INTRODUCTION

Algorithms for antibiotic therapy in febrile neutropenic patients derive primarily from the randomized trials of Pizzo et al. carried out in the 1970s and early 1980s [1–3]. Patients are classified as low and high risk based on duration of fever and neutropenia, comorbidities, and therapeutic strategies were examined.

Results. Twenty-seven prospective trials and five reviews were identified. The child with cancer and low-risk febrile neutropenia is clinically well and afebrile within 24–96 hr of antibiotic therapy and has evidence of marrow recovery with a rising phagocyte count. Disqualifying comorbidities include leukemia at diagnosis or in relapse, uncontrolled cancer, age under 1 year, medical condition(s) that would otherwise require hospitalization and social or economic conditions that may potentially compromise access to care or compliance. Therapeutic strategies include parenteral or oral antibiotics in the hospital with early discharge or parenteral antibiotics in the outpatient setting followed by oral or parenteral therapy and daily reassessment. Although as many as 25% of low-risk patients require modification of therapy and/or hospitalization, life-threatening or fatal infection is exceptional. Conclusion. One-third to one-half the children with febrile neutropenia are at low-risk of serious infection. In the context of clinical trials, they can be safely managed with inpatient or outpatient strategies that maintain close follow-up and reduce the burden of antibiotic therapy. Adoption of these alternative strategies as the standard of care should proceed with caution guided by written protocols. Med Pediatr Oncol 2002;39:77–85.

Key words: febrile neutropenia; childhood cancer

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comorbidities, diagnoses or therapeutic strategies that warrant consideration, nor do they address the special circumstances of children [25]. Many of the published studies include both children and adults. There are, however, age-related differences in type, site, and course of underlying cancer and in outcomes of empiric antibiotic therapy [26]. Pediatric patients have a lower incidence of bacteremia, shock, and death from infection and in many instances are subjected to more intensive treatment protocols with curative intent [26].

In this report, we re-examine recent risk-assessment models and prospective pediatric trials in which low-risk patients receive alternative antibiotic therapy, and we propose an evidence-based algorithm for classifying and managing patients that may serve for future trials of alternative strategies.

METHODS AND MATERIALS

Studies were identified using Medline and Pub Med databases, searching by fever and neutropenia, prospective or feasibility studies, ages 0–18 and pediatric cancer. The references of these studies were also searched. Twenty-seven prospective trials and five reviews that include pediatric cancer patients were identified. The results are organized in three categories: (1) those defining comorbidities; (2) those examining duration of fever and absolute neutrophil count and/or absolute monocyte count (AMC) as variables and; (3) those evaluating alternatives to standard antibiotic therapy. Outcomes were assessed in terms of success or failure as defined by the investigators.

RESULTS

Comorbidity

Among adults with febrile neutropenia, factors other than fever and ANC correlate with treatment failure, life-threatening infection, and death [13]. These factors are called comorbidities. In the initial report of Talcott et al., comorbidities were inpatient status at time of febrile neutropenia, cancer that is uncontrolled, and any other medical problem that otherwise requires hospitalization [13]. There is now a long list of comorbidities that characterize a pediatric patient with febrile neutropenia as being at high risk of treatment failure or otherwise unsuitable for a low-risk strategy (Table I).

Many comorbidities involve complex medical management that would independently warrant hospital care. Serious infection such as sepsis, bacteremia, pneumonitis, severe mucositis, or signs of shock or compensated shock, dehydration, hypertension, respiratory distress or compromise, or failure of a major organ are universally acknowledged as predictors of potentially serious infection, modification of antibiotics and prolonged hospital stays [15,18,22,24,27–31]. Mucosal ulceration, vomiting, and diarrhea are comorbidities that increase risk of prolonged fever, infection, or complex medical management. Patients with advanced cancer are not low-risk. The cancer itself may impair their ability to control their infections and to recover from therapy-induced neutropenia. Palliative care programs are often managed with antibiotic regimens that suit the mutual goals of patients, parents, and staff. Patients who are allergic to antibiotics that could be given at home or cannot swallow or absorb oral antibiotics cannot take advantage of these options. Pediatric studies include time to travel from home to the hospital of less than 1 or 2 hr and parenteral reliability as essential features for maintaining the safety of low-risk strategies [31].

Information regarding the impact of a number of important demographic features such as age and underlying cancer is limited. Infants have been excluded from some studies, and where they are included, their numbers are too small to allow any recommendation. Two major randomized studies of oral antibiotic therapy are limited to patients over age 5 years [20,21]. Age over 5 years may increase compliance and may lessen the hypothetical risk of joint injury associated with quinolones, the most
common alternative for oral or outpatient gram-negative antimicrobial coverage. Pappo and Buchanan and Jones et al. specifically cite infancy as a risk factor in pediatric cancer patients [32,33].

Not explicitly excluded in most pediatric studies are patients treated with dose-intensive therapies such as those used to treat acute myeloid leukemia (AML), recurrent acute lymphoblastic leukemia (ALL), and disseminated lymphomas or neuroblastoma. In these settings, the duration of neutropenia is rarely less than 10 days even with hematopoietic growth factors. Recent therapies for AML have been associated with an infectious mortality of 10% or higher [31–36]. High dose Ara-C containing regimens have also been associated with high infectious mortality particularly from Streptococcus viridans or fungi and cannot be considered low-risk. Stem cell transplant has not necessarily been a criterion for risk-stratification, but the numbers of pediatric patients in published series is small and the populations heterogeneous. The data are insufficient to support managing these patients as low-risk out of the context of a clinical trial.

A number of studies in adults have identified leukemia and metastatic lymphoma as a high-risk feature. Most pediatric studies identify leukemia in relapse as a risk factor [8,37]. Jones et al. find a tight correlation between the diagnosis of leukemia in relapse or at diagnosis and failure of early discontinuation of antibiotics [8]. In patients with ALL in induction or in relapse, failure rate was 74% when the ANC was zero, 69% at an ANC < 100 × 10⁹/L, and 38% at < 200 × 10⁹/L. In those with solid tumors, antibiotics could be discontinued safely at an ANC of > 100 mm³ [8]. In contrast, a study of all febrile neutropenic patients, Lucas et al. found a 57% failure rate in patients with leukemia at relapse or diagnosis and a 45% rate in 56 patients with these diseases in remission. However, both rates are higher than in most other studies because the patients were not risk-stratified for other comorbidities [9]. Wehl et al. analyzed 19(2.3%) fatalities among 603 episodes of febrile neutropenia [38]. Thirteen were causally linked to infection, 12 of the 13 were in the 297 episodes involving patients with leukemia or lymphoma or other hematologic disorders, and one was in a child with stage IV neuroblastoma not in remission [38]. In contrast, 6 deaths among 306 patients with solid tumors were attributed primarily to tumor progression.

In the only prospective multicenter evaluation of risk factors associated with serious bacterial infection (SBI) in of febrile neutropenia, Santolaya et al. address several of the controversial comorbidities at presentation [37]. All patients received standard parenteral, broad spectrum antibiotics in the hospital. In univariate analysis, C-reactive protein (CRP) ≥ 90 mg/L, hypotension, relapse of leukemia, platelets ≥ 50,000 × 10⁹/L, and chemotherapy within 7 days were significantly associated with invasive bacterial infections whereas ANC or AMC < 100 × 10⁹/L were not. In the absence of any risk factor, SBI occurred in 2% of episodes, with one risk factor, 22%, and in the presence of 2 or more factors, 48%. Elevated CRP was the single strongest risk factor carrying a 38% risk of SBI. In contrast neither Buchanan et al. nor Preis et al. found elevation of CRP to be sufficiently sensitive or specific for clinical use [12,15].

A probing history of present and recent past illness thorough physical examination and complete blood count identify most of the comorbidities listed in Table I. Knowledge of the protocol is necessary to predict the duration of neutropenia, and experience with the patient and family allow assessment of resources and compliance.

### Absolute Neutrophil Count, Absolute Monocyte Count, and Fever

A patient with a probable duration of neutropenia > 7–10 days is at high-risk for treatment modification and treatment failure [1–3,38], as is any patient whose fever does not resolve promptly [8,9]. The initial studies of Pizzo et al. [1–3] identified three subsets of patients whose fever resolved within 7 days. First were those who had an ANC greater than 500 × 10⁹/L and who were afebrile on or before day 7. Antibiotics were safely discontinued in these patients as soon as the neutrophil count reached 500 × 10⁹/L. Second were those who were well and afebrile on day 7 but continued to have a neutrophil count of < 500 × 10⁹/L. Discontinuation of antibiotics on day 7 led to failure in 41% [1,2]. Third was a group who were afebrile and stable but had persistent neutropenia on day 14 [3]. Discontinuation or continuation of antibiotics was associated with recurrent fever in one-third of the patients. Groups 2 and 3 entailed a minimum of 7 days of observation and antibiotic therapy. Their high incidence of failure disqualified them for consideration of low-risk therapy [3].

The high failure rates in the latter two groups may have been a result of suppression of flora by prolonged antibiotic therapy followed by exuberant recovery when antibiotics were stopped. Hence, some potentially low-risk patients may have been rendered high-risk by virtue of prolonged exposure to antibiotics. For this reason, a number of investigators examined early discontinuation of antibiotics and/or discharge in clinically well patients. Table II lists five prospective, observational trials in children with cancer whose parenteral antibiotic therapy or hospital stay was terminated before the ANC reached 500 × 10⁹/L. Eligibility criteria varied among the studies in Table II, but absence of fever and of serious bacterial infection were common to all. Failure was variously defined as recurrent fever, recurrent hospitalization,
development of bacteremia, sepsis, or death. The proportion of patients considered low-risk ranged from 40 to 84% of all children with febrile neutropenia. Failure rate ranged from 0 to 47%. Most failures consisted of hospitalization for persistent or recurrent fever usually without serious or documented infection. However, in the first published prospective trial two deaths occurred in patients deemed low-risk, both with an advanced state of the primary cancer who did not even have neutropenia at the time of discharge but whose ANC was falling [4].

Comparisons of failure rate within and across low-risk studies show a consistent trend for more failures in patients with an ANC < 100 × 10^9/L or with an ANC that is falling at the time of discharge or discontinuation of antibiotics (Table II). Summarizing the results of four consecutive studies involving 555 low-risk episodes discharged with an ANC < 500 × 10^9/L, Aquino noted that 32 of the 38 failures were in patients with no evidence of marrow recovery [22]. Cohen et al. found that a decline in ANC, ANC of < 100 × 10^9/L or ≤ 25% rise in APC were each predictors of recurrent febrile neutropenia and readmission (Table I) [39]. Griffin et al. showed that rise in total white blood cell count, platelet count, and monocytes anticipate an ANC of 500 < 100 × 10^9/L by about 4 days and were all harbingers of marrow recovery [5].

In those studies that specifically address an ANC or AMC of zero, total absence of phagocytes is consistently associated with a higher failure rate [22,39,40]. Three studies in Table II examined monocyte count: there were more failures when the AMC was less than 100 × 10^9/L than when it was higher [8,22,40]. While the results in Table I do not clarify whether AMC is a better predictor than ANC of when one can safely discontinue parenteral antibiotics, AMC seems to be an excellent indicator of marrow recovery and may identify a subset of patients who do not need hospitalization.

Based on these observations, Rackoff et al. developed a predictive model using AMC and temperature as variables (Table III) [10]. Among patients otherwise at low-risk at the time of presentation of fever and neutropenia, an absolute monocyte count < 100 × 10^9/L and fever > 39°C conferred a 19% risk of bacteremia while an AMC > 100/ mm^3 was not associated with any positive blood cultures regardless of the degree of the fever. Of note, in only 17% of 115 episodes was the AMC > 100/ mm^3. In a validation study of this model, while fever did not emerge as a variable (Table III) [28], monocyte count remained a good predictor of serious bacterial infection. In contrast, Santolaya et al. found that neither fever > 39°C nor monocyte count at presentation were good predictors [37]. However, the patient population in that included patients with numerous comorbidities.

Although Pizzo et al. recommended empiric antifungal therapy after 7 days of fever, 48 hr of persistent fever may be sufficient to define a high-risk patient. For example, among 509 episodes of pediatric febrile neutropenia, 10 patients required admissions to the ICU [9]. Nine of the ten were among the 177 episodes where both fever and ANC < 100 × 10^9/L persisted for more than 48 hr. Two of the nine patients died. Recent prospective

**TABLE II. Observational Studies Retrospectively Correlating Failures of Early Discharge or Discontinuation of Antibiotics With Neutrophil or Monocyte Count in Low-Risk Pediatric Patients With Febrile Neutropenia**

<table>
<thead>
<tr>
<th>Episodes</th>
<th>ANC &lt; 100 × 10^9/L</th>
<th>ANC &gt; 100 × 10^9/L</th>
<th>AMC &lt; 100 × 10^9/L</th>
<th>AMC &gt; 100 × 10^9/L</th>
<th>No ANC/AMC rise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Low risk</td>
<td>Total</td>
<td>Fail</td>
<td>Total</td>
<td>Fail</td>
</tr>
<tr>
<td>Mullen</td>
<td>114</td>
<td>77 (68)</td>
<td>11 (16)</td>
<td>3 (27)</td>
<td>66 (84)</td>
</tr>
<tr>
<td>Bash</td>
<td>131</td>
<td>82 (62)</td>
<td>29 (24)</td>
<td>4 (13)</td>
<td>53 (76)</td>
</tr>
<tr>
<td>Jones</td>
<td>213</td>
<td>83 (40)</td>
<td>16 (19)</td>
<td>10 (63)</td>
<td>67 (81)</td>
</tr>
<tr>
<td>Cohen</td>
<td>32</td>
<td>15 (47)</td>
<td>4 (26)</td>
<td>17 (53)</td>
<td>15 (0)</td>
</tr>
<tr>
<td>Wacker</td>
<td>88</td>
<td>74 (84)</td>
<td>36 (48)</td>
<td>2 (5)</td>
<td>38 (52)</td>
</tr>
</tbody>
</table>

ANC, absolute neutrophil count; AMC, absolute monocyte count; na, not available.

**TABLE III. Absolute Monocyte Count (AMC) and Fever as Predictors of Bacterial Infection in Low-Risk Pediatric Patients Presenting With Febrile Neutropenia**

<table>
<thead>
<tr>
<th>AMC × 10^9/L</th>
<th>Temperature</th>
<th>Bacteremia</th>
<th>SBI</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100 × 10^9/L</td>
<td>&lt; 39°C</td>
<td>19%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>&lt; 100 × 10^9/L</td>
<td>&gt; 39°C</td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 100 × 10^9/L</td>
<td>Any</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rackoff

| N = 115 | 75 | 21 | 19 |
| Bacteremia | 19% | 48% | 0% |

Klasson et al. [28]

| N = 227 | 143 |
| Bacteremia | 10% | 27% | 5% |
| SBI | 18% | 35% | 8% |

Validation set

| N = 36 | 33 | 46 | 57 |
| Bacteremia | 21% | 22% | 5% |
| SBI | 24% | 26% | 12% |

SBI, serious bacterial infection.
studies in low-risk patients remove the patient from low-risk therapy after 4 days of fever [15,18,22–24,27–31].

**Therapeutic Strategies**

Table IV lists the prospective trials that have investigated alternative antibiotic strategies in pediatric or mixed pediatric and adult patients with low-risk febrile neutropenia. There are three major variables: (1) the site of care, i.e., in the hospital, in an outpatient clinic or short-stay unit, or in the home; (2) the route of antibiotics, and (3) the duration of antibiotics. Definitions of low-risk vary among the studies.

Studies 1 and 2 investigated early discontinuation of antibiotics in the hospital. Both studies included patients with no evidence of marrow recovery and with some comorbidities listed in Table I. As described in the preceding section in Study 1, when the ANC was zero, the rate of recurrent fever was unacceptably high (38% with solid tumor to 74% with ALL) and was high in patients with leukemia in relapse regardless of ANC [8]. In Study 2, Santolaya et al. randomly assigned low-risk patients to continue or discontinue antibiotics after 72 hr regardless of counts [41]. Bacterial infection occurred in 9% of those who continued and 6% of those who discontinued antibiotics.

Studies 3–5 tested safety and efficacy of oral antibiotics in the hospital. Studies 3 and 4 were multi-institutional double-blind randomized comparisons of intravenous cephalosporins and oral ciprofloxacin/amoxicillin in low-risk hospitalized cancer patients 5–85 years old [20,21]. In both, there were many modifications to treat organisms that were recovered initially or that emerged and to deal with intolerance to the randomized regimens. In Study 3 [20], 2% of the patients randomized to the oral regimen and 4% of those randomized to the ceftriaxone died, but age, other comorbidities, and cause of death were not given. Study 5, a single institution trial, randomized low-risk patients after 48 hr to continue parenteral therapy or to switch to oral Cefixime [42].

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Dx</th>
<th>Age (year)</th>
<th>Design</th>
<th>Strategy</th>
<th>Setting</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al [8]</td>
<td>83</td>
<td>Any</td>
<td>2–23</td>
<td>OP</td>
<td>PBSA x 2 days→stop Hosp/Home</td>
<td>0–76%; 1 death</td>
<td></td>
</tr>
<tr>
<td>Santolaya et al. [41]</td>
<td>89</td>
<td>Any</td>
<td>2–11</td>
<td>PR</td>
<td>PBSA     Hosp</td>
<td>9% SBI</td>
<td></td>
</tr>
<tr>
<td>Kern et al. [20]</td>
<td>333</td>
<td>Any</td>
<td>5–85</td>
<td>RDBPC</td>
<td>CFTRXN   Hosp</td>
<td>16% modify; 4% death</td>
<td></td>
</tr>
<tr>
<td>Freifeld et al. [21]</td>
<td>232</td>
<td>Any</td>
<td>5–74</td>
<td>RDBPC</td>
<td>CIPRO/Amox Hosp</td>
<td>32% modify</td>
<td></td>
</tr>
<tr>
<td>Shenep et al. [42]</td>
<td>200</td>
<td>Any</td>
<td>1.3–19</td>
<td>RC</td>
<td>PBSA→PBSA Hosp</td>
<td>13% modify</td>
<td></td>
</tr>
<tr>
<td>Lau et al. [43]</td>
<td>23</td>
<td>Any</td>
<td>0.3–18</td>
<td>OP</td>
<td>PBSA→PO Abx ED/C</td>
<td>1% FUO</td>
<td></td>
</tr>
<tr>
<td>Paganini et al. [29]</td>
<td>154</td>
<td>Any</td>
<td>0.7–18</td>
<td>RC</td>
<td>PBSA→PBSA ED/C</td>
<td>1% FUO</td>
<td></td>
</tr>
<tr>
<td>Paganini et al. [30]</td>
<td>90</td>
<td>Any</td>
<td>0.9–16</td>
<td>RC</td>
<td>PBSA→PBSA ED/C</td>
<td>2% worsening</td>
<td></td>
</tr>
<tr>
<td>Cohen et al. [39]</td>
<td>32</td>
<td>Any</td>
<td>0.8–18</td>
<td>OP</td>
<td>PBSA→CIPRO ED/C</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Wacker et al. [40]</td>
<td>74</td>
<td>Any</td>
<td>2–12</td>
<td>OP</td>
<td>PBSA→stop ED/C</td>
<td>8% bacteremia; 8% FUO</td>
<td></td>
</tr>
<tr>
<td>Aquino [44]b</td>
<td>580</td>
<td>Any</td>
<td>0.16–20</td>
<td>OP</td>
<td>PBSA→CIPRO ED/C</td>
<td>3% FUO</td>
<td></td>
</tr>
<tr>
<td>Klassen [11]</td>
<td>88</td>
<td>Any</td>
<td>0.5–18</td>
<td>RDBPC</td>
<td>PBSA→PO Abx ED/C</td>
<td>1% FUO</td>
<td></td>
</tr>
<tr>
<td>Preis et al. [15]</td>
<td>64</td>
<td>Any</td>
<td>1–22</td>
<td>OP</td>
<td>PBSA→stop ED/C</td>
<td>14% FUO; 3% bacteremia; 3% fever</td>
<td></td>
</tr>
<tr>
<td>Mustafa et al. [18]</td>
<td>19</td>
<td>Any</td>
<td>2–15</td>
<td>OP</td>
<td>CFTRXN   OPT</td>
<td>19% FUO; rising CRP</td>
<td></td>
</tr>
<tr>
<td>Sahu et al. [45]</td>
<td>1,300</td>
<td>Any</td>
<td>2–15</td>
<td>OP</td>
<td>CFTRXN/Amik OPT</td>
<td>5% worsening</td>
<td></td>
</tr>
<tr>
<td>Karthaus et al. [23]</td>
<td>126</td>
<td>Any</td>
<td>0.5–72</td>
<td>OP</td>
<td>CFTRXN   OPT</td>
<td>6% SBI</td>
<td></td>
</tr>
<tr>
<td>Shenesh et al. [47]</td>
<td>42</td>
<td>Any</td>
<td>0.9–19</td>
<td>OP</td>
<td>BSAbx    ED→home</td>
<td>13% FUO; 6% SBI</td>
<td></td>
</tr>
<tr>
<td>Kaplinsky et al. [46]</td>
<td>50</td>
<td>Any</td>
<td>0.8–19</td>
<td>OP</td>
<td>CFTRXN   ED→home</td>
<td>14% FUO; 4% SBI</td>
<td></td>
</tr>
<tr>
<td>Aquino et al. [22]</td>
<td>45</td>
<td>ST</td>
<td>2–20</td>
<td>OP</td>
<td>CAZ→CIPRO OPT</td>
<td>4% SBI; 1% HZV; 2% NC</td>
<td></td>
</tr>
<tr>
<td>Mullen et al. [31]</td>
<td>73</td>
<td>ST</td>
<td>≥2</td>
<td>RC</td>
<td>CAZ→CAZ OPT</td>
<td>3% emesis; 3% worsening</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAZ→CIPRO OPT</td>
<td>10% fever; 5% emesis; 5% NC, other</td>
<td></td>
</tr>
<tr>
<td>Petrilli et al. [24]</td>
<td>116</td>
<td>ST</td>
<td>3–20</td>
<td>RC</td>
<td>CFTRXN   CIPRO</td>
<td>23% modify; 2% worsen</td>
<td></td>
</tr>
</tbody>
</table>

OP, observational prospective; PBSA, parenteral broad-spectrum antibiotics; ED/C, early discharge; RDBPC, randomized double-blind placebo controlled; RC, randomized controlled; PO Abx, oral antibiotics; CAZ, cefazidime; Amox-C, amoxicillin-clavulanate; CIPRO, oral ciprofloxacin; CFT, CFTRXN, ceftriaxone; OPT, outpatients; Hosp, hospital.

bAquino [44] reviews includes four separate studies by one team; there were two deaths in the initial study of Mullen et al. [4].
Failure as defined by microbiologically or clinically documented bacterial infection, recurrent fever or early discontinuation of randomized therapy occurred in 28% of those who continued parenteral therapy and 27% of those who switched. Oral therapy was deemed as safe and effective as parenteral therapy.

Studies 6–12 were studies of early discharge. Parenteral antibiotic therapy was initiated in the hospital; patients with evidence of marrow recovery were discharged before achieving an ANC of $500 \times 10^9/L$ \cite{43,44}, 97; \cite{11,29,39,40}. In Study 6, patients received oral antibiotics until the ANC reached $500 \times 10^9/L$ \cite{43}. In Studies 7 and 8, parenteral and oral continuation therapy were randomly compared \cite{29,30}. There was no apparent advantage to the parenteral route. Studies 10 and 11 also discharged patients early but prescribed oral antibiotics upon clinical indication only \cite{39,40,44}. Study 11 was a randomized controlled comparison of continuation of oral antibiotics or placebo in low-risk patients with no specific clinical indication for antibiotic therapy. In the placebo group, 3% returned with bacteremia and 3% with fever; in the control group, 14% had recurrent fevers. There are a total of 3 deaths out of 1,416 children in the studies of early discontinuation or early discharge \cite{4,8}. The three deaths occurred among the patients who were not low-risk because of advanced cancer \cite{4,8,44}. In recent studies that specify comorbidities, there have been no life-threatening or fatal complications \cite{18,23,45–47}.

Studies 13–18 (Table IV) evaluated parenteral broad-spectrum antibiotic therapy, usually once daily ceftazidime or ceftriaxone, in the outpatient setting. In Studies 12–16, the outpatient setting was a clinic or short-stay unit where the patient was observed for up to 24 hr followed by daily outpatient visits; in Studies 17 and 18, the patients were discharged from the emergency department to home \cite{46,47}. In the very large study of Sahu et al., medically stable Indian patients received ceftriaxone and amikacin plus oral antiviral or antifungal antibiotics as clinically indicated \cite{45}. The failure rate of 6% included patients with fever and neutropenia longer than 7 days; 34% of failures were for positive blood cultures with pseudomonas being the most common species. While the microbiological breakthrough rate was high, remarkably, there were no deaths. However, the authors acknowledge that follow-up was incomplete in some patients. In the other studies, 5–14% of the patients had antibiotic therapy modified because of positive cultures and/or were admitted to the hospital for persistent or recurrent fever or clinical deterioration. There were no serious complications in these patients.

In the final group of Studies 19–21, outpatient therapy began with either ceftazidime or ceftriaxone and continued with oral ciprofloxacin with or without amoxicillin-clavulanate \cite{22,24,31}. In Study 19, a feasibility trial involving 45 low-risk patients, three patients required admission for bacterial infection, one patient for zoster, and two for noncompliance \cite{22}. Studies 20 and 21 were randomized comparisons of parenteral and oral continuation therapy \cite{24,31}. Failure occurred in 4–25% of patients requiring modification of therapy for fever, intolerance, noncompliance with the oral regimen or other logistic problems. Clinical deterioration occurred in 5 of the 189 patients and was no more common in the oral regimen.

**DISCUSSION**

These studies show one-third to one-half or more of the children with febrile neutropenia associated with cancer chemotherapy are at low-risk of life-threatening or fatal infectious complications \cite{12,27,32,48–50}. The remainder consists of children with prolonged fever, prolonged neutropenia, and/or comorbid conditions requiring hospitalization and traditional care. In addition, there are insufficient data and infants or patients 1 month to 1 year from stem cell transplantation to support low-risk strategies outside of a study context.

The low-risk patient can be identified by a history elicited by a knowledgeable nurse or physician, physical examination and complete blood count (Fig. 1). If the child is clinically well and has no disqualifying comorbidities, he or she may be eligible to initiate therapy in the outpatient setting or to follow a low-risk strategy with oral or parenteral antibiotics in the hospital with expectation of early discharge. The *sine qua non* for early discharge is wellness and evidence of marrow recovery as evidence by a rising ANC or AMC. In patients with leukemia at diagnosis and in relapse on APC $\geq 100 \times 10^9$ and rising seems advisable. Continuation of oral antibiotics does not appear to be necessary except as indicated to treat minor bacterial infections.

Except for nine patients in the study of Petrilli et al. \cite{24}, the studies of outpatient therapy involve at least one parenteral dose of a broad-spectrum antibacterial antibiotic and hours of observation in a clinic or short-stay unit followed by daily reassessment. Continuation antibiotics may be oral or parenteral: failure rates are similar. While oral therapy is more convenient, it may invite noncompliance \cite{27}. In the outpatient setting, evidence of a serious bacterial infection, fever persistent for longer than 4 days, clinical deterioration, intolerance to the therapy, non-compliance or unfeasibility should prompt change to a standard inpatient strategy. Failure may occur in as many as 25% of patients. Failure rates of parenteral and oral continuation antibiotics are similar.

Finberg and Talcott warn that one cannot extrapolate from the collective data to assume that outpatient oral antibiotics will be safe, nor can we assume that these strategies are standard of care and can be administered.
outside of clinical trials [51]. There are no pediatric studies of outpatient oral antibiotics without at least one dose of parenteral therapy. In the combined pediatric and adult experience involving 5,208 pediatric and adult low-risk patients, there have been 87 deaths [48]. Of these deaths, 84 occurred in patients with advanced cancer or other comorbidities. Three were inpatients who fulfilled strict definitions of low-risk [48]. Mullen warns of the potential abuse of oral antibiotics by parents, patients, and staff who become so comfortable with outpatient therapy that they bypass the careful evaluation and follow-up that have assured the safety of alternative strategies in clinical trials [27]. Caution, written protocols, algorithms, and regular review of outcomes are essential.

CONCLUSIONS

This large body of prospective trials has defined the pediatric patient with cancer who has low-risk febrile neutropenia and has demonstrated the safety of strategies involving early discharge and/or outpatient therapy. Well-designed, randomized studies in pediatric patients with febrile neutropenia are important. The goals of these studies are to reduce antibiotic usage, duration of hospitalization and cost, to increase convenience without compromising safety, and to refine the definition of the low-risk patient. Future studies may examine the risks and benefits of total oral therapy or investigate new broad-spectrum antibiotics such as Gataflaxacin or Cefepime. Eligibility criteria need to specify age, diagnosis, antecedent therapy, ranges of vital signs, and disqualifying comorbidities. Sample size estimates and stopping rules for serious infections, clinical deterioration or failures are necessary. Any death attributed to inadequate therapy or non-compliance warrants suspension of the study.

SUMMARY

The prospective studies of the past 11 years define the low-risk febrile neutropenic pediatric cancer patient as one who is clinically well with evidence of marrow recovery and no disqualifying comorbidities. Treatment strategies include parenteral or oral antibiotics in the hospital with early discharge or parenteral antibiotics followed by either parenteral or oral antibiotics in the outpatient setting with a protocol for reassessment and modification.
Patients require reassessment, and those whose fevers persist beyond 3 or 4 days and whose neutropenia is unresolved usually require hospital admission. Clinicians may pursue these alternative strategies with strict attention to eligibility and with daily follow-up. There are still many areas where additional clinical trials are warranted. These would include the testing of some newer broad-spectrum antibiotics, such as ceftazidime or some of the fluoroquinolones which have not yet received pediatric labeling. Additional studies in younger children are necessary to assess feasibility of oral therapy.

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REFERENCES