with a clinically or microbiologically identified source of infection, while 121 (56%) febrile episodes had no identified source. The most common clinically identified sources of fever included radiographically identified pulmonary infiltrates (n = 16) or respiratory symptoms (n = 11), and mucositis (n = 26). Other localized sources of infection included; wound or anal fissure (n = 9), clinical evidence of abdominal infection, clinical evidence of central line infection (n = 1), symptoms suggesting meningitis (n = 2), urinary symptoms (n = 2). In addition, in 19 febrile episodes there were multiple suspected sites of infection, most commonly mucositis and pulmonary infection (n = 12). Of note, there were three episodes of positive urine cultures in patients with dysuria but no fever; these were not included in the tables.

Microorganisms were isolated in 36/140 cultures (Table IV), including blood (n = 30), urine cultures (n = 5), and stool (n = 1). There were 27 bacterial, four fungal and five polymicrobial cultures. The most common organism grown from blood was coagulase negative staphylococcus (n = 14) followed by gram-negative bacteria (n = 10).

Antibiotic therapy was administered during all but 10 of the 228 febrile episodes. In 35 episodes, patients were treated with one antimicrobial agent such as a cephalosporin or amoxicillin derivative, while combination antibiotic therapy was used in the others. The most common antibiotic regimen started for fever in neutropenic patients was a cephalosporin (ceftriaxone or ceftazidime) alone or with an aminoglycoside (typically amikacin or gentamicin). After several days of fever, the patient would often be switched to vancomycin and imipenem with or without an antifungal agent. The antibiotic regimen was changed in 103 episodes (73 episodes in patients with AML, 30 in patients with ALL) usually due to a continued fever. Antifungals, including amphotericin B, fluconazole, and voriconazole were used in 62 episodes (50 episodes in patients with AML, 12 in patients with ALL). Vancomycin was used in 83 episodes (68 episodes in patients with AML, 15 episodes in patients with ALL).

Thirty-five patients died during this 1-year period, including 20 with AML and 15 with ALL. Infection either caused or was a contributing factor in 24 (69%) of these deaths (Table V, Fig. 1), including 11 patients with fever but no identified source, nine patients with a clinical diagnosis of infection in addition to fever, and four patients with a microbiologically identified source. The clinically identified infection-related deaths included seven with

TABLE V. Deaths in Patients With Acute Leukemia Related to Infection or Fever Without Other Definite Cause

Age (yr)	Sex	Dx	Infectious etiology	Chemotherapy phase when fever began	Length of final hospital stay	Onset of fever in hospital	Microbiological evidence	Anti-fungal therapy
23	F	AML	Pneumonia on CXR	Consolidation #2	23 days	Yes	Acinetobacter and coag negative staph in blood	Yes
3	M	AML	Pneumonia on CXR	Pre-induction	11 days	Yes	Cultures negative	No
15	F	AML	Undetermined	Pre-induction	6 days	Yes	n.d.	No
16	M	AML	Undetermined	Induction	17 days	Yes	Cultures negative	No
28	M	AML	Pneumonia on CXR	Pre-induction	49 days	Yes	Cultures negative	No
8	F	AML	Undetermined	Induction #2	Unknown (died at home)	Yes	Cultures negative	Yes
1	F	AML	Undetermined	Pre-induction	1 day	No	n.d.	No
23	F	AML	Undetermined	Induction	30 days	Yes	n.d.	Yes
17	F	AML	Undetermined	Pre-induction	1 day	No	n.d.	No
12	M	AML	Sepsis, pneumonia on CXR	Induction	14 days	Yes	Cultures negative	Yes
5	M	AML	Undetermined	Pre-induction/Induction	7 days	No	n.d.	No
13	F	AML	Pneumonia, alveolar opacities on CT scan	Pre-induction/Induction	Transferred	No	Blood: *Staph saphrophyticus*	Yes
0.5	M	AML	Undetermined	Pre-induction	9 days	No	Cultures negative	No
12	F	AML	Pneumonia on CT	Induction #2	14 days	No	n.d.	No
1	F	AML	Undetermined	Pre-induction	22 days	No	Ear swab: *Klebsiella* ESBL	No
8	F	AML	Fever with sepsis syndrome	Consolidation	17 days	Yes	Cultures negative	No
6	F	ALL	Undetermined	Pre-induction	Unknown (died at home)	No	Cultures negative	No
29	F	ALL	Undetermined	Relapse	20 days	Yes	n.d.	Yes
3	F	ALL	Pneumonia on chest CT	Induction	13 days	No	Cultures negative	Yes
11	M	ALL	Urosepsis	Pre-induction	14 days	No	Urine: *Enterococcus*	No
6	F	ALL	Mucositis	Post-intensification	6 days	No	n.d.	No
5	F	ALL	Mucositis	Intensification	Unknown (not recorded)	No	Culture negative	No
3	M	ALL	Typhlitis	Intensification	Unknown (died at home)	No	n.d.	No
1	M	ALL	Undetermined	Pre-induction	1 day	No	n.d.	No

M, male; F, female; Dx, diagnosis; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CXR, Chest X-Ray; n.d., not done; CT, computed tomography.

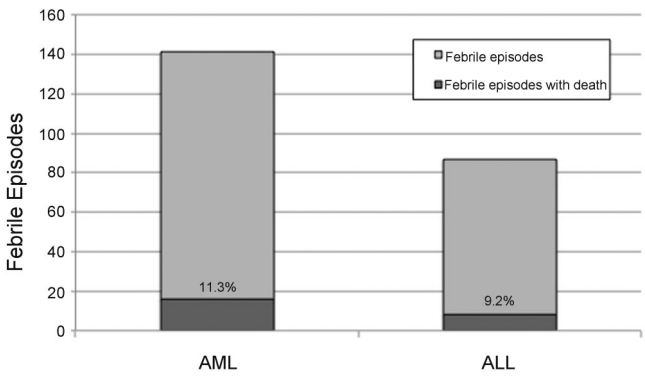

Fig. 1. Comparison of febrile episodes and mortality in patients with acute myeloid leukemia (AML; n = 51) and acute lymphoblastic leukemia (ALL; n = 115). Number of inpatient febrile episodes (gray bar) for AML, n = 141; ALL, n = 87. Number of febrile episodes associated with death (black bar) were AML, n = 16 (11.3%); ALL, n = 8 (9.2%).

pneumonia, two mucositis, one typhlitis, one urinary infection, and one sepsis syndrome. The four with identified micro-organisms were acinetobacter (blood), *Staphylococcus* (blood), *Klebsiella* (ear) and *Enterococcus* (urine). The rate of deaths per febrile illness was 11.3% (16/141) in patients with AML, and 9.2% (8/87) in patients with ALL. Among those with non-infectious causes of death, four were patients with AML and seven were patients with ALL. Within these 11 patients, all four patients with AML and two patients with ALL died before starting chemotherapy. Two patients with ALL died during induction, one died during interphase, and two died after relapse on palliative care. There were also two ICU admissions and four other patients who were candidates for ICU admission but were not admitted due to a lack of beds. All patients admitted to the ICU died.

DISCUSSION

This study aimed to describe the incidence of febrile illness and documented infection in children treated for acute myeloid

leukemia (AML) and acute lymphoblastic leukemia (ALL) in two centers in Morocco during 2011, as well as the etiologies and outcomes of these infections. The incidence of febrile illness in patients with AML, with a median of three episodes per patient in one year was similar to that of HIC, in accord with the fairly intensive therapy adapted from the MRC-UKAML10 study [12]. In one multicenter study in the UK [13], children with AML developed an average of 3.03 febrile episodes per patient over the course of one year. In this same study, children with ALL developed on average 2.04 episodes per patient, greater than the one episode per patient found in our study, possibly due to more intensive therapy or to more inpatient therapy of ALL patients in the UK.

Though the incidence of febrile illness was similar in Morocco, mortality from infection was much greater than in HICs, where mortality from febrile neutropenia in the 1990s was approximately 1% [5]. In a large UK phase III trial of intensive therapy for AML, only 5% of patients died during induction or consolidation from infectious causes [12]. In a German series, 2.6% of children died from toxicity (including infections) while being treated for ALL in a similar chemotherapy protocol to that used in Morocco [14]. In our study, 24 out of 166 (14%) patients died over the course of one year with infection as the primary or a contributing factor, including 29% of AML and 7% of ALL patients. The rate of deaths per febrile illness was also high, at 11.3% in patients with AML, and 9.2% in patients with ALL. Similarly to HIC, the infectious deaths in patients with AML occurred early, whereas in ALL several deaths occurred during delayed intensification or relapse. This may have corresponded with the times of most severe neutropenia in these illnesses.

Possible contributing factors to the high death rate associated with infection were co-morbidities and delayed access to antibiotics. We found few documented co-morbidities apart from low BMI in 17%, with no reported cases of HIV and only two possible cases of tuberculosis. Delays in antibiotic administration and in time to hospitalization may have been an important factor in the high infectious death rate. Although the precise time from fever onset to hospital admission and to antibiotic administration was not well documented, antibiotics were given >24 hours after fever onset in 44/228 episodes (19.3%). Additionally, there has been an ongoing severe hospital bed shortage in Casablanca, resulting in delays of 1–3 weeks from diagnosis of leukemia to admission. This likely added significant delays in antibiotic administration and played a large role in the high rate of early mortality. Access to prompt hospitalization and initiation of antibiotics are needed to reduce the death rate in this population.

In our study population, 40% of febrile episodes included clinical or radiographic evidence of infection while only 14.5% of episodes included microbiologic evidence of infection, leaving over half of febrile episodes without identified microbiologic or clinical source of infection (these numbers do not total 100% as some patients had both clinical and microbiologic evidence of infection). Additionally, blood cultures were recorded in only 44% of febrile episodes, leaving uncertainty about whether all microorganisms would have been identified. In contrast, in the Dommett study [13], while 41.1% of episodes similarly included clinical and/or radiologic evidence of infection, a much larger proportion, 42.3%, had microbiologic evidence, and 40% of febrile episodes had no identified microbiologic or clinical focus of infection (numbers do not add up to 100% as some febrile episodes had both clinical and microbiologic evidence). In other studies in HICs, microbiologic documentation can be as low as 16–20% [15,16], which is more consistent with our results. The limited data from LIC/MIC's is also consistent with our results. In one study in India [6], microbiologic evidence of infection was present in less than 20% of patients. However, the low incidence of proven microbiologic source raises the question of whether cultures were taken every time this was indicated and whether the laboratory support was adequate.

Specific microbiological causes of febrile neutropenia vary from institution to institution. However, some patterns in HICs have been described in the literature. In general, gram-positive cocci, including coagulase-negative *Staphylococci* are the most common organisms found on blood culture, and there are increasing rates of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Enterococcus* (VRE) isolated as infectious etiologies [17,18]. *E. coli* and *Pseudomonas* are also important causes of infection [15]. In our study, we found the coagulase negative staphylococcus was the most commonly isolated microbe, followed by gram-negative bacteria. The high rate of coagulase negative staphylococcus, along with reports of the need to improve hygiene techniques for blood draws, suggested that skin contamination may be occurring, and gram-negative bacteria may comprise the true majority of infections [19]. Additionally, in Morocco central lines are used infrequently, and location of blood draw (central vs. peripheral) is not documented, thus it was difficult to assess the rate of contamination. According to the physicians in Casablanca, coagulase negative staphylococcus is typically treated when two or more cultures are positive in a 12-hour span.

Other limitations to our study included incomplete documentation, particularly in the outpatient setting, as well as difficulty interpreting handwritten charts even with help from other staff members. In addition, nursing charting of vital signs and medications was irregular, so relation of fever to exact start date and type of antibiotic started was not always recorded. Certain data such as duration of neutropenia or precise time from fever onset to first administration of antibiotic were incompletely documented and therefore not collected. Likewise, documentation of central lines was incomplete, and therefore those data were not included in our analysis. Additionally, though the microbiology laboratories at both sites were consulted, we were unable to verify all of the culture results with both laboratories. Therefore, if a test was performed but the result not recorded in the physical chart and the results were not recorded with the notes, it may have been missed.

According to a recent report on the pediatric oncology center in Rabat (M. Caniza, personal communication), new priorities among the hospital staff include improving the hygiene of the hospital, including hand hygiene and compliance, and requesting better access to microbiology laboratories, as the hospital laboratory has limited supplies and blood cultures are sent out of the hospital to a private commercial laboratory service for analysis. This report also described the intermittent access to broad-spectrum antibiotics and antifungals as a limitation to patient care. In 2011, access to amphotericin B was limited, though other antibiotics were more consistently available than in previous years.

Though the rate of infection in children with acute leukemia in Morocco is similar to that seen in HICs, our investigation

shows evidence of the high mortality due to febrile illnesses in patients with AML and ALL in Morocco compared to HICs. These data highlight the potential for improvement in survival through initiatives to decrease delay in initiation of antibiotics after fever onset and increase hygiene, laboratory access and expertise, antibiotic availability, and nursing education and training.

ACKNOWLEDGMENT

This work was supported in part by the University of California, San Francisco (UCSF) Global Health Pathway, and the Mildred V. Strouss Chair in Translational Oncology, the Campini Foundation and the Conner Research Fund at UCSF. Special thanks to Madhavi Dandu and Chris Stewart from UCSF Global Health as well as the data managers in Casablanca and Rabat (Saida El Mouazzen, Khadija Loumatine, Dalila Fekni). Additionally, this work was aided by Naima El Madaghri and Maha Soussi, laboratory staff. Special thanks also to Mhamed Harif for providing information about the hospital capacity in Morocco.

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