An Integrated Review: Outpatient Care and Management of Fever and Neutropenia Among the Pediatric Oncology Population

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An Integrated Review: Outpatient Care and Management of Fever and Neutropenia

Among the Pediatric Oncology Population

Sarkis Makarovich

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Second Advisor: Dr. Serafin-Dickson
Abstract
In the pediatric population, comprehensive cancer treatment and its associated side effects significantly impact their physical and emotional well-being. Though chemotherapy drugs are valuable agents against cancer cells, they also damage healthy dividing cells, such as bone marrow, thus weakening the immune system. Febrile neutropenia (FN) and associated infections remain the most critical complications of the extensive chemotherapy regimen and can threaten life if not appropriately addressed. Appropriate primary evaluation and treatment of FN in children with cancer includes administering proper broad-spectrum antibiotics. Ongoing research has focused on improving quality of life (QoL); yet, FN has persisted as the main reason for unplanned hospitalization. By contrast, studies have shown that the immediate initiation of neutropenic precautions, home management, and proper oral antibiotics have effectively and safely treated low-grade FN. This integrated review sought to address the effectiveness and significance of this treatment and management of FN. Carefully administering low-grade FN treatment at home will reduce unnecessary emergency department visits and increase patient QoL.

Keywords: pediatric oncology, fever, febrile neutropenia, infection, antibiotic therapy, home versus hospitalization management, quality of life, chemotherapy administration, safety, patient outcomes, patient satisfaction
An Integrated Review: Outpatient Care and Management of Fever and Febrile Neutropenia Among the Pediatric Oncology Population

Pediatric cancer and treatment-associated side effects can be among the most unbearable and overwhelming of individual challenges. Chemotherapy-induced febrile neutropenia (FN), and consequent infections are some of the most severe complications of the extensive chemotherapy regimen for children with cancer and can be life-threatening if not treated properly (Davis & Wilson, 2020; Stergiotis et al., 2021). For the reasons mentioned above, pediatric oncology patients frequently visit emergency departments (ED) for low-grade temperatures and assumed infections. The immediate administration of neutropenic precautions and prompt hospitalization, supported by intensive intravenous (IV) broad-spectrum antimicrobials, appears effective (Manji et al., 2012). However, studies have proposed that home treatment of low-grade fever in patients with FN lessens the anxiety related to hospitalization and supports quality of life (QoL) (Bavle et al., 2017; Morgan et al., 2018).

Background

Chemotherapy and its associated side effects significantly burden the emotional and physical well-being of patients and families alike (Delebarre et al., 2016). Febrile neutropenia and associated infections are counted as the most common chemotherapy treatment complications (Delebarre et al., 2016). Neutropenia, a state in which neutrophils in the bloodstream are lower than expected, occurs after chemotherapy treatment and mainly in the bone marrow (Manji et al., 2012). Typically, neutrophils correspond to the invasive pathogens defending the body and preventing infection; thus, the lower neutrophil count reduces the body’s protective mechanism and enhances susceptibility to infection (Centers for Disease Control & Prevention [CDC], 2020). Accordingly, children undergoing chemotherapy must frequently be
monitored for white blood cell counts (WBC) and absolute neutrophil counts (ANC) to reduce and prevent infection.

Numerous studies have demonstrated that intensive inpatient antibiotic treatment can burden patients’ physical and emotional well-being (Crothers et al., 2021; Delebarre et al., 2016; Li et al., 2010). Studies have shown that managing low-risk FN at home significantly supports QoL and favorable patient outcomes (Haeusler et al., 2021; Manji et al., 2012). Properly training parents on the prevention and management of low-grade FN, with the safe performance of antibiotic administration at home or in the outpatient setting, is vital to favorable outcomes. The current practice is to admit high and low-risk pediatric oncology patients with FN for observation, blood and urine studies, and IV antibiotic treatments. This integrated review sought evidence and guidelines to address the effectiveness and significance of treatment and home management of FN in the pediatric population, thus increasing QoL.

**Search Methodology**

Cross-sectional research used several databases: CINAHL, Cochrane, and PubMed. Applied inclusion or exclusion criteria were based on FN treatment in the pediatric oncology population, focusing on QoL results. Search terms included *fever AND neutropenia, pediatric oncology, inpatient OR outpatient*. Features such as age, article type, language, text availability, date of publication (2010-2022); and modifiers, such as “advanced search” and truncation, “AND,” ”OR,” and “NOT” narrowed the search process, and included/excluded relevant articles to the pediatric population. The search yielded 59 articles, of which 27 were deemed relevant and appropriate for further examination. The Johns Hopkins Nursing Evidence-Based Practice (JHEBP) appraisal tool (Dang & Dearholt, 2018) was used to evaluate the quality of studied articles. The appraisal scores and levels of evidence-based practice articles reviewed in this
manuscript were classified as levels I, III, and V, as well as high-quality, peer-reviewed articles (JHEBP, 2018) (see Appendix A).

**Literature Review**

**Outpatient Antibiotic Proposal and Management**

Due to intensive multidrug chemotherapy regimens and supportive care, the pediatric cancer survival rate has increased by 80% over the past five decades (O’Leary et al., 2008; Mavrides & Pao, 2014). However, these treatments have also resulted in unpleasant side effects, such as FN (Mueller et al., 2015; Paolino et al., 2019). Febrile neutropenia can be severe, life-threatening conditions that require immediate intervention and inclusive antibiotic treatment to avoid further complications or death (Orme et al., 2014). Due to the necessary treatment and prompt intervention, parents must be careful and alert and take their children to the hospital for a complete evaluation when responding to the presence of FN (Anderson et al., 2018). Although outpatient supervision of pediatric patients with FN is recognized as a low risk for complications or fatality, most patients (95%) are still hospitalized (Baugh et al., 2019). A retrospective cohort analysis conducted over a 5-year period on pediatric patients revealed that nearly one in five ED visits with a primary diagnosis of FN (82.3%) resulted in admission for comprehensive treatment and observation, whereas admissions for fever without FN accounted for only 17.3% of the total admissions (Mueller et al., 2015). Hence, managing FN in low-risk patients admitted to the ED and subsequent inpatient treatment impacts patient and family QoL.

Studies have examined the effectiveness of outpatient and inpatient supervision of children with low-risk FN, comparing oral and parenteral antibiotic therapy (Manji et al., 2012; Orme et al., 2014; Sung et al., 2004). Implementing clinical practice guidelines that aid standardized care for patients presenting with FN will improve consistent preparation guidance
for healthcare professionals (Anderson et al., 2018). Clinical practice guidelines may include the choice of empiric antimicrobials and criteria for their modification and aid in standardizing care for FN patients to improve consistent preparation guidance for healthcare professionals (Anderson et al., 2018; Lehrnbecher et al., 2012). By implementing a quality change intervention, such as having a supply of broad-spectrum antibiotics readily available in the emergency cart, healthcare professionals can hasten antimicrobial administration and lower the risk of complications in pediatric oncologic patients experiencing FN (Amado et al., 2011).

Cefepime, a fourth-generation cephalosporin, is considered a safe and effective option due to its wide range of coverage and long half-life, which enables it to be scheduled twice a day, making it suitable for managing FN in an outpatient setting (Orme et al., 2014). According to another study, 40% of the patients treated in an outpatient setting didn’t experience any complications, which led to a reduction of 240 days in hospital admissions (Paolino et al., 2019). According to Manji et al. (2012), therapy failure was less likely in the outpatient setting with the antibiotic change; whereas, in the inpatient group, therapy had to be frequently modified due to sepsis or secondary infections acquired in the hospital (HAIs), which responded well to changes in therapy. However, no noticeable distinction was found between oral or intravenous antibiotic treatment. (Manji et al., 2012; Morgan et al., 2018).

Febrile neutropenia imposes a considerable psychosocial burden on patients and their families (Paolino et al., 2019), as reported by families and patients. Nevertheless, some centers persisted with inpatient only treatment (Szymczak et al., 2017). Choosing oral outpatient therapy was linked to the better-expected QoL for both the parent and child at home (Sung et al., 2004).

Tailoring care to align with patient and family preferences can lead to higher satisfaction levels and fewer conflicts with the care team. Studies on FN management revealed that many
parents opted for inpatient care when given the choice, but still believed that their QoL would improve with at-home management (Szymczak et al., 2017). Therefore, the guidelines for low-risk FN patients suggested outpatient treatment settings to decrease HAIs, decrease psychosocial burdens associated with therapy, and support QoL for patients and their families (Paolino et al., 2019; Sung et al., 2004).

**Family-Centered Preferences and Outcomes**

Considerable research on the management of FN has suggested that antibiotic initiation in an outpatient setting in low-risk septic patients supported patient QoL (Cheng et al., 2011; Haeusler et al., 2021). Parents’ recognition of risk stratification and assessment strategy implies that increased communication of a child’s risk level may support shared decision-making between families and healthcare professionals. Examining parental and healthcare provider choices for FN management among lower-risk pediatric patients revealed the complicated burden that hospital admissions present to patient QoL; thus making outpatient therapy the preferred option (Mueller et al., 2015). Identifying hospitalization outcomes is essential for healthcare providers to effectively address low-grade FN and decrease unnecessary hospitalizations (Orme et al., 2014; Szymczak et al., 2017).

Research-based interviews have proven the significance and impact of anticipated distress and uncertainty in families dealing with FN in addition to clinical symptoms (Anderson et al., 2018). It is important to observe and address the needs of both child and family during unplanned hospital admissions to minimize or avoid significant negative impacts (Anderson et al., 2018). Therefore, fully understanding how parents manage and perceive FN in their daily routines can help healthcare professionals inform their clinical practices for more effective and successful outcomes (Anderson et al., 2018).
Accommodating family preferences is essential. In-depth qualitative research outcomes reported that parental support toward children significantly reduced the burden of therapy for children. Although some parents experienced reduced anxiety during hospitalization, others reported poor sleep, emotional impact on siblings, and stress on their co-parent relationships (Morgan et al., 2018; Szymczak et al., 2017). In low-risk pediatric FN, when safety events are not affected by the treatment location, collaborative decision-making benefits cases where research indicates minimal variation in results between treatment choices (Morgan et al., 2018).

Furthermore, clarifying the level of risk for a child may reduce the emotional responses of healthcare professionals regarding lessened therapy strategies (Morgan et al., 2018). The guideline designates minimum care criteria for pediatric patients treated with FN (Lehrnbecher et al., 2012). The factors that influence the preference for outpatient oral antibiotics versus IV antibiotic treatment differ between parents and healthcare professionals; however, 53% of parents preferred outpatient oral antibiotic administration for low-risk FN (Sung et al., 2004).

**Clinical Approaches for Home Surveillance of FN**

There may be discrepancies in defining FN, as well as variations in the initial empirical treatment and subsequent second-line regimens. Additionally, disparities between different centers can arise due to disagreement on treatment guidelines. Patients less prone to complications can benefit from outpatient monitoring. To determine a less intensive treatment plan, the professional must identify the risk of developing a complication associated with infection (Delebarre et al., 2016).

The United Kingdom National Institute for Health and Care Excellence (NICE) described FN as a temperature ≥38°C with an ANC of fewer than 500 cells/microlitre. The ANC cut-off is based on an increased risk of sepsis when ANC falls below 0.5 x 10⁹/L. Several guidelines
suggested more detailed descriptions for FN, such as a single fever of \( \geq 38.3^\circ C \), a temperature of \( \geq 38^\circ C \) for more than one hour, or two episodes of fever of more than 38°C within a 12-hr period (Davis & Wilson, 2020). Specific exceptions are based on regional protocols consistently employed in the presence of the FN without acknowledging the individuals’ risk (Delebarre et al., 2016). Thus, guidelines advise risk stratification for possible outpatient therapy (Gottlieb, 2019). The guidelines highlight the main risk factors associated with sepsis risk and adverse consequences of FN in the pediatric oncology population. Guidelines suggested adopting a validated risk stratification method, such as facilitating reduced-intensity treatment and home-based management in patients identified as low-risk (Haeusler et al., 2020).

**Determination of Risk Stratification**

According to Davis and Wilson (2020), the determination of low-risk FN is based upon several aspects, including:

- State of the patient
- Cancer classification
- Assertiveness of chemotherapy
- Anticipated course of FN
- Symptoms of the central nervous system, pulmonary, gastrointestinal, and central venous catheter sites, such as erythema or swelling.

Therefore, protocols for the pediatric population may support harmonizing preparation for the individual-driven approach (Delebarre et al., 2016). There is significant concern regarding varying viewpoints on advancing the practice procedures and policies, such as clinical guidelines, introducing new plans of care, the study of clinical experiments, and healthcare support (Sung et al., 2004). Defining and analyzing parents’ and healthcare experts’ preferences
regarding outpatient oral antibiotics versus inpatient parenteral antibiotic therapy in low-risk FN is evident and the focus of the studies (Sung et al., 2004). As stated by Mueller et al. (2015), there is variation in all parts of FN management, from admission criteria to inpatient clinical practices to discharge standards. Actual clinical practice is likely derived from issued guidelines, provider knowledge, and patient choices, but more is required about the interaction among these elements. Parameters involving decision-making of outpatient management are linked with frequent clinic visits and a likelihood of demanding hospitalization due to constant fever or worsening situation. Moreover, inpatient and outpatient interventions may require admission to the intensive care unit (ICU) with an associated risk of death, necessarily affecting treatment preferences (Sung et al., 2004). Further suggestions include close interdisciplinary collaboration among the home and community care, hospital-based community outreach, and healthcare providers to optimize safety improvement strategies and increased QoL (Orme et al., 2014).

A Shift in the Management Protocol

This literature review revealed a present and vital need for healthcare professionals to enhance and improve their practices. It is evident that modifying existing methods and treatment interventions will increase favorable outcomes (Amado et al., 2011). According to researchers, it is feasible to treat low-risk FN with outpatient care and oral antibiotics (Manji et al., 2011; Morgan et al., 2018; Orme et al., 2014). Furthermore, Orme et al. (2014) indicated that low-risk patients who received antibiotic treatment at home coupled with close collaboration with healthcare providers experienced notable improvements in QoL. Clearly, more can be done to adapt current treatment protocols for better outcomes.

Discussion
Fever and chemotherapy-associated FN frequently create significant life disturbances among the pediatric oncology patient population. Clinical techniques to treat and manage them differ among organizations with regard to hospital admission criteria, treatment options, discharge measures, and outpatient management. This manuscript sought evidence to manage home treatment for FN bouts in low-risk pediatric patients for higher QoL. It reviewed parental and healthcare provider perspectives regarding the safe management of FN in low-risk pediatric populations in an outpatient setting. Most studies revealed that early discharge was possible, safe, and well-managed by patients, families, and healthcare providers. However, while Morgan et al. (2018) found that early discharge did not increase intensive care admissions or deaths, it did promote the likelihood of readmission by up to 14%. The literature further discussed variations in healthcare policies related to FN and the corresponding antibiotic treatment methods, but despite evidence for outpatient management for FN and the subsequent reduction in patient anxiety, some institutions continue to resist this approach and propose that more research explore the relationship among admission standards, treatment alternatives, discharge criteria, and outpatient surveillance. In general, most literature confirmed the specific guidelines for safe treatment and care of FN in the outpatient setting.

To ensure the safety of FN patients, it is advisable to adhere to specific guidelines based on high-quality, peer-reviewed articles. These guidelines have been thoroughly researched and are of high quality. The appraisal scores for evidence-based practice articles were categorized into levels I, III, and V, as well as high-quality peer-reviewed articles. Therefore, because home care minimally disrupts the personal lives of patients and their families, healthcare professionals must closely observe indications and symptoms of FN and offer timely treatment that follows guidelines.
Nursing Implication

Unexpected admissions to the hospital for treatment of FN during cancer therapy burdens patients and their families (Orme, 2014). Hospital admissions put oncology patients at risk for missed treatments; HAIs, including iatrogenic infections; and overall decreased QoL. It is essential to develop new approaches to safely decrease inpatient antibiotic treatment in pediatric cancer patients with FN, thus allowing children with malignancies more time at home and improved QoL (Miedema et al., 2015). Deciding if outpatient surveillance is as safe and practical as inpatient management of low-risk patients is crucial (Gottlieb, 2019).

According to evidence-based literature, the management of low-grade FN in an outpatient setting is effective and safe when feasible (Manji et al., 2012). However, it requires a clinical approach for practical interdisciplinary cooperation and adequate support from pediatric hematology oncology, pediatric subspecialties, general pediatricians, and the nursing team (Cantrell & Ruble, 2011) (see Table 1, p. 20).

Conclusion

Among the pediatric population undergoing cancer treatment, infection related to FN is the leading cause of ED visits, subsequent unexpected hospitalizations, and reduced QoL. In many low-grade FN cases, the current approach to care is hospitalization and prompt initiation of broad-spectrum antibiotics. Febrile neutropenia remain ongoing complications. Appropriate education of parents on the prevention and management of FN, with the safe administration of antibiotics at home or in the outpatient setting, may reduce unplanned hospital admissions and increase patient QoL and satisfaction. Incorporating existing guidelines into practice settings will provide a standardized measure for managing fever in low-risk patients; however, each patient must be examined and evaluated carefully before treatment initiation. Providing clear
information on preventing, recognizing, and treating infections will maximize favorable outcomes for patients and their families.
References


*Multinational Association of Supportive Care in Cancer, 29*(3), 1609–1617.

https://doi.org/10.1007/s00520-020-05654-z


Table 1

American Academy guidelines for multidisciplinary teams in pediatrics for cancer centers

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<td>1.</td>
<td>Board certified/eligible or equivalent pediatric hematologist/oncologist</td>
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<td>2.</td>
<td>Board certified pathologist(s) committed to handling specimens according to COG protocols</td>
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<td>3.</td>
<td>Nurses with additional training in the management of children and adolescents with cancer and blood disorders, and documented in-house training in chemotherapy administration</td>
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<td>4.</td>
<td>Clinical research associates trained in data management support of cooperative research</td>
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<td>5.</td>
<td>Respiratory therapists with expertise in pediatrics</td>
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<td>6.</td>
<td>Anesthesiologist with expertise in the management of children</td>
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<td>7.</td>
<td>Radiologist with expertise in the management of children</td>
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<td>8.</td>
<td>Pharmacist with expertise in chemotherapy</td>
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<td>9.</td>
<td>Social worker with additional training in the management of children and adolescents with cancer and blood disorders</td>
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Adapted from the PubMed Central (PMC). Journal of Multidisciplinary Healthcare: Published online 2011 May 30. doi: 10.2147/JMDH.S7108

Abbreviation: COG, Children’s Oncology Group.
## Appendix A

<table>
<thead>
<tr>
<th>Purpose of Article or Review</th>
<th>Design/Method/Conceptual Framework</th>
<th>Sample/Setting</th>
<th>Major Variables Studied (and their Definitions)</th>
<th>Measurement of Major Variables</th>
<th>Data Analysis</th>
<th>Study Findings</th>
<th>Level of Evidence (Critical Appraisal Score)/ Worth to Practice/ Strengths and Weaknesses/ Feasibility/ Conclusion(s)/ Recommendation(s)</th>
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### Study Design:
- Chart review before and after observation of time to antibiotic delivery.
- Leaving first dose of broad-spectrum antibiotics available in emergency cart.

### Sample:
- 25 pediatric oncology patients undergoing chemotherapy.

### Setting:
- Pediatric ICU.

### Data Collection:
- Date of birth, sex, date and time of admission, oncologic diagnoses, date of last chemotherapy, surgery in last 3 months, use of central venous catheter, use of antibiotic and/or antifungal prophylaxis, neutrophil count, period of hospitalization, last febrile date, time of antibiotic administration, antibiotic use in first 24 hours and in first 72 hours, results of cultures, date of hospital discharge, need for hemodialysis, mechanical ventilation use, and vasoactive drug use.

### Data Analysis:
- SPSS 16.0 software used for statistical analysis.

### Study Findings:
- Data were analyzed with Fisher exact test for proportions and t-test or Mann-Whitney U test for continuous variables. Time to antibiotic administration is also plotted as a Kaplan-Meier curve, with log-rank statistics. A bicaudal P-value of less than .05 was considered significant.

### Results:
- Results recommend that simple interventions can lessen time of antibiotic administration in a group of patients in a pediatric ICU.

### Level of Evidence (Critical Appraisal Score):
- Level V

### Worth to Practice:
- Keeping a dose of antibiotic available in emergency cart does not require additional costs or complicated multi-professional efforts and reduces time to antibiotic delivery in pediatric febrile oncologic patients.

### Weaknesses/ Limitations:
- Statistical fragility, small changes in numerator and denominator could eliminate the observed statistical significance.

- Hawthorne effect, where time to antibiotic delivery could have been decreasing because of house staff being observed during the study.

### Strengths:
- This quality improvement project’s costs are irrelevant to the costs involved in assembling multi-professional teams to educate staff or elaborate a new protocol. It is also more efficient to implement.
neutropenia (FN).

2. To study delays in antibiotic delivery unrelated to time to diagnosis or misdiagnosis or access to emergency room physician.

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<td>Feasibility: It requires multi-professional team collaboration and applying QI standards, such as the availability of broad-spectrum antibiotics in patients’ charts to reduce delivery time and increase the treatment’s effectiveness.</td>
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<tr>
<td>Febrile neutropenia necessitates immediate evaluation and antimicrobial treatment. It is one of the most frequent reasons for unplanned hospital admission in pediatric oncology. Due to necessary treatment and prompt intervention, parents must take their child to the nearest hospital for assessment if a fever is present. Immediate intervention and antimicrobial treatment are crucial, and delays in therapy are</td>
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<td>Study Design: To understand and describe the phenomenon experienced by the parent of a child with cancer rather than through the interpretive lens of the researcher.</td>
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<td>Method: Phenomenology research aims to find meaning within a lived experience.</td>
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<td>Search Strategy: Telephone interview</td>
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<td>Conceptual Framework: Descriptive phenomenological concepts</td>
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<td>Sample: Nine parents of children between ages of 0 and 18 years with cancer. Sampling continued until data saturation occurred.</td>
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<td>Setting: Queensland hospital, Australia</td>
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<td>Gender, location of residence (metropolitan/regional), location of treating hospital for febrile neutropenia, age of child 0-4 years, 5-9 years, 10-14 years, time from child’s diagnosis 0-6 months, 7-12 months, 13-18 months, 19+ months, type of CVAD Port-a-cath, Hickman central line, Peripheral line were considered.</td>
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<td>Three major issues: being heard, confidence in the capabilities of healthcare professionals, and living with expected distress and uncertainty. The open nature of the interviews meant that parents reflected and discussed current and prior experiences, allowing greater insight into the influence of repeated, unexpected admissions on parents of children with cancer.</td>
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<td>Interviews were audio-recorded and transcribed precisely by one researcher. Accuracy of transcribed data was supported by listening to the recorded interviews and reading transcripts by a second researcher. Using NVivo software, two researchers separately coded data from all discussions and grouped codes into themes. Final coding structure was agreed upon by comparing and contrasting coding systems, emerging</td>
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<td>Parent experiences were shaped by their understanding of being heard by healthcare providers, their confidence in the capabilities of healthcare professionals, and living with anticipated distress and uncertainty.</td>
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<td>Level: Systemic review, JHNEBP Appendix E: Level III</td>
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<td>Worth to practice: Because the main objective of this study was to recognize patient and family concerns related to hospitalization, it is worth continuing to design guidelines that focus on patients’ families regarding their feelings.</td>
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<td>Strengths/Weaknesses/Limitations: Small sample size</td>
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<td>This study emphasizes parental experience related to the level of advocacy required for patient care.</td>
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<td>Feasibility: It is feasible to conduct an in-depth qualitative measurement focusing on families’ experiences rather than solely managing FN.</td>
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<td>associated with more unsatisfactory results; nevertheless, delays are expected.</td>
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To review guidelines recommending reduced-intensity management strategy based on stratification of infectious risks. Some studies have highlighted practice disparities in different countries and within the same country. Our aim was to assess the current management strategies for treatment of chemotherapy-induced FN in children in France.

**Study Design:** A nationwide descriptive survey including 184 items, most of which (95%) were simple yes/no or multiple-choice questions. A few open-ended questions enabled better analyses of the answers. The long questionnaire could still be completed in fewer than 20 minutes.

**Method:** Questionnaire with seven sections: (i) characteristics of the hematology-oncology department; (ii) definitions of FN; (iii) choices of empirical variables; type of cancer, patients’ age, neutropenia, 1st or nth episodes of FN, Non-hospitalized patients, Parent reliability.

**Sample:** 30 French pediatric hematology-oncology reference centers.

**Setting:** Pediatric hematology-oncology reference centers and two pilot centers in northern France of reference centers in Lille.

**Measurement of Major Variables**

- Fever ≥ 38.5°C once or ≥ 38.0°C twice.
- ANC lower than 500/mm3 (n=18) as lower than 500/mm3 or 1,000/mm3 and decreasing (n=10)

“Microsoft Excel software enabled data entry and analysis of the descriptive statistics. Statistical Package for the Social Sciences R_ used to compare continuous variables with a nonparametric Mann–Whitney test. Differences were defined as significant when P < 0.05.”

Completing an average of 88% of the questionnaire items with 100% of items completed for FN definition, management of episodes, and reduced management strategies. Definitions of FN among centers. In all, 42 probabilistic first-line antibiotic treatments were identified. After 48 hrs of apyrexia, 17 units applied different forms of step-down therapy.

**Purpose of Article or Review**

- To review guidelines recommending reduced-intensity management strategy based on stratification of infectious risks.

**Design/Method/Conceptual Framework**

- A nationwide descriptive survey including 184 items, most of which (95%) were simple yes/no or multiple-choice questions. A few open-ended questions enabled better analyses of the answers. The long questionnaire could still be completed in fewer than 20 minutes.

**Sample/Setting**

- Pediatric hematology-oncology reference centers and two pilot centers in northern France of reference centers in Lille.

**Major Variables Studied (and their Definitions)**

- Variables: type of cancer, patients’ age, neutropenia, 1st or nth episodes of FN, Non-hospitalized patients, Parent reliability.

**Measurement of Major Variables**

- Fever ≥ 38.5°C once or ≥ 38.0°C twice.
- ANC lower than 500/mm3 (n=18) as lower than 500/mm3 or 1,000/mm3 and decreasing (n=10)

“Microsoft Excel software enabled data entry and analysis of the descriptive statistics. Statistical Package for the Social Sciences R_ used to compare continuous variables with a nonparametric Mann–Whitney test. Differences were defined as significant when P < 0.05.”

**Data Analysis**

- Completing an average of 88% of the questionnaire items with 100% of items completed for FN definition, management of episodes, and reduced management strategies. Definitions of FN among centers. In all, 42 probabilistic first-line antibiotic treatments were identified. After 48 hrs of apyrexia, 17 units applied different forms of step-down therapy.

**Study Findings**

- “Microsoft Excel software enabled data entry and analysis of the descriptive statistics. Statistical Package for the Social Sciences R_ used to compare continuous variables with a nonparametric Mann–Whitney test. Differences were defined as significant when P < 0.05.”

**Level of Evidence (Critical Appraisal Score)/Worth to Practice/Strengths and Weaknesses/Feasibility/Conclusion(s)/Recommendation(s)/**

- **Level:** Systemic review, JHNEBP Appendix E: Level III

- **Worth to practice:** Based on recommendations, risk stratification with validated tools is essential to facilitate the implementation of the guidelines in management of FN.

- **Weaknesses/Limitations:**
  1. Criteria for stratification of risk of severe infection differ from one center to another.
  2. Limited data in children to enhance the safe use of risk-adapted strategies.

- **Strengths:** “All French pediatric oncology-hematology reference centers completed the questionnaire, with good response rates for each item (>88%) and full concordance between answers and each center guidelines for those who provided it.”

- **Feasibility:** Feasible; however, requires adaptation of national standard guidelines in management of FN.
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<td>antibiotic treatments; (iv) guidance on the nature and timing of empirical and additional therapies; (v) criteria used for stopping antibiotic therapy for FN without infectious documentation; (vi) use of reduced intensity management strategies, including alternative treatment or early discharge, and the criteria applied for their use; and (vii) the existence of any local protocol for FN management</td>
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**Search Strategy:**
E-mail questionnaire sent to all 30 French pediatricians,
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<td>hematology oncology reference centers after pilot testing by all physicians (pediatric oncologists or hematologists) at the two reference centers in Lille (northern France)</td>
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<td><strong>Inclusion:</strong> All French pediatric oncology-hematology reference centers.</td>
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<td><strong>Conceptual framework:</strong> None</td>
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<td>1. To decide if variations exist in the effectiveness of outpatient and inpatient management of children with low-risk FN.</td>
<td>Study Design: 1. Performed observational studies in epidemiology guidelines for reports. 2. Electronic searches of Ovid Medline, EMBASE, and the Cochrane Central Register of Controlled Trials. Method: Trials, and limited studies to prospective pediatric trials in low-risk FN. Search Strategy: Medical Subject Headings and text words “fever” &amp; “neutropenia,” in English. Conceptual Framework: None</td>
<td>Sample: Pediatric oncology patients with FN Setting: Outpatient vs. inpatient</td>
<td>1. To identify, calculate, and compare outcomes between inpatient and outpatient protocols 2. To evaluate whether route of drug administration impacts outcomes of low-risk pediatric FN. 3. Risk in FN is likely to be a continuous variable.</td>
<td>Examined four potential sources of bias: study participation, study attrition, confounding variables, and measurement of outcome. Elements were rated as low, medium, or high risk of bias. Using SAS statistical program, sub-groups were defined based on: 1. Treatment setting (outpatient or inpatient) 2. Route of administration (oral or parenteral). 3. Heterogeneity test across subgroup results to determine if outcomes were modified based upon treatment setting or route of administration, with statistical significance defined as P&lt;0.10. Results</td>
<td>1. Meta-analysis combined data at the study level and not at the individual patient level. 2. The meta-analysis was performed using Review Manager (RevMan) (Version 5.1.0, The Cochrane Collaboration, Oxford, England).</td>
<td>1. No differences in infection-related mortality rates between inpatient and outpatient settings. 2. No significant rise in treatment failure associated with oral treatment.</td>
<td>Level: Systemic review, JHNEBP Appendix E: Level 1 Worth to practice: No significant differences between inpatient and outpatient outcomes regardless of route of drug administration. Weaknesses/Limitations: 1. Relying on each study protocol’s definition of low-risk criteria. 2. Variability in definition of primary outcome, treatment failure, across all studies. 3. Uncertainty in children continues to involve inpatient parenteral antibiotics. Oral antibiotic therapy has been limited by too few randomized trials conducted in pediatrics. Strengths: Comprehensive results of this study verify efficacy of these approaches in pediatric patients. Feasibility: If follows low-risk FN management with outpatient or oral antibiotics as reflected by international treatment guidelines in adult population.</td>
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<td>A systematic review of pediatric low-risk FN observed that outpatient care is reliable, with low rates of treatment failure. Nevertheless, review, and a subsequent meta ethnography recommended that early discharge of these patients may not be acceptable to stakeholders. The study explored struggles and attitudes of patients, parents, and healthcare experts included in pediatric FN care in the UK. <strong>Study Design:</strong> Data from a current UK survey were used to recognize centers with various strategies to risk stratification, low-risk protocols shared care assistance and geographical spread of patients. <strong>Sample:</strong> Thirty-two participants participated in eight focus group discussions. <strong>Settings:</strong> Three different centers within the UK, national survey on differences in service structure and FN management. <strong>Major Variables Studied (and their Definitions):</strong> 1. Febrile neutropenia 2. Low-risk 3. High-risk episodes 4. Parents of under 13 years 5. Parents of over 13 years. A meta-ethnography of the current qualitative literature investigating early discharge unveiled possible difficulties surrounding effective logistics, social, or emotional matters determined by fear, timing, and resources. Each transcript was individually coded by JEM with input from KA. No analytical software was used. Personal views were followed within the focus groups to distinguish codes which happened more frequently, or with various quality, dependent on the features of people. The study revealed earlier underestimated impairments of admission for FN and parents’ decision-making, with the frustrations and difficulties for all individuals associated with FN treatment. It proved how stakeholders can use the exact statistics created by systematic reviews to evaluate risk differently and how families can view the impairments of therapeutic opportunities different from the results practiced within the literature. It supported a reassessment of current treatment. <strong>Level:</strong> Systemic review, JHNEBP Appendix E: Level III <strong>Worth to practice:</strong> This study primarily explored the experiences/perceptions of patients, parents, and healthcare professionals involved in pediatric FN to gain greater understanding and improved best practice. <strong>Weaknesses/Limitations:</strong> The ability to communicate in English. Small focus groups. Difficulty recruiting. <strong>Strengths:</strong> Multiple centers facilitated agreement of the influence of service design and center culture on participants’ judgments. <strong>Feasibility:</strong> Feasibility requires an understanding of parents’ and healthcare stakeholders’ justification of treatment strategies and reassessing guidelines and policies to aid decision-making.</td>
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**Inclusion:**
Selection of the multiple centers to comprehend the impact of service design and center culture on participants’ understandings.

**Conceptual framework:**
None
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<tr>
<td>This study primarily examined reasons indicating emergency department (ED) visits and circumstances associated with hospital admission in the United States over a 5-year period.</td>
<td><strong>Study Design:</strong> A retrospective cohort analysis of pediatric ED visits from 2006-2010 <strong>Method:</strong> Clinical Classification Software to identify pediatric patients with cancer. <strong>Search Strategy:</strong> The Healthcare Cost and Utilization Project’s (HCUP) Nationwide Emergency Department Sample (NEDS) Agency for Healthcare Research and Quality</td>
<td><strong>Sample:</strong> 294,289 ED visits by pediatric patients ages 0-19 over a 5-year study period.</td>
<td>To identify sample following variables were considered. “Demographic and hospital characteristics were evaluated including: patient’s age, sex, primary expected payer, median household income of the patient’s ZIP code, hospital trauma designation, and hospital teaching status. The disposition categories that were analyzed included: discharged (patient treated and released from the ED), admitted (patient admitted to same institution), transferred (patient transferred to another short-term hospital), or died in the ED.”</td>
<td>“Descriptive statistics were used to demonstrate the distribution of demographic and hospital characteristics. A weighted multivariate logistic regression model was used to estimate factors associated with admission for pediatric patients with cancer and to account for clustering of patients by hospital.”</td>
<td>Statistical analyses were performed using STATA version 12.0</td>
<td>Fever and FN were the two common determinations for hospitalization, counting almost 20% of ED visits. Forty-four percent of pediatric patients with cancer were accepted to the same hospital, with admission rates up to 82% for FN.</td>
<td><strong>Level:</strong> Systemic review, JHNEBP Appendix E: High quality <strong>Worth to practice:</strong> The justification of management of FN requires close collaboration among patients, their families, and the multidisciplinary healthcare team. <strong>Weaknesses/Limitations:</strong> 1. Only a single diagnostic code per patient was used to analyze the effect of the reason for ED presentation. 2. Underestimation of patients with FN since those with neutropenia only had very similar disposition patterns. 3. Administrative databases do not hold detailed information regarding patients’ cancer staging, therapy regimens, vital signs or laboratory values. 4. Counts of visits may be overestimated due to patient transfer between facilities; therefore, ED visits may have produced two encounters within the NEDS. <strong>Strengths:</strong> 1. Baseline evaluation of the ED utilization of pediatric patients 2. Data are highly generalizable</td>
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3. Key areas have been highlighted for future investigation and intervention.
4. Longitudinal analyses of the multi-institutional allow for changes in clinical practice guidelines and evidence-based practices on an institutional or national level.
5. Demonstrates the benefit of research and emphasizes the importance of pursuing innovative approaches to data collection.

**Feasibility:** Based on the authors’ suggestions utilizing a research study to pursue contemporary approaches for data collection and management of FN is feasible.
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<td>Highlighted collaboration between patients/families and healthcare providers to address low-grade FN to avoid hospitalization. The antibiotic Cefepime usage twice a day in-home management of the patients with LRFN will reduce the chance of hospitalization and improve quality of life.</td>
<td>Study Design: An unblinded randomized controlled trial comparing inpatient and outpatient antibiotic management of FN in children receiving chemotherapy for malignancy. (Quantitative Randomized controlled trial)</td>
<td>Sample: 81 pre-consented patients presented to ED with 159 episodes of fever (between 1 and 21 years old, receiving low/moderate intensity chemotherapy).</td>
<td>Major Variables: 1. Seven patient variables (well-being, mood, independence, appetite, concentration, sleep and activity level of the patient). 2. Six parent variables (ability to keep up with home tasks, time spent with spouse and siblings as well as level of anxiety, confidence in patient care and satisfaction with care).</td>
<td>Using a visual analog of a linear 10 cm scale provided a 25-40% increase in mean score on six QoL scales. All data were processed using a software database (Access software database, 2003, Microsoft, Redmond, WA) for statistical calculation. Also, a chi-square test was performed for dichotomous and t-tests for parametric variables. QoL scores were itemized as 95% confidence intervals.</td>
<td>The benefits of outpatient management with Cefepime contain reduced cost burden and reduction in nosocomial infections. It is long established that outpatient management increases QoL; however, parents mention anxiety re: supporting sick children with FN outside the acute hospital setting. The broad coverage and long half-life of Cefepime twice daily</td>
<td>Level: Systemic review, JHNEBP Appendix E: Level I</td>
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**Worth to practice:** This study recommends the development of a clinical guideline. It demands strong interdepartmental collaboration and essential dedication to a hospital-based community care program.

**Weaknesses/Limitations:**
1. Too few study participants.
2. Did not track and record reasons for ineligibility and refusals of patients.
3. Fever criteria used for presentation to ED regardless of measurement being axillary, oral, or tympanic, allowing for inconsistencies in presentation and enrollment.
4. Different views of parents.

**Strengths:**
1. Benefit of bed utilization
2. Cost effectiveness.
3. No significant adverse events.

**Feasibility:** Outpatient cefepime management of LRFN contributed to improved parents and patients several QoL domains; therefore, it appears to be both safe and feasible.

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<td>Search Strategy: None</td>
<td>Conceptual Framework: None</td>
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<td>intervals. Finally, the questionnaires were analyzed based on two mean scores: the mean of the day of FN treatment and the mean of each question.</td>
<td>have been reported as a safe and feasible choice childhood cancer patients with FN.</td>
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<td>A multi-disciplinary collaboration between patients and their families with healthcare providers, carefully focusing on LRFN management in outpatient settings. The early detection of FN and prompt antibiotic regimen reduces the incidence of hospitalization and increases QoL for all involved.</td>
<td>Study Design: To estimate the influence of the implementation of the clinical pathway, a retrospective analysis of all FN events over fifty-five months was carried to establish the safety and efficacy of this pathway. <strong>Method:</strong> An implantation of clinical pathway a retrospective review of FN episodes over 55-month period <strong>Search Strategy:</strong> 1. A close collaboration with clinic, ED, and inpatient teams 2. Following standards, all patients and families were instructed to observe for fevers at home</td>
<td>Sample: 169 cases of febrile neutropenia, between April 1, 2013, and October 1, 2017. <strong>Setting:</strong> Massachusetts General Hospital for Children, Outpatient setting</td>
<td>Characterization of risk status, duration of hospitalization when applicable, rates of bacteremia, complications, and rates of subsequent admission during the FN episode. A complete blood count (CBC) with differential blood culture, and initiation of a single dose of IV levofloxacin.</td>
<td>“The primary outcome of interest was defined as the rate of major medical complications, specifically the incidence of intensive care unit (ICU) admissions and death. The rate of subsequent admission to the hospital, avoidance of hospitalization, and length of stay were assessed as important secondary outcome measures.” Fever over 38°C and ANC below 500 Resolution of fever and ANC greater than 200 as the end of the episode</td>
<td>A retrospective review and comprehensive chart review of all FN episodes.</td>
<td>The majority of patients selected as low risk in the outpatient setting successfully achieved treatment plan without significant morbidity or mortality.</td>
<td>Level: Systemic review, JHNEBP Appendix E: Level III</td>
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### Purpose of Article or Review

Throughout at-risk periods and report them fevers in real-time to the on-call oncology team.

#### Inclusion:
1. Low risk inclusion criteria adopted from Talcott et al for low risk management of adult oncology and pilot study that was conducted in the pediatric population in MGHfC
2. Levofloxacin as the antibiotic of choice

#### Feasibility:
- Continuous measurement of patients’ outcomes by the study team.
- Periodically reviewed the pathway with pediatric residents, pediatric oncology staff, and pediatric ED staff.

#### Feasibility: Outpatient
Levofloxacin administration of low-grade fever appears to be both safe and reasonable.
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<td>to be in remission.</td>
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<td>6. Children with acute myeloid leukemia (AML), bone marrow or stem cell transplant in the prior 100 days.</td>
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<td>1. Down syndrome as a high risk.</td>
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<td>2. Concern with family's ability or adherence to communicate by phone and return to hospital if necessary.</td>
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<td>To explain and analyze parents’ and healthcare professionals’ willingness for outpatient oral antibiotic treatment vs. inpatient parenteral antibiotic treatment for low-risk FN in pediatric oncology patients with goal to recognize predictors of the strength of choices for oral outpatient treatment.</td>
<td>Study Design: Parental interviews using a questionnaire. Method: Parents of children &lt;18 years of age were interviewed in the oncology clinic or during admission to the hospital. Search Strategy: Personal interviews conducted by three trained research assistants. Conceptual Framework: None</td>
<td>Sample: 75 parents and 42 healthcare-professionals.</td>
<td>Sociodemographic and Clinical Characteristics of Parents and Their Children. Fear and anxiety Comfort levels. Parents, professional and children estimated QoL. Copes (poorly). Bad experiences</td>
<td>T-test (for independent groups) used to compare differences between parent and healthcare professional responses. Wilcoxon rank sum test used for continuous variables, and Fisher’s exact test for categoric variables. All analyses were performed using the SAS statistical program for PC. Version 8.2.</td>
<td>53% of parents preferred outpatient oral antibiotic administration for low-risk FN. Predictors of preference scores for outpatient oral antibiotics vs. parenteral antibiotic treatment varied between parents and healthcare professionals.</td>
<td>Level: Systemic review. JHNEBP Appendix E: Level III</td>
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**Worth to practice:** Since over 50% of respondents preferred outpatient management, it is worth investigating patient and family concerns regarding improving quality of life during FN treatment.

**Weaknesses/Limitations:**
1. Relatively small sample size
2. Results obtained using a hypothetical judgment task by parents acting as proxy decision makers.
3. Potential discrepancies between parent and provider preferences

**Strengths:** Not listed

**Feasibility:** As suggested by the author, designing a randomized control trial will reveal patients and family choices regarding treatment options.
To expose hospitalization as generally stressful, affecting both patients and their families’ QoL. Practical therapeutic approaches to identify patient and family-centered outcomes in the pediatric presenting with FN. Patient and siblings’ emotional distress, parents’ anxiety, and patients’ sleep disturbances were examined.

**Study Design:** Open-ended qualitative.

**Method:** In-depth, semi-structured interviews with children and their families who completed AML chemotherapy at 1 of 9 children’s hospitals across the U.S. Five of the hospitals implemented home management of neutropenia.

**Search Strategy:** Interviews conducted at institutions where FN was managed in the hospital or at home to investigate variation in experience.

**Sample:** 116 eligible individuals to participate in our study. 86 respondents from 57 families with child with AML enrolled in study. Response rate: 74.1%.

**Setting:** Inpatient versus at-home management.

1. Distress on siblings related to prolonged hospitalizations.
2. Mothers of hospitalized children reported worrying about balancing needs of multiple children.
3. Anxiety related to preventing infection, managing central line care at home.
4. Monitoring for fever, and their ability to transport child to hospital in timely fashion.
5. Significant sleep disturbances due to frequent interruptions for monitoring of vitals.
6. Dysfunctional sleep patterns.
7. Characteristics, including time out of therapy, race/ethnicity, socioeconomic status, and family structure.

1. Open-ended qualitative study modified using open coding text.
2. The questionnaire and open-ended interview on the patient and family experience of neutropenia.

Data modified using open coding text, and audio files were transcribed and uploaded for analysis using NVivo 11 qualitative data analysis software.

Results revealed that parents are significant to minimizing burden of treatment for children; therefore, understanding their preferences was crucial. Some parents reported less anxiety during hospitalization regarding required medical care, while others reported emotional stress among patients and their siblings, in addition to sleep disturbances, affecting their QoL.

**Level of Evidence (Critical Appraisal Score)/Worth to Practice/Strengths and Weaknesses/Feasibility/Conclusion(s)/Recommendation(s)/**

**Level:** Systemic review, JHNEBP Appendix E: Level III

**Worth to practice:** Because the primary purpose of this study was to identify patient- and family-centered outcomes related to fever and FN management, it is worth continuing to design studies that focus on patient QoL regardless of treatment options.

**Weaknesses/Limitations:**
1. Utilization of a qualitative design limited generalizability of findings.
2. Respondents’ different characteristics that influenced their willingness to participate in comparison to those who declined to participate.
3. Cannot exclude unmeasured differences affecting participation decisions related to specific positive/negative experiences during treatment.

**Strengths:**
More comprehensive understanding of comparative difference in at-home vs. inpatient management of FN, which facilitated a structured
<table>
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<th>Purpose of Article or Review</th>
<th>Design/Method/Conceptual Framework</th>
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<th>Level of Evidence (Critical Appraisal Score)/Worth to Practice/Strengths and Weaknesses/Feasibility/Conclusion(s)/Recommendation(s)/</th>
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</table>
| **Inclusion:**  
2. If they were within 6–12 months of completion of the second course of chemotherapy or up to 3 years after completion of all frontline AML chemotherapy.  
**Conceptual Framework:**  
Social-ecological framework | | | | | | | questionnaire for a prospective multi-institutional trial.  
**Feasibility:** While feasible, it required meticulous quantitative and qualitative measurement and comparison of patient- and family-centered outcomes amongst the FN pediatric population. |

Definitions of abbreviations: Intensive Care Unit (ICU), Fever and Neutropenia (FN), Quality of Life (QoL), Emergency Department (ED), Acute Myeloid Leukemia (AML), Johns Hopkins Nursing Evidence-Based Practice (JHNEBP), Low Rate Fever and Neutropenia (LRFN)