COMPARISON OF DIFFERENT STRATEGIES FOR THE MANAGEMENT OF FEBRILE NEUTROPENIA IN CHILDREN – A COST-UTILITY ANALYSIS

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science (Clinical Epidemiology & Health Care Research)
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Abstract

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Introduction: There is uncertainty whether low-risk febrile neutropenia (FN) episodes in children with cancer are best managed in the inpatient or outpatient setting.

Methods: A cost-utility model was created to compare four different treatment strategies for low-risk FN in pediatric cancer patients. Outcome measures were quality-adjusted FN episodes (QAFNE), costs (Canadian dollar), and incremental cost-effectiveness ratios (ICER).

Results: The most cost-effective strategy was outpatient treatment with intravenous antibiotics. It was cost saving ($2,732 versus $2,757) and more effective (0.66 QAFNE versus 0.55 QAFNE) as compared to outpatient treatment with oral antibiotics. An early discharge strategy after 48 hours in hospital was slightly more effective but significantly more expensive than outpatient treatment with intravenous antibiotics resulting in an unacceptably high ICER of more than $130,000 per QAFNE. Inpatient care was the least cost-effective strategy.

Conclusions: Outpatient strategies for treatment of low-risk FN in children are more cost-effective than traditional inpatient care.
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CHAPTER 1 – INTRODUCTION

1.1. FEBRILE NEUTROPENIA IN CHILDREN WITH CANCER

1.1.1 Definitions

Both implementation of new strategies and refinement of existing treatment modalities have substantially improved overall survival rates in pediatric oncology over the last four decades. (1) Systemic chemotherapy, which is the mainstay of antineoplastic treatment in children, is, however, associated with significant burdens in terms of adverse effects. A common hematological complication, for example, is neutropenia, which is characterized by a reduced number of neutrophil granulocytes in the peripheral blood. Neutropenia increases the risk for serious infection in cancer patients and is associated with significant morbidity and mortality. (2, 3) The term ‘febrile neutropenia’ (FN) is a condition marked by fever and a lower-than-normal number of neutrophils in the blood. The Infectious Diseases Society of America 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer defines fever as a single oral temperature of ≥38.3°C (101°F), or a temperature ≥38.0°C (100.4°F) for more than 1 hour. (4) Neutropenia is defined as an absolute neutrophile count (ANC) of less than 500 cells/μL, or less than 1000 cells/μL with an anticipated decrease to <500 cells/μL. (4)

1.1.2 Incidence and Etiology

Febrile neutropenia is a common manifestation of infection in pediatric oncology. (1) Available data on the incidence of fever during chemotherapy-induced neutropenia in children with cancer are generally derived from randomized clinical trials. (5) Only limited information is provided on the overall incidence of FN regardless of specific eligibility criteria. A recent prospective study in children with cancer reported that one third of neutropenic periods was associated with
a febrile episode, accounting for a rate of 0.76 episodes per 30 days at risk. (6) The highest proportions of neutropenic periods with primary febrile episodes were observed after autologous hematopoietic stem cell transplantation (58 percent), aggressive treatment for acute leukemia or non-Hodgkin lymphoma (48 percent), and allogeneic hematopoietic stem cell transplantation (44 percent); the lowest proportion (9 percent) was observed during maintenance chemotherapy for acute leukemia.

Microbiological and clinical characteristics of neutropenic infections vary with the geographic location of the treatment center. (6-12) Positive blood cultures can be obtained in about 10 to 35 percent of FN episodes in pediatric cancer patients. This is probably a conservative estimate in view of the frequently inadequate blood volume drawn for blood cultures in pediatric patients and the difficulty in recovering some organisms, which can be fastidious to culture (e.g., yeast). (13) The pattern of microbiologically relevant organisms in FN is constantly changing. Over the last decades, the focus has shifted towards an increased prevalence of gram-positive organisms, which now represent more than 50 percent of blood cultures of pediatric patients with FN. (6)

1.1.3 Age-Related Differences in Febrile Neutropenia

While facing the issue of FN in children with cancer, it is important to note that pediatric cancer patients are different from their adult counterparts in multiple ways. (6, 14) These include a different spectrum of oncologic diagnoses, greater intensity of chemotherapy regimens (with a larger percentage of children with cancer who are treated with a curative goal), and decreased incidence and severity of co-morbid medical conditions in children as compared to adults. In addition, the use of prophylactic antimicrobials, the percentage of patients with indwelling central venous catheters, the community exposure to infectious pathogens, the maturation of the
immune system, and the ability to take oral medication may be different based on age. Due to those differences, research questions related to FN in children have to be addressed separately. Noncritical adoption or extrapolation from adult studies would be inappropriate.

1.1.4 Treatment of Febrile Neutropenia

Without adequate treatment, patients with FN may experience fatal complications of bacterial sepsis. Therefore, any FN episode should be managed as a potential emergency. (15) One of the most important advances in supportive oncology care leading to improved survival has been the prompt initiation of empirical treatment with intravenous (IV) broad-spectrum antibiotics in patients presenting with FN. Before this approach was instituted in the early 1970s, the mortality rate from gram-negative infections, especially *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*, approached 80%. (2, 3, 16, 17) Consequently, FN episodes have traditionally been managed entirely in an inpatient setting, and the discharge of patients has been delayed until resolution of fever and sustainable hematopoietic recovery. Initial antibiotic regimens typically consist of a 2-drug IV combination of an aminoglycoside plus an antipseudomonal penicillin, a cephalosporin, or a carbapenem. Alternatively, monotherapy with a cephalosporin or a carbapenem may be administered. (4)

It is important to note that regular surveillance of local microbiological data is necessary to inform the best choice of first-line empiric therapy. (18) The current FN guidelines at The Hospital for Sick Children (SickKids) in Toronto/Canada, for example, suggest initial empiric IV therapy with piperacillin-tazobactam plus gentamicin for higher-risk patients (without penicillin allergy) and piperacillin-tazobactam monotherapy for lower-risk patients presenting with FN. (19)
1.2. TREATMENT STRATEGIES FOR LOW-RISK FEBRILE NEUTROPENIA

1.2.1 Safety and Efficacy of Different Treatment Strategies

The standard of care for FN in pediatric cancer patients, inpatient management with IV antibiotic treatment, together with modern supportive care, is associated with an overall mortality rate as low as 1 to 3 percent. (14, 20) However, this management scheme is associated with disruption of family life, prolonged hospital admission, high medical costs, nosocomial complications, and increasing resistance to antibiotics. More recently, it has become clear that not all children with FN are at equal risk for significant morbidity and mortality. Thus, current attention has turned to the possibility of distinguishing between children at high risk of developing bacterial sepsis, where an aggressive approach is required, and those at low risk, who could be managed at home. (21)

Several randomized controlled trials (RCT) in the pediatric population have evaluated safety and efficacy of outpatient and/or oral antibiotic treatment for low-risk FN. The first pediatric study providing evidence that outpatient strategies might be safe and efficacious alternatives for patients with low risk FN was published by Mullen et al. in 1999. (22) The authors did not find a significant difference in treatment failure between patients receiving ceftriaxone IV and patients receiving oral ciprofloxacin, when both were administered in an ambulatory setting. Several other studies published between 2000 and 2009 reported similar findings, with no deaths occurring in these trials, thereby indicating safety and efficacy of such an approach. (23-27) Interestingly, the first RCT comparing inpatient with outpatient management in the pediatric setting was not published before 2004. (28) Santolaya et al. showed that treatment failure did not significantly differ between outpatient management (ceftriaxone plus teicoplanin) and inpatient management (ceftriaxone plus teicoplanin) in low-risk FN
episodes. In this study one patient assigned to inpatient treatment died due to infectious complications.

1.2.2 Definition of Low-Risk Febrile Neutropenia

A consensus panel from the Multinational Association for Supportive Care in Cancer (MASCC) developed a set of criteria which could be used to define the ‘low-risk’ adult patients: acquisition of fever out of hospital, age younger than 60 years, absent or moderate symptoms, no hypotension, no chronic bronchitis, and no history of fungal infection were all predictors of a good prognosis in a validated scoring system.(29) However, the MASCC risk index has no value in the pediatric setting. At least two of the seven independent risk factors (age younger than 60 years and chronic bronchitis) do not apply to pediatric patients. Whereas several studies have attempted to develop risk stratification tools for children based on history, physical findings, and laboratory values, no consensus has been reached among pediatric oncologists.(30-33).

A recent multi-centre study from the United Kingdom evaluated the safety and efficacy of a step-down oral antibiotic strategy for low-risk pediatric FN.(34) All patients commenced empirical IV antibiotic therapy, and after 48 hours those with blood culture-negative episodes designated ‘low-risk’ were eligible for discharge on oral amoxicillin-clavulanate. The authors reported a low hospital readmission rate (8/143 episodes; 5.6 percent), no intensive care admissions and no deaths in low-risk episodes. The following risk factors were used to exclude patients from the low-risk protocol:

- Age <1 year
- Shock or compensated shock, hemorrhage, dehydration, metabolic instability, altered mental status, pneumonitis, mucositis (unable to tolerate oral fluids or requiring IV
analgesia), respiratory distress/compromise, perirectal or other soft tissue abscess, rigors, irritability/meningism, or organ failure

- Acute lymphoblastic leukemia (ALL) at diagnosis/relapse <28 days, ALL not in remission (>28 days), acute myeloid leukemia (AML), infant ALL, intensive B-NHL (non-Hodgkin lymphoma) protocols, hematopoietic stem cell transplant, or sequential high dose chemotherapy with peripheral blood stem cell rescue

- Intensive care admission during last FN episode, non adherence (for example social concerns), or inability to tolerate oral antibiotics

- Positive blood culture result at 48 hours, ANC <100/μL at 48 hours, or child not clinically well at 48 hours (clinical judgment)

Whereas this detailed list of risk factors may serve as an important decision aid for early discharge strategies, it cannot be considered as a validated risk prediction tool for initial risk stratification in pediatric patients.

1.2.3 Inconsistent Treatment Strategies for Children

There is clear evidence in the literature that no consensus so far has been reached among pediatric oncologists in regard to a uniform stratification or treatment strategy for children with low-risk FN. Three recently published practice surveys from Canada, the United Kingdom, and Australia/New Zealand indicate substantial inter- and intra-country variability among treatment approaches for low-risk FN in children. (35-37) Boragina et al. reported results of a cross-sectional mailed survey of 17 tertiary pediatric centers in Canada. Only three out of seventeen centers carried out exclusively traditional inpatient management. The remaining 14 centers offered modified treatment approaches for low-risk children. The majority (n=10) carried out an
early discharge approach. The remaining 4 centers implemented complete outpatient management.

Two issues may be associated with this variability; first, the lack of a commonly accepted risk prediction tool for children with FN (see above), and second, remaining uncertainty regarding the best treatment strategy for low-risk FN in pediatric cancer patients.

1.2.4 Costs Associated with Febrile Neutropenia

Information about the economic burden of FN mainly arises from the adult literature. (38) Limited data are available about costs in the pediatric setting. (28, 39) However, two studies from Canada reported the substantial cost-saving potential of outpatient management as compared to inpatient care for FN in children. (40, 41) Whereas cost information from adult cancer patients cannot easily be translated into pediatric ‘numbers’, they may nevertheless provide some general background information for the purpose of the present study.

A recent systematic review evaluating the economic burden of neutropenia indicated that direct costs of neutropenia ranged from $US2,893 to $US38,583 (2006 values $US4,842 to $US49,917) per episode for inpatients (United States; US). (38) For outpatients, the costs were $US1,893 (2006 value $US2,632) per episode. Outside of the US, the costs per episode ranged from $US300 (2006 value) for non-febrile cases to $US32,395 for elderly breast cancer patients with neutropenic complications. In general, the cost of neutropenia appeared to be lower in other countries compared with the US, with most estimates being <$US7,000 (2006 value) per episode. Hospitalization was the largest driver of the cost of neutropenia, comprising as much as 82 percent of the total direct medical costs for neutropenia. Major components of the hospital costs included the room (36-38 percent of hospital costs), pharmacy (27-33 percent), supplies (4-17 percent) and blood bank products (3-14 percent). (38)
Whereas the costs may vary between different geographic regions, disease types, or patient ages, there are consistent data indicating that outpatient management for FN is substantially cost-saving as compared to traditional inpatient treatment.

1.2.5 Patients’ Preferences for Different Treatment Strategies

Different treatment strategies for FN may be associated with different profiles of short-term and long-term expected health-related quality of life (HRQL). Optimal decision-making requires an understanding of expected health during these different treatment strategies in addition to knowledge of probabilities of treatment success and valuation of different outcomes from the child, family and healthcare provider perspectives. (42)

In addition to health profile measures (e.g. Child Health Questionnaire or the Pediatric Quality of Life Inventory (PedsQL™)), health utility measures represent an alternative approach to assessing the outcomes of treatment strategies. Arising out of classical economic theory and the practical need of health economists for health outcomes to be used in economic evaluation, health utilities provide a way of summarizing morbidity and mortality outcomes in a single metric. (43, 44) Health utilities reflect quantitative assessments of the strength of individual preferences for health states when measured under conditions of uncertainty. (44) Health utilities may be elicited in different ways. Preferences for health states can be obtained directly using scaling techniques such as the standard gamble approach, the time trade-off approach, or rating scales. (45, 46) Health utilities may also be obtained indirectly through multi-attribute utility measures such as the Health Utilities Index (HUI) or the EQ-5D. (45) The HUI and EQ-5D assess quality of life through multiple attributes such as vision, hearing, speech, self-care, mobility, dexterity, emotion, cognition and pain.
In general, adults typically can self-report their own HRQL. However, in pediatrics, proxy respondents are commonly required. The ability of children to describe HRQL will change over time, with a greater ability to complete rating scales at an earlier age compared with more cognitively difficult methods such as the standard gamble. In addition, completion of some HRQL instruments requires the respondent to be able to read, which may be problematic in younger children.

Very limited data are available that describe health utilities in children in the context of FN. Sung et al. elicited parents’ and healthcare providers’ preferences for management strategies of low-risk FN in children. In their study, only 53 percent of parents would choose outpatient oral antibiotics management, whereas 71 percent of healthcare providers would prefer such a strategy for febrile neutropenic children ($P = 0.08$). Estimated HRQL scores were higher for oral outpatient management (parents 0.69; healthcare provide 0.74) than scores for parenteral inpatient management (parents 0.52; healthcare provide 0.38). For parents, stronger preference for oral outpatient therapy was associated with higher anticipated quality of life for the parent and child at home relative to hospital, lower importance rank for "fear/anxiety," and higher importance rank for "comfort." Conversely, for professionals, only lower importance rank for "fear/anxiety" was associated with higher strength of preference scores for outpatient oral antibiotic management.

A more recent study by the same research group elicited parents’ preferences considering four different treatment strategies for low-risk FN in children, namely inpatient management, treatment at home after an initial observation in hospital, entire outpatient management with IV antibiotics, and entire outpatient management with oral antibiotics. Parent proxy-report revealed mean utilities of 0.67 (inpatient management), 0.71 (treatment at home after an initial observation in hospital), 0.70 (entire outpatient management with IV
antibiotics), and 0.60 (entire outpatient management with oral antibiotics) respectively. Remarkably, and in contrast to the previous study, preference scores for outpatient oral therapy were lower than those of inpatient care. A possible explanation might be that alternative outpatient strategies were offered in the latter study. It is also important to note that different elicitation techniques have been used in the two studies (threshold technique versus rating scale technique).

1.2.6 Trade-Offs between Different Treatment Strategies

Currently, medical decision-making in clinical practice is often an imperfect process. Very rarely, evidence, values, and economic burdens are systematically captured and synthesized logically before final decisions are made. To provide a comprehensive framework for this study, risks and benefits of different treatment strategies for low-risk FN in children have to be considered. Table 1 outlines the risks and benefits of four different treatment strategies, namely inpatient management, treatment at home after an initial observation in hospital, entire outpatient management with IV antibiotics, and entire outpatient management with oral antibiotics. The four options were chosen based on clinical judgment and treatment scenarios published in the literature.(22-28, 39)
Table 1. Risks and benefits for different treatment strategies in febrile neutropenia

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INPATIENT</strong>&lt;br&gt;IV ANTIBIOTICS</td>
<td>Patient’s preference&lt;br&gt;Safety (clinicians present)&lt;br&gt;No pills</td>
<td>Healthcare-related infections&lt;br&gt;IV access (pain, infection)&lt;br&gt;Costs (healthcare payer)&lt;br&gt;Distance to hospital (family)</td>
</tr>
<tr>
<td><strong>EARLY DISCHARGE</strong>&lt;br&gt;PO ANTIBIOTICS</td>
<td>Patient’s preference&lt;br&gt;Psychosocial environment&lt;br&gt;Lower costs (healthcare payer)</td>
<td>Adverse effect PO (for example gastrointestinal side effects)&lt;br&gt;Clinic visits&lt;br&gt;Readmission&lt;br&gt;Anxiety (no clinicians present)&lt;br&gt;Work load (family)</td>
</tr>
<tr>
<td><strong>OUTPATIENT</strong>&lt;br&gt;IV ANTIBIOTICS</td>
<td>Patient’s preference&lt;br&gt;Psychosocial environment&lt;br&gt;Lower costs (healthcare payer)&lt;br&gt;No pills&lt;br&gt;Reduced risk of healthcare-related infections</td>
<td>Adverse effect IV&lt;br&gt;IV access (pain, infection)&lt;br&gt;Clinic visits&lt;br&gt;Need for homecare nurse&lt;br&gt;Readmission&lt;br&gt;Anxiety (no clinicians present)&lt;br&gt;Work load (family)</td>
</tr>
<tr>
<td><strong>OUTPATIENT</strong>&lt;br&gt;PO ANTIBIOTICS</td>
<td>Patient’s preference&lt;br&gt;Psychosocial environment&lt;br&gt;Lower costs&lt;br&gt;Very small risk of healthcare-related infections</td>
<td>Adverse effect PO (for example gastrointestinal side effects)&lt;br&gt;Clinic visits&lt;br&gt;Readmission&lt;br&gt;Anxiety (no clinicians present)&lt;br&gt;Work load (family)</td>
</tr>
</tbody>
</table>

IV indicates intravenous, PO oral; the table was created based on clinical judgment and reports in the literature as outlined in the previous paragraphs.

1.2.7 Decision Analysis and Cost-Utility Analysis

Decisions about problems are often complex, and the ability to integrate complicated information and arrive at a rational decision is often imperfect. Specifically, medical decision-making is often difficult because it may involve trade-offs between benefits and risks or costs. Decision analysis is a technique that supplements reasoning, and helps us avoid reasoning errors. Decision analysis uses models to explicitly describe and quantitatively compare all
possible outcomes of alternative diagnostic or therapeutic strategies for clinical problems. Therefore, decision analysis may be useful in determining the optimal treatment strategy in pediatric oncology patients with FN because of the trade-offs between inpatient and outpatient management, and oral and parenteral regimens, respectively, as outlined in the previous section.

In essence, decision tree models are a sequence of decisions and chance events over time where every chance event is assigned a probability. Each path through the decision tree consists of a combination of the decision node (square at the left end of the tree) and chance nodes (circles within the tree) and is associated with a final pathway designated by a terminal node (triangle at the right end of the tree). Each decision alternative is evaluated with weighted utility values calculated from data entered at the terminal nodes of the decision analysis tree and the proportions of weighting entered below the branches. The preferred decision is defined as the alternative with the largest expected value.

While the outcomes associated with terminal nodes are often in the form of utility values, other values such as dollars ($), $/quality-adjusted life-years (QALY), life-years, or visual acuity, can be used depending upon what is being studied. This thesis project will focus on costs per quality-adjusted time period. Such an analysis is also referred to by the term cost-utility analysis.

There are a number of types of decision-analytic models. The most basic one is a simple decision analysis tree (see above). Simple decision trees are usually employed to examine events that will occur in the near future. They are therefore best suited to evaluate interventions to prevent or treat illnesses of a short duration, such as acute infectious diseases. They may also be used to evaluate chronic diseases that may be cured (for example, by surgical intervention). When these trees are used to evaluate diseases that change over time, they are sometimes not the most appropriate tool to be chosen.
For chronic or complex diseases, it is best to use a state transition model. This type of model allows researchers to incorporate changes in health states over time into the analysis. For example, if a person has cancer, there is a chance that the person will recover within a year and then relapse. There is also a chance that the person will remain sick for some time or will die soon. With every passing month (or year), the chances of survival, recovery, or deterioration change. These models, which are also called Markov models, allow researcher to track changes in quality of life, the quantity of life, and the cost of disease over time when different health interventions are applied. (56, 57)

1.3. PURPOSE OF THE STUDY
The philosophy behind outpatient treatment strategies assumes several potential advantages, such as convenience for children and their families, improved quality of life, reduction of the incidence of healthcare-related infections, and reduction in healthcare payer’s costs. (21) However, there is substantial uncertainty related to these assumptions. Some of the uncertainty is related to questions about whether there are any clinically important differences in the safety or efficacy of the different management strategies. (58) Further, assumptions related to HRQL and preferences of the patients and their families in the context of FN remain speculative. There are only limited data reporting preferences for children with FN. (47, 48) In contrast, there is a strong body of published evidence suggesting that the cost of in-hospital treatment are greater than the costs of ambulatory care for FN. (28, 38, 40, 41) A major limitation of current data is whether the higher costs of inpatient care can be justified on the basis of safety and efficacy considerations, or patients’ preferences.
1.4. STUDY OBJECTIVE

The goal of this study is to determine the most cost-effective treatment strategy for low-risk FN in children with cancer.

In general, two different approaches are possible to address this issue; first, a RCT, and second, a decision-analytic model. Whereas the former approach is generally considered to be the gold standard to answer clinical queries related to therapy strategies, it is always associated with significant logistic challenges and substantial economic burdens. The comparison of four different treatment strategies, as proposed in this thesis project, would further hamper the feasibility of a clinical trial, especially in a pediatric setting. Thus, a decision-analytic model was created to answer the research question as outlined above. For the purpose of this thesis project, there are several advantages of creating such a model as compared to conducting a RCT. First, completion of a decision-analytic model requires much less time and far fewer resources compared with a RCT, thus making this approach more feasible. Second, the nature of a decision-analytic model allows flexibility in terms of inclusion of several treatment strategies. Evaluating more than two strategies in a pediatric RCT would substantially increase the sample size and threaten feasibility. Finally, review of the literature indicated that a sufficient amount of information would be available to populate a decision-analytic model, which is a critical precondition to perform a decision analysis.

Specifically, a cost-utility model was constructed to determine the optimal treatment strategy for low-risk FN in children with cancer. In this study, costs and effectiveness (measured as quality-adjusted FN episodes; QAFNE) of four different treatment strategies for low-risk FN were examined. These included entire inpatient management, treatment at home after an initial observation in hospital, entire outpatient management with IV antibiotics, and entire outpatient management with oral antibiotics.
CHAPTER 2 – METHODS

2.1. COST-UTILITY MODEL

2.1.1. Overview and Definitions

Pediatric cancer patients (age 1-18 years) receiving standard dose and schedule chemotherapy with a first episode of low-risk FN were entered into a decision-analytic model as a hypothetical cohort. The analysis adopted the healthcare payer’s perspective in Canada and included all relevant direct health costs. The Ontario Health Insurance Plan (OHIP) covers direct health costs associated with FN, however, outpatient drug costs are paid by the patients separately. For the purpose of this study, we also included outpatient drug costs that are not covered by OHIP, as these are often covered by private or governmental payers in several jurisdictions.

The time frame of the model encompassed one episode of FN limited to 30 days. There are no data in the literature indicating that long-term implications of a single low-risk episode significantly differ between strategies.\(^{(22-24, 26-28)}\) Due to the short time frame and the non-fatal nature of low-risk FN, a simple decision-analytic model was chosen instead of a Markov model. As explained earlier (section 1.2.7) this is an appropriate choice for FN, whereas for chronic or complex diseases, it would be better to use a state transition model (Markov model).\(^{(56, 57)}\)

Death was not included as an outcome in the model, because this is a very unusual event in low-risk FN in children. Considering 788 FN episodes in 6 RCT for children with low-risk FN, there was only a single case of death in one inpatient episode.\(^{(22-24, 26-28)}\) These data are supported by findings of a recent prospective multi-center observational study in the UK evaluating safety and efficacy of an early discharge strategy. In 143 episodes managed on their low-risk protocol, no deaths were observed. Thus, there is strong evidence in the literature that
death rates are negligible and do not appreciably differ between the different management strategies in children with low-risk FN. Consequently, inclusion of death would not substantially contribute to preferences for any one strategy.

As outlined in section 1.2.2, no consensus has been reached among pediatric oncologists regarding a uniform definition of ‘low-risk’. However, for the purpose of this decision analysis, studies evaluating low-risk FN episodes had to consider criteria such as: 1) hemodynamic stability, 2) no organ failure, 3) ability to take oral medication, 4) no allergy to suggested antibiotics, 5) no pregnancy or lactation and, 6) not acute leukemia undergoing induction therapy. These criteria did not serve as rigid inclusion/exclusion criteria for studies selected for the cost-utility analysis, but provided a theoretical framework for the general concept of low-risk FN episodes.(34)

2.1.2. Decision-Analytic Model

A decision-analytic model was constructed using TreeAge Pro 2009 (release 1.0.2) and examined 4 strategies:

1. Entire treatment in hospital with IV antibiotics
2. Early discharge consisting of 48 hours inpatient observation with IV antibiotics followed by oral outpatient treatment
3. Entire outpatient management with IV antibiotics
4. Entire outpatient management with oral antibiotics

The structure of the decision tree is illustrated in Figure 1.
Figure 1. Clinical decision model to compare different treatment strategies for low-risk febrile neutropenia in pediatric cancer patients; four treatment strategies are evaluated: (1) entire treatment in hospital with intravenous antibiotics (HospIV), (2) early discharge consisting of 48 hours inpatient observation with intravenous antibiotics followed by oral outpatient treatment (EarlyDC), (3) entire outpatient management with intravenous antibiotics (HomeIV), and (4) entire outpatient management with oral antibiotics (HomePO). HCR infection indicates healthcare-related infection.
Each strategy was associated with a similar pathway of events: (1) the probability of treatment failure, and (2) the probability of a healthcare-related infection. All strategies other than entire inpatient treatment also included the probability of hospital admission and readmission, respectively. For all strategies, patients’ preferences (health utilities) and costs were also included.

Treatment failure was defined as a composite end-point comprising one or more of the following: persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; and any addition to, or modification of the assigned intervention, including toxicity and readmission to hospital (if applicable). This was necessary to harmonize the outcome ‘treatment failure’ due to inconsistent definitions of failure in studies evaluating efficacy of different treatment strategies in children with low-risk FN (see Appendix A).

Definitions and assumptions related to the four treatment strategies are outlined in the next section. Assumptions were either justified by published literature or by the author’s clinical experience. Assumptions exclusively based on the author’s experience were discussed with, and confirmed by, other practicing oncologists. Moreover, sensitivity analyses performed on the final model considered the uncertainty related to these assumptions. The antibiotic choices are in line with recommendations from the Infectious Diseases Society of America. (4) Consistent with the published literature, average treatment duration was defined as 6 days for all four strategies. (22-24, 26, 28)

Strategy 1: Entire treatment in hospital with IV antibiotics

- First-line in hospital antibiotics IV = piperacillin-tazobactam (every 8 hours) & gentamicin (every 24 hours) = cost ABIV1 (4)
- Failure, when it occurs, happens 3 days after treatment initiation
- Inpatient treatment failure is treated with second-line antibiotics = meropenem, vancomycin & gentamicin = cost ABIV2
- Treatment failure adds another 6 days of treatment (in addition to the initial 3 days prior to failure)
- Empiric anti-fungal treatment was not considered for low-risk FN
- The occurrence of a healthcare-related infection is not directly related to treatment success but to length of treatment
- Healthcare-related infections add another 6 days of treatment (in addition to the initial 3 days before healthcare-related infections)
- Healthcare-related infections increase treatment costs (baseline antibiotics x 1.5) for specific treatment modification
- Healthcare-related infections and treatment failure can be managed at the same time, thus, having both adds a total of 6 days to total treatment duration
- Treatment failure and healthcare-related infection are associated with independent utility multiplication with factors of 0.8 and 0.5, respectively (59)

Strategy 2: Early discharge consisting of 48 hours inpatient observation with IV antibiotics followed by oral outpatient treatment

- First-line in hospital antibiotics IV = piperacillin-tazobactam (every 8 hours) & gentamicin (every 24 hours) = cost ABIV1 (4)
- First-line antibiotics PO = amoxicillin/clavulanate (every 8 hours) & ciprofloxacin (every 12 hours) (4, 23)
- Patients treated in an ambulatory setting are seen every other day in the outpatient clinic
- Treatment failure in the early discharge strategy can only happen after discharge
• Failure, when it occurs, happens 24 hours after early discharge (3 days after treatment initiation)

• Outpatient treatment failure with readmission are treated with second-line antibiotics = meropenem, vancomycin & gentamicin = cost ABIV2

• Outpatient oral treatment failure without readmission increases costs (cost = ABIV1_home)

• Treatment failure adds another 6 days of treatment (in addition to the initial 3 days prior to failure)

• Empiric anti-fungal treatment was not considered for low-risk FN

• Patients in ambulatory care are also susceptible to healthcare-related infections (blood-stream and non-blood-stream related infections)

• The relative risk for a healthcare-related infections in the outpatient setting is 0.1 (oral) as compared to inpatient management (60-62)

• The occurrence of a healthcare-related infection is not directly related to treatment success but to length of treatment

• Healthcare-related infections, when present, occur at 24 hours after early discharge

• Healthcare-related infections are treated in the setting in which they occurred

• Healthcare-related infections add another 6 days of treatment (in addition to the initial 3 days before healthcare-related infections)

• Healthcare-related infections increase treatment costs (baseline antibiotics x 1.5) for specific treatment modification

• Healthcare-related infections and treatment failure can be managed at the same time, thus, having both adds a total of 6 days to total treatment duration

• Treatment failure, readmission, and healthcare-related infection are associated with independent utility multiplication with factors of 0.8, 0.5, and 0.5, respectively (59)
Strategy 3: Entire outpatient management with IV antibiotics

- First-line outpatient antibiotics IV = ceftriaxone (every 24 hours) & amikacin (every 24 hours) = cost ABIV1_home (4, 23, 26)
- Outpatient IV antibiotics will be administered once daily by a home care nurse
- Patients treated in an ambulatory setting are seen every other day in the outpatient clinic
- Failure, when it occurs, happens 3 days after treatment initiation
- Outpatient treatment failure with readmission is treated with second-line antibiotics = meropenem, vancomycin & gentamicin = cost ABIV2
- Outpatient IV treatment failure without readmission increases costs (cost ABIV2)
- Treatment failure adds another 6 days of treatment (in addition to the initial 3 days prior to failure)
- Empiric anti-fungal treatment was not considered for low-risk FN
- Patients in ambulatory care are also susceptible to healthcare-related infections (blood-stream and non-blood-stream related infections)
- The relative risk for a healthcare-related infections in the outpatient setting is 0.2 (IV) as compared to inpatient management (60-62)
- The occurrence of a healthcare-related infection is not directly related to treatment success but to length of treatment
- Healthcare-related infections, when present, occur at 3 days after treatment initiation
- Healthcare-related infections are treated in the setting in which they occurred
- Healthcare-related infections add another 6 days of treatment (in addition to the initial 3 days before healthcare-related infections)
- Healthcare-related infections increase treatment costs (baseline antibiotics x 1.5) for specific treatment modification
Healthcare-related infections and treatment failure can be managed at the same time, thus, having both adds a total of 6 days to total treatment duration.

Treatment failure, readmission, and healthcare-related infection are associated with independent utility multiplication with factors of 0.8, 0.5, and 0.5, respectively (59).

**Strategy 4: Entire outpatient management with oral antibiotics**

- First-line antibiotics PO = amoxicillin/clavulanate (every 8 hours) & ciprofloxacin (every 12 hours) (4, 23)
- Patients treated in an ambulatory setting are seen every other day in the outpatient clinic
- Failure, when it occurs, happens 3 days after treatment initiation
- Outpatient treatment failure with readmission is treated with second-line antibiotics = meropenem, vancomycin & gentamicin = cost ABIV2
- Outpatient oral treatment failure without readmission increases costs (cost = ABIV1\_home)
- Treatment failure adds another 6 days of treatment (in addition to the initial 3 days prior to failure)
- Empiric anti-fungal treatment was not considered for low-risk FN
- Patients in ambulatory care are also susceptible to healthcare-related infections (blood-stream and non-blood-stream related infections)
- The relative risk for a healthcare-related infections in the outpatient setting is 0.1 (oral) as compared to inpatient management (60-62)
- The occurrence of a healthcare-related infection is not directly related to treatment success but to length of treatment
- Healthcare-related infections, when present, occur at 3 days after treatment initiation
- Healthcare-related infections are treated in the setting in which they occurred
• Healthcare-related infections add another 6 days of treatment (in addition to the initial 3 days before healthcare-related infections)

• Healthcare-related infections increase treatment costs (baseline antibiotics x 1.5) for specific treatment modification

• Healthcare-related infections and treatment failure can be managed at the same time, thus, having both adds a total of 6 days to total treatment duration

• Treatment failure, readmission, and healthcare-related infection are associated with independent utility multiplication with factors of 0.8, 0.5, and 0.5, respectively (59)

The model was designed to obtain the probabilistically weighted average cost and effectiveness of each strategy. Specifically, the outcome measures were QAFNE, costs (Canadian dollar), and incremental cost-effectiveness ratios (ICER). The following sections will describe how event probabilities (section 2.2), utilities (section 2.3), and costs (section 2.4) were obtained. Section 2.5, finally, will provide a detailed list of all parameter inputs of the model, including plausible ranges for each parameter.
2.2. EVENT PROBABILITIES

A systematic review was performed to establish the best available evidence related to outpatient management of FN in children with cancer. Event probability data obtained from included studies were applied to the cost-utility model. The systematic review was performed according to the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.(63)

As part of the data collection process for the cost-utility analysis, the output of the systematic review will also be displayed within this methods section.

2.2.1 Data Sources and Searches

Biomedical literature databases and conference proceedings were searched for relevant articles:

1) OVID MEDLINE from 1950 to January 2010
2) EMBASE from 1980 to January 2010
3) The Cochrane Central Register of Controlled Trials (CENTRAL) to first quarter of 2010
4) Web of Science database (conference proceedings) from 2007 to 2010
5) Scopus database (conference proceedings) from 2007 to 2010

The following search terms were used for CENTRAL and MEDLINE:

(((agranulocytosis/ or neutropenia/ or leukopenia/) AND (fever/ or "fever of unknown origin"))
OR (febrile adj5 (neutropen* or granulocytop* or agranulocyto* or leukocytop??ni*)).ti,ab.)
AND (exp Anti-Bacterial Agents/ or exp Bacterial Infections/) AND (Ambulatory Care/ or Home Care Services/ or Outpatient Clinics, Hospital/ or inpatients/ or outpatients/ or "length of stay"/ or patient discharge/ or (early adj5 discharg*).ti,ab. or (domiciliary or ambulatory or
inpatient* or outpatient* or "out-patient*" or admission* or admitted or home).mp.)

In addition to the mentioned search strategy, the Robinson-Dickersin search strategy was applied. (64) This is a sensitive search strategy designed to identify RCT.

The following terms were used for EMBASE:

((Febrile Neutropenia/) OR ((leukopenia/ or agranulocytosis/ or granulocytopenia/ or neutropenia/) AND (fever/ or pyrexia idiopathica/)) OR ((febrile adj5 (neutropen* or granulocytop* or agranulocyto* or leukocytop??ni*).ti,ab.)).ti,ab.)) AND (exp Antibiotic Agent/ or exp Bacterial Infection/) AND (ambulatory care/ or ambulatory care nursing/ or home care/ or home intravenous therapy/ or hospital care/ or "length of stay"/ or outpatient/ or exp hospital patient/ or outpatient care/ or hospital department/ or outpatient department/ or oncology ward/ or child hospitalization/ or hospital admission/ or hospital discharge/ or hospitalization/ or hospital readmission/ or (early adj5 discharg*).ti,ab. or (domiciliary or ambulatory or inpatient* or outpatient* or "out-patient*" or admission* or admitted or home).mp.) AND (ct.fs. or clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/ or randomized controlled trial/ or multicenter study/ or meta analysis/ or cohort analysis/ or crossover procedure/ or cross-sectional study/ or double blind procedure/ or single blind procedure/ or triple blind procedure/ or ct.fs. or (rct or rcts or ((singl: or doubl: or tripl: or trebl:) and (mask: or blind:))).mp. or comparative study/ or exp evaluation studies/ or follow-up studies/ or prospective studies/ or cross-over studies/ or (control$ or prospective$ or volunteer$).mp.)
2.2.2 Study Selection

RCT comparing any outpatient antibiotic treatment to any inpatient antibiotic treatment, for the management of FN in pediatric cancer patients, were included. The outpatient strategy could be initiated at presentation, or as part of an early discharge strategy in which all patients were initially treated as inpatients and those allocated to outpatient treatment were switched to outpatient therapy after a predefined time period independent of neutrophil count. Classification of age was performed according to trial definition; in general, children included ages up to 18 years.

Further, RCT comparing any oral antibiotics to any IV antibiotics, for the outpatient management of FN in pediatric cancer patients, were included. The oral antibiotics could be initiated at presentation in patients allocated to oral treatment, or as part of a sequential IV to oral strategy. In the sequential strategy, all patients were initially treated with IV therapy and those allocated to oral treatment were switched to oral therapy after a predefined time period independent of the neutrophil count. Classification of age was performed according to trial definition; in general, children included ages up to 18 years.

One reviewer (MOT) evaluated the titles and abstracts of publications identified by the search strategy. Any publication felt to be potentially relevant was retrieved in full and evaluated by 2 reviewers (MOT and Marie-Chantal Ethier (MCE)). Final inclusion of studies in the meta-analysis was determined by agreement of both reviewers. Agreement between reviewers was evaluated by using the kappa statistic. Strength of agreement as evaluated by the kappa statistic was defined as slight (0.00 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), or almost perfect (0.81 to 1.00). (65) SAS software (version 9.2) was used to calculate the kappa statistic.
2.2.3 Data Extraction and Quality Assessment

Two review authors (MOT and MCE) independently extracted data from included trials. Data extraction was performed using a standardized data collection form (Appendix B). This systematic review was part of a broader research question, thus, the data collection sheet covers aspects that are not relevant for this study.

The primary outcome measure for both objectives was treatment failure at 30 days. As described earlier (section 2.1.2), treatment failure was defined as a composite end-point comprising one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; and any addition to, or modification of the assigned intervention, including readmission. Secondary outcome measures were: (1) all-cause mortality at 30 days; (2) adverse events requiring discontinuation/modification of therapy; and (3) readmission to the hospital.

To assess methodological quality and risk of bias, included articles were examined for: (1) sequence generation; (2) allocation concealment; (3) blinding; (4) incomplete outcome data, and (5) intention-to-treat (ITT) analysis (see data collection sheet; Appendix B).

2.2.4 Data Extraction for the Cost-Utility Model

A key element in most systematic reviews is the statistical synthesis of the data, or the meta-analysis. However, a formal meta-analysis was not considered for the purpose of this study. All included studies obtained from the literature compared two different interventions, either inpatient versus outpatient management or outpatient IV versus oral outpatient management. On the contrary, the decision-analytic model proposed in this study considered four different treatment strategies. Thus, the summary effect (weighted mean of the individual effects) of a meta-analysis would not be applicable to the decision-analytic model. Instead, the (non-
weighted) mean rates of the relevant outcomes were extracted from the included studies accordingly for the distinct strategies in the model.

2.2.5 Results of the Systematic Review

Figure 2 illustrates the flow diagram of trial identification and selection. A total of 1,448 titles and abstracts were reviewed, and 21 full articles were retrieved. Of these, seven satisfied eligibility criteria, and were included for data extraction.(22-24, 26-28, 39) The reasons for excluding 14 articles were: no outpatient episodes assessed (3 articles)(67-69), trial not randomized (3 articles)(70-72), both treatment arms outpatient sequential IV to oral treatment (one article)(25), and adult trials (7 articles)(73-79).

![Flow diagram of trial identification and selection](image)

**Figure 2.** Flow diagram of trial identification and selection
The reviewers had almost perfect agreement on articles for inclusion, with a kappa statistic of 0.90 (95% CI, 0.70 to 1.00). The ratings of the two reviewers are outlines in Table 2.

**Table 2.** Inter-rater agreement of articles - Inclusion/Exclusion

<table>
<thead>
<tr>
<th></th>
<th><strong>Reviewer 1 (MOT)</strong></th>
<th><strong>Reviewer 2 (MCE)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Included studies</strong></td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td><strong>Excluded studies</strong></td>
<td>1</td>
<td>13</td>
</tr>
</tbody>
</table>

Whereas the study of Ahmed et al. fulfilled the *a priori* inclusion criteria, it was excluded subsequently from the model because it evaluated early discharge strategies only in patients with prolonged episodes of FN.(39) Data from this study were not considered to be appropriate for the cost-utility model because this trial excluded patients with anticipated FN episodes of less than 7 days, which would be the majority of patients with low-risk FN. Consequently, six trials were finally used for data extraction.

Clinical characteristics of the 6 included studies are presented in Table 3. One study assessed inpatient *versus* outpatient management (28) and 5 studies compared oral *versus* IV antibiotics in the outpatient setting (22-24, 26, 27), representing a total of 868 FN episodes.

The study comparing inpatient *versus* outpatient management involved IV drug administration for either strategy, and considered an early discharge approach for the outpatient group after 24-36 hours of inpatient observation.(28) In studies comparing outpatient IV with outpatient PO management, entire outpatient management and early discharge strategy were found in four studies (22-24, 27) and one study (26), respectively. Further study characteristics including antibiotics selected in the different studies, length of treatment duration, proportions...
of episodes with fever of unknown origin, hematologic malignancies, and absolute neutrophil counts below 100 per microliter within each study, are outlined in Table 3.

Some exclusion criteria were similar among the studies including hemodynamic instability, organ failure, inability to take oral medication, allergy to study drugs, pregnancy and lactation. However, there was considerable variation between the trials regarding exclusion of patients with hematologic malignancies, hematopoietic stem cell transplantation, or specific source of infection (e.g. pneumonia or cellulitis). Definitions of low-risk (or exclusion criteria for a low-risk protocol) used in the different studies are shown in Appendix C.
Table 3. Characteristics of included studies: Inpatient *versus* outpatient management (upper part of the table) and outpatient parenteral antibiotics *versus* outpatient oral antibiotics (lower part of the table)

<table>
<thead>
<tr>
<th>Group / Author</th>
<th>Year</th>
<th>FN Episodes</th>
<th>Discharge</th>
<th>Inpatient Drug and Treatment Duration (days, mean)</th>
<th>Outpatient Drug and Treatment Duration (days, mean)</th>
<th>FUO(^1) [%]</th>
<th>L&amp;L(^2) [%]</th>
<th>ANC &lt;100(^3) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santolaya (28)</td>
<td>2004</td>
<td>149</td>
<td>after 24-36 h</td>
<td><strong>IV</strong>: ceftriaxone &amp; teicoplanin 6.4</td>
<td><strong>IV</strong>: ceftriaxone &amp; teicoplanin 6.1</td>
<td>38</td>
<td>45</td>
<td>NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Intravenous</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>199</td>
<td>immediate</td>
</tr>
<tr>
<td></td>
<td>ceftriaxone &amp; amikacin</td>
<td>6* ofloxacin &amp; amoxicillin/clav.</td>
</tr>
<tr>
<td>Paganini (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>177</td>
<td>immediate</td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>ciprofloxacin (seq)</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Paganini (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>154</td>
<td>after 72 h</td>
</tr>
<tr>
<td></td>
<td>ceftriaxone &amp; amikacin</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>cefixime (seq)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Petrilli (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>116</td>
<td>immediate</td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>ciprofloxacin</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>4(^a)</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Mullen (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>73</td>
<td>immediate</td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>ciprofloxacin (seq)</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td>89</td>
<td>30(^b)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

FN indicates febrile neutropenia; IV indicates intravenous treatment; seq indicates sequential IV-oral therapy; *median; \(^1\)fever of unknown origin defined as no clinical focus with negative microbiological tests; \(^2\)percent of leukemia and lymphoma patients in the entire study population; \(^3\)percent of patients with absolute neutrophil count less than 100 per microliter; \(^a\)only lymphoma \(^b\)only leukemia (lymphoma reported together with solid tumors). NR not reported.
Study quality characteristics are shown in Table 4. Allocation generation was reported for 4 of 6 trials (67 percent). None of the studies reported concealment information, and none of the studies were blinded. Withdrawal information could be retrieved from 4 of the 6 published articles (67 percent), and intention-to-treat analysis was reported in 4 studies (60 percent).

Table 4. Methodological quality of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation Generation</th>
<th>Allocation Concealment</th>
<th>Blinding</th>
<th>Withdrawal Information</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santolaya (28)</td>
<td>unclear</td>
<td>unclear</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Gupta (23)</td>
<td>adequate</td>
<td>unclear</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Paganini (24)</td>
<td>adequate</td>
<td>unclear</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Paganini (26)</td>
<td>adequate</td>
<td>unclear</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Petrilli (27)</td>
<td>unclear</td>
<td>unclear</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Mullen (22)</td>
<td>adequate</td>
<td>unclear</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

To assess methodological quality and risk of bias, included articles were examined for: (1) sequence generation; (2) allocation concealment; (3) blinding; (4) incomplete outcome data, and (5) intention-to-treat (ITT) analysis. Criteria definitions were applied according to the Cochrane Handbook for Systematic Reviews of Interventions (66); see also Validity Checklist in Appendix B.

2.2.6 Data Extraction for the Cost-Utility Model: Results

The mean rates of treatment failure and hospital readmission were extracted from the included studies to populate the cost-utility model with event probabilities. The range of possible outcomes for the sensitivity analysis was estimated from studies describing the most extreme results. The relevant data of each study are shown in Table 5 and Table 6.
Table 5. Event probabilities extracted from included studies: Treatment failure

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Studies</th>
<th>Failure Rate</th>
<th>Average Rate</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>Santolaya (28)(^a)</td>
<td>3 / 70</td>
<td>NA</td>
<td>0.043</td>
</tr>
<tr>
<td>Early discharge</td>
<td>Paganini (26)(^b)</td>
<td>9 / 74</td>
<td>NA</td>
<td>0.122</td>
</tr>
<tr>
<td>Home IV</td>
<td>Mullen (22)</td>
<td>7 / 33</td>
<td>41 / 237</td>
<td>0.173</td>
</tr>
<tr>
<td></td>
<td>Paganini (24)(^b)</td>
<td>14 / 89</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Petrilli (27)</td>
<td>14 / 57</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gupta (23)</td>
<td>6 / 58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home PO</td>
<td>Mullen (22)</td>
<td>12 / 40</td>
<td>51 / 248</td>
<td>0.206</td>
</tr>
<tr>
<td></td>
<td>Paganini (24)(^b)</td>
<td>18 / 88</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Petrilli (27)</td>
<td>10 / 59</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gupta (23)</td>
<td>11 / 61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) one fatal inpatient episode was excluded because dead was not included into the model
\(^b\) published and unpublished data (personal communication)

Table 6. Event probabilities extracted from included studies: Readmission

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Studies</th>
<th>Failure Rate</th>
<th>Average Rate</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>Santolaya (28)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Early discharge</td>
<td>Paganini (26)(^b)</td>
<td>1 / 74</td>
<td>NA</td>
<td>0.014</td>
</tr>
<tr>
<td>Home IV</td>
<td>Mullen (22)</td>
<td>2 / 33</td>
<td>8 / 237</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>Paganini (24)(^b)</td>
<td>4 / 89</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Petrilli (27)</td>
<td>2 / 57</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gupta (23)</td>
<td>0 / 58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home PO</td>
<td>Mullen (22)</td>
<td>8 / 40</td>
<td>21 / 248</td>
<td>0.085</td>
</tr>
<tr>
<td></td>
<td>Paganini (24)(^b)</td>
<td>6 / 88</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Petrilli (27)</td>
<td>4 / 59</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gupta (23)</td>
<td>3 / 61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^b\) published and unpublished data (personal communication)
In the decision-analytic model, readmission was conditional on treatment failure; therefore, the readmission rate was determined as follows:

- Early discharge strategy: 1 of 9 = 0.111
- Home IV strategy: 8 of 41 = 0.195
- Home oral strategy: 21 of 51 = 0.412

2.2.7 Event Probabilities of Healthcare-Related Infections

Probabilities related to healthcare-related infections were not reported in the six RCT retrieved for this analysis. A systematic review of nosocomial infections in patients with cancer published in 2009 was chosen as the background paper to obtain event probabilities related to healthcare-related infections.(80) Nosocomial infections (the term healthcare-related infection will be used instead in this thesis) were defined as infections that become evident 48 hours or more after a patient is admitted for treatment in a hospital or in another healthcare setting. Limited data are available regarding healthcare-related infections in an ambulatory setting (clinic visits); however, both blood-stream and non-blood-stream (e.g. infections of the upper airways, wound/skin) infections can occur.(60-62) All assumptions related to these probabilities are listed within section 2.1.2.

2.3. HEALTH UTILITIES

Health utilities were obtained from a recently conducted study at The Hospital for Sick Children (SickKids) in Toronto, Canada.(48) It is important to state that the acquisition of utilities itself was not part of the thesis, and data will only be presented on an aggregate level.

One QAFNE (30 days) was calculated under the assumption that no deaths would occur
among the patients. Health utilities for the hypothetical health states were derived from 149 parents (parent proxy-report) of children with cancer that were on active treatment for any type of cancer at SickKids. A current episode of FN was not mandatory for inclusion.

A visual analog scale (VAS) was used to determine patients’ preferences for the four different health states (strategies). VAS scores are not usually considered utilities, but they are related to standard gamble utilities in a nonlinear fashion and can be transformed to the latter using a power function. The following conversion algorithm was used in this study for deriving a standard gamble score: \(1-(1-VAS)^{1.61}.\) (81, 82) The base case for the model considered mean standard gamble values. To account for uncertainty related to this decision, sensitivity analyses were performed applying the median standard gamble value, the crude mean VAS score (utility = VAS score / 10), or the crude median VAS score instead of the mean standard gamble value (see Table 7).

**Table 7.** Febrile neutropenia-related health utilities obtained from 149 parents of children with cancer

<table>
<thead>
<tr>
<th></th>
<th>Hospital</th>
<th>Early Discharge</th>
<th>Home IV</th>
<th>Home oral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VAS</td>
<td>SG</td>
<td>VAS</td>
<td>SG</td>
</tr>
<tr>
<td>mean</td>
<td>0.56</td>
<td><strong>0.67</strong></td>
<td>0.57</td>
<td><strong>0.71</strong></td>
</tr>
<tr>
<td>SD</td>
<td>0.30</td>
<td>0.30</td>
<td>0.22</td>
<td>0.22</td>
</tr>
<tr>
<td>median</td>
<td>0.55</td>
<td>0.72</td>
<td>0.57</td>
<td>0.74</td>
</tr>
<tr>
<td>min</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>max</td>
<td>1.00</td>
<td>1.00</td>
<td>10.0</td>
<td>1.00</td>
</tr>
</tbody>
</table>

VAS indicates visual analog scale, SG standard gamble, SD standard deviation, min minimum, max maximum; VAS was converted to SG using: \(SG = 1-(1-VAS)^{1.61}\); numbers in bold were used for the base case analysis;

The health utilities obtained reflect the patients’ preferences for the four different
treatment strategies. They do not account for the complications that might occur subsequently. No pediatric data were available to estimate utility deduction for treatment failure, readmission, and healthcare-related infections. Therefore, baseline estimates for those values were made using clinical judgment (see section 2.1.2 and Table 9). The estimate for utility deduction for hospital readmission was supported by adult data indicating an utility reduction of 50 percent for patients with FN in case of hospital admission.(59)

2.4. HEALTHCARE COSTS

When evaluating a cost-utility analysis, a critical question that must be answered is the cost perspective the researcher has taken to determine the analysis. There are several cost perspectives encountered in the healthcare economic literature, such as the third-party insurer (healthcare payer’s) perspective, the governmental perspective, and the societal perspective.(57)

Whereas the healthcare payer’s perspective only considers direct health costs (e.g. hospitalization, doctor fees, drugs), the other two approaches also consider some (governmental) or even all (societal) indirect health costs (e.g. transportation, day care, productivity loss). The Panel on Cost-Effectiveness in Health and Medicine has recommended that the societal perspective should be applied for cost-utility analyses.(83) Nonetheless, there is no agreement as to exactly what costs should be utilized in the societal perspective.(84) This is a major problem because a lack of agreement and inconsistent utilization of indirect health costs across different studies could make them incomparable. This issue is even more complicated in the context of outpatient management of FN in children with cancer due to the lack of data reporting indirect health costs associated with different strategies. Thus, a healthcare payer’s perspective – considering all direct health costs – was chosen for the purpose of this study.

Direct medical costs associated with hospitalization, initial consultation, outpatient visits,
home care nursing, and medications were obtained from the following sources: 1) webpage of the Ontario Ministry of Health and Long-Term Care (http://www.health.gov.on.ca → Ontario Health Insurance (OHIP) Schedule of Benefits and Fees); 2) local finance offices at SickKids (hospital fees / charges, and home care nurse visits); and 3) the Department of Pharmacy at SickKids (drug costs). Antibiotic costs were calculated for a child with a weight of 20 kg. The following range was applied to the sensitivity analyses: lower limit = baseline estimate x 0.5; upper limit = baseline estimate x 2. Other assumptions made relating to antibiotics considered in the model, and all other assumptions associated with costs, are listed in section 2.1.2. All costs are quoted in 2009 Canadian dollars. As all outcomes occurred within a 30-day time frame, no discounting was applied. Table 8 displays detailed information related to the cost estimates used in the final model.
Table 8. Healthcare payer’s costs included in the analysis

<table>
<thead>
<tr>
<th>Cost Factor</th>
<th>Canadian Dollars</th>
<th>Source / Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital Stay per Day</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospital stay per day</td>
<td>2,323.65</td>
<td>rounded to 2,300</td>
</tr>
<tr>
<td>re-assessment (physician fee)</td>
<td>55.65</td>
<td>C264 (Schedule of Benefits for Physician Services under the Health Insurance Act)</td>
</tr>
<tr>
<td><strong>Consultation</strong></td>
<td><strong>498.50</strong></td>
<td>rounded to 500</td>
</tr>
<tr>
<td>initial consultation (without physician fee)</td>
<td>238.00</td>
<td>excluding diagnostic procedures/doctors' fees</td>
</tr>
<tr>
<td>initial consultation (physician fee)</td>
<td>165.00</td>
<td>C265 (Schedule of Benefits for Physician Services under the Health Insurance Act)</td>
</tr>
<tr>
<td>complete blood count</td>
<td>8.00</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>sodium</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>potassium</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>chloride</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>glucose</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>creatinine</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>urea</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>bilirubin</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>blood culture (aerob+anaerob)</td>
<td>30.00</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>urine culture</td>
<td>10.00</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td><strong>Re-Assessment</strong></td>
<td><strong>319.15</strong></td>
<td>rounded to 320</td>
</tr>
<tr>
<td>re-assessment (clinic; without physician fee)</td>
<td>238.00</td>
<td>excluding diagnostic procedures/doctors' fees</td>
</tr>
<tr>
<td>re-assessment (physician fee)</td>
<td>55.65</td>
<td>C264 (Schedule of Benefits for Physician Services under the Health Insurance Act)</td>
</tr>
<tr>
<td>complete blood count</td>
<td>8.00</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>sodium</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>potassium</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>chloride</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>glucose</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>creatinine</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
</tbody>
</table>
Table 8 continued

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>urea</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
<tr>
<td>bilirubin</td>
<td>2.50</td>
<td>OHIP lab benefits</td>
</tr>
</tbody>
</table>

| **Home Care Nurse Visit** | **90** | Community Care Access Center, Toronto (includes staff/material costs; not drug costs) |

<table>
<thead>
<tr>
<th><strong>Antibiotics</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>piperacillin/tazobactam &amp; gentamicin</td>
<td>14</td>
<td>Department of Pharmacy, Sickkids</td>
</tr>
<tr>
<td>ceftriaxone &amp; amikacin</td>
<td>19</td>
<td>Department of Pharmacy, Sickkids</td>
</tr>
<tr>
<td>meropenem &amp; gentamicin &amp; vancomycin</td>
<td>74</td>
<td>Department of Pharmacy, Sickkids</td>
</tr>
<tr>
<td>ciprofloxacin + amoxicillin / clavulanate</td>
<td>4</td>
<td>Department of Pharmacy, Sickkids</td>
</tr>
</tbody>
</table>

OHIP indicates Ontario Health Insurance Plan

### 2.5. Parameter Inputs of the Model

Based on the previous sections, table 9 provides a detailed list of all parameter inputs of the model, including a column of plausible ranges for each parameter.
Table 9. Summary of parameters used in the model: numeric baseline values, parameter range used in sensitivity analyses, and references

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Mean</th>
<th>Plausible Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Event Probabilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>probability of failure for hospital IV</td>
<td>0.043</td>
<td>0.01-0.30</td>
<td>(11)</td>
</tr>
<tr>
<td>probability of failure for early discharge</td>
<td>0.122</td>
<td>0.01-0.30</td>
<td>(9)</td>
</tr>
<tr>
<td>probability of failure for outpatient IV</td>
<td>0.173</td>
<td>0.103-0.246</td>
<td>(6-8,10)</td>
</tr>
<tr>
<td>probability of failure for outpatient oral</td>
<td>0.206</td>
<td>0.157-0.30</td>
<td>(6-8,10)</td>
</tr>
<tr>
<td>probability of readmission for early discharge*</td>
<td>0.111</td>
<td>0.01-0.30</td>
<td>(9)</td>
</tr>
<tr>
<td>probability of readmission for outpatient IV*</td>
<td>0.195</td>
<td>0.143-0.286</td>
<td>(6-8,10)</td>
</tr>
<tr>
<td>probability of readmission for outpatient PO*</td>
<td>0.412</td>
<td>0.273-0.667</td>
<td>(6-8,10)</td>
</tr>
<tr>
<td>rate of HCRI</td>
<td>0.005</td>
<td>0.004-0.006</td>
<td>(20-22)</td>
</tr>
<tr>
<td>relative risk of HCRI for outpatient IV*</td>
<td>0.20</td>
<td>0.15-0.25</td>
<td>(20-22)</td>
</tr>
<tr>
<td>relative risk of HCRI for outpatient oral</td>
<td>0.10</td>
<td>0.075-0.125</td>
<td>(20-22)</td>
</tr>
<tr>
<td><strong>Utilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>utility for inpatient IV</td>
<td>0.67</td>
<td>0-1</td>
<td>see 2.3</td>
</tr>
<tr>
<td>utility for early discharge</td>
<td>0.71</td>
<td>0-1</td>
<td>see 2.3</td>
</tr>
<tr>
<td>utility for outpatient IV</td>
<td>0.70</td>
<td>0-1</td>
<td>see 2.3</td>
</tr>
<tr>
<td>utility for outpatient oral</td>
<td>0.60</td>
<td>0-1</td>
<td>see 2.3</td>
</tr>
<tr>
<td>utility reduction if failure (factor)</td>
<td>0.80</td>
<td>0.60-1.00</td>
<td>assumed</td>
</tr>
<tr>
<td>utility reduction if HCRI (factor)</td>
<td>0.50</td>
<td>0.375-0.625</td>
<td>assumed</td>
</tr>
<tr>
<td>utility reduction if readmission (factor)</td>
<td>0.50</td>
<td>0.375-0.625</td>
<td>assumed</td>
</tr>
<tr>
<td><strong>Costs (CAD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>costs per inpatient stay per day</td>
<td>2300</td>
<td>1150-4600</td>
<td>see 2.4</td>
</tr>
<tr>
<td>costs of initial consultation</td>
<td>500</td>
<td>250-1000</td>
<td>see 2.4</td>
</tr>
<tr>
<td>costs for outpatient visit</td>
<td>320</td>
<td>160-640</td>
<td>see 2.4</td>
</tr>
<tr>
<td>costs of home care nurse per visit</td>
<td>90</td>
<td>45-180</td>
<td>see 2.4</td>
</tr>
<tr>
<td>costs of first-line IV antibiotics per day</td>
<td>14</td>
<td>7-28</td>
<td>see 2.4</td>
</tr>
<tr>
<td>costs of first-line IV antibiotics per day (home)</td>
<td>19</td>
<td>9.50-38</td>
<td>see 2.4</td>
</tr>
<tr>
<td>costs of second-line IV antibiotics per day</td>
<td>74</td>
<td>37-148</td>
<td>see 2.4</td>
</tr>
<tr>
<td>costs of oral antibiotics per day</td>
<td>4</td>
<td>2-8</td>
<td>see 2.4</td>
</tr>
<tr>
<td>increase in costs of antibiotics for HCRI (factor)</td>
<td>1.5</td>
<td>1.125-1.875</td>
<td>assumed</td>
</tr>
<tr>
<td><strong>Time Parameter (days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>duration of inpatient stay for hospital IV</td>
<td>6</td>
<td>3-12</td>
<td>(11)</td>
</tr>
<tr>
<td>duration of inpatient stay for early discharge</td>
<td>2</td>
<td>1-4</td>
<td>(6-9)</td>
</tr>
<tr>
<td>duration of outpatient treatment for early discharge</td>
<td>4</td>
<td>2-8</td>
<td>(6-9)</td>
</tr>
<tr>
<td>duration of outpatient treatment</td>
<td>6</td>
<td>3-12</td>
<td>(6-9)</td>
</tr>
<tr>
<td>prolongation of therapy related to complication*</td>
<td>6</td>
<td>3-12</td>
<td>assumed</td>
</tr>
<tr>
<td>time to complication</td>
<td>3</td>
<td>1.5-6</td>
<td>assumed</td>
</tr>
<tr>
<td>time to complication for early discharge at home</td>
<td>1</td>
<td>0.5-2</td>
<td>assumed</td>
</tr>
</tbody>
</table>

* conditional on failure of therapy; † complication = failure, readmission, healthcare-related infection; IV indicates intravenous, PO oral, HCRI healthcare-related infection, and CAD Canadian dollars.
2.6. SENSITIVITY ANALYSES

Baseline parameter estimates and the range of plausible values for each estimate are listed in Table 9. All variables were tested in a one-way (plausible & extreme range) sensitivity analysis.

A probabilistic sensitivity analysis (PSA) was also performed to address the joint uncertainty of all model parameters simultaneously. Ten thousand second-order Monte Carlo simulations were performed, and a cost-effectiveness acceptability curve was generated that used net benefits to graph the changing percentage of simulations for which each comparator is cost-effective relative to all other strategies.

Similar to deterministic one-way sensitivity analysis, Monte Carlo probabilistic sensitivity analysis recalculates expected values in a tree multiple times, and is used to understand the impact of parameter uncertainties on the model results. Monte Carlo simulation is a type of sensitivity analysis in which each variable in a decision-analytic model is assigned a probability distribution to represent measures of central tendency and plausible range of the data. Each distribution is then repeatedly sampled (for example 10,000 times) to obtain a mean and distribution for the overall value of interest (for example cost-effectiveness). One advantage of PSA is that any number of parameter uncertainties can be incorporated into an analysis. Sampling also enables greater weight to be placed on likely parameter values and combinations of parameters. PSA results estimate the total impact of uncertainty on the model, or the confidence that can be placed in the analysis result. Before using Monte Carlo simulation to perform PSA in TreeAge, uncertain parameters must be defined using distributions. A total of five different distributions were applied to describe the best fit between available data and theoretical distributions:

1) Normal distribution, where: standard deviation = mean * 0.125
Parameter: rate of healthcare-related infection, relative risk of healthcare-related infection for outpatient IV, relative risk of healthcare-related infection for outpatient oral, utility reduction if failure, utility reduction if healthcare-related infection, utility reduction if readmission;

2) **Beta distribution**, where: \( \alpha = r \), \( \beta = n-r \); standard deviation = \((\text{high-low})/4\);

\[ n = \left( \frac{\text{mean} \times (1-\text{mean})}{\text{standard deviation}^2} \right) - 1; \]

\[ r = \text{mean} \times n \]

Parameter: all event probabilities other than probability of failure for hospital IV (see below);

3) **Gamma distribution**, where: \( \alpha = (\text{mean}/\text{standard deviation})^2 \); \( \lambda = \text{mean}/\text{standard deviation}^2 \); standard deviation = \((\text{high-low})/4\);

Parameters: all cost parameter and all time parameters;

4) **Triangular distribution**, with mean = peak;

Parameter: probability of failure for hospital IV (a beta distribution could not fit the given mean with the given plausible range)

5) **Table distribution**, individual values are describing the distribution;

Parameter: the utilities of the four treatment strategies (since all 149 data points were available, a table distribution was chosen);

For the base case, the willingness-to-pay (WTP) threshold was set at $4,000 per QAFNE, with a range testing from $0 to $20,000. Four thousand dollars per QAFNE (time frame = 30 days) was used as baseline value since this approximates a WTP threshold of $50,000 per QALY, a threshold commonly used in health economic evaluations.(85) However, the issues around determining an appropriate WTP threshold for transient health states such as low-risk FN will be addressed in the discussion section of the thesis.
CHAPTER 3 – RESULTS

3.1. BASE CASE ANALYSIS

Table 10 lists the average costs per person and effectiveness of the 4 strategies under study. The model predicted that the costs for IV outpatient management for pediatric cancer patients with low-risk FN ($2,732 per person per episode) would be lower than the costs for oral outpatient management ($2,757), for the early discharge strategy ($5,579), and for standard in-hospital management ($14,493). The reduction in the prevalence of treatment failure and hospital readmission explains reduced costs associated with the IV outpatient strategy as compared to oral outpatient management.

Considering quality of life, IV outpatient management yielded a QAFNE of 0.663 (equivalent to 19.9 quality-adjusted life days (QALD), and 0.055 QALY). This was superior to oral outpatient treatment (0.553 QAFNE; 16.6 QALD; 0.046 QALY) and the inpatient strategy (0.650 QAFNE; 19.5 QALD; 0.054 QALY), but inferior to the early discharge option (0.684 QAFNE; 20.5 QALD; 0.057 QALY). The results are summarized in Table 10 and illustrated in Figure 3.

These findings indicate that outpatient IV management was associated with both better health outcomes (effectiveness) and lower costs as compared to oral outpatient management. In economic terms, this means that the outpatient IV strategy dominates the outpatient oral therapy. The early discharge strategy was slightly more effective but significantly more expensive than the outpatient IV option resulting in an unacceptably high ICER of $136,148 per QAFNE. The most expensive strategy, in-hospital treatment, was less effective than the early discharge strategy (this is referred to as dominated in economic terms).
Table 10. Base case cost-utility analysis

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs</th>
<th>Incremental Cost</th>
<th>Effectiveness</th>
<th>Incremental Effectiveness</th>
<th>C/E</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>HomeIV</td>
<td>$2,732</td>
<td></td>
<td>0.6632</td>
<td></td>
<td>$4,119</td>
<td></td>
</tr>
<tr>
<td>HomePO</td>
<td>$2,757</td>
<td>$26</td>
<td>0.5534</td>
<td>-0.1098</td>
<td>$4,983</td>
<td>(Dominated)</td>
</tr>
<tr>
<td>EarlyDC</td>
<td>$5,579</td>
<td>$2,847</td>
<td>0.6841</td>
<td>0.0209</td>
<td>$8,154</td>
<td>$136,148</td>
</tr>
<tr>
<td>HospIV</td>
<td>$14,493</td>
<td>$8,914</td>
<td>0.6496</td>
<td>-0.0345</td>
<td>$22,309</td>
<td>(Dominated)</td>
</tr>
</tbody>
</table>

Effectiveness = quality-adjusted febrile neutropenia episode; C/E indicates cost-effectiveness ratio; ICER incremental cost-effectiveness ratio (incremental cost divided by incremental effectiveness);
Note: All costs are given in Canadian dollars;
HomeIV indicates outpatient management with intravenous antibiotics; HomePO, outpatient management with intravenous antibiotics; Early DC, treatment at home after an initial observation in hospital; HospIV, entire inpatient management;
* Dominated refers to the finding that this strategy is both less effective and more costly than other strategies.

Figure 3. Incremental cost-effectiveness ratio (ICER) graph. The x-axis displays utilities and the y-axis displays costs. Two options connected by a line represent an ICER. Options not bound to a line are dominated strategies.
3.2. SENSITIVITY ANALYSES

When tested within the plausible range, the model was sensitive to a total of four variables: 1) costs for home care nurse per visit, 2) duration of outpatient treatment, 3) utility for outpatient IV, and 4) utility for outpatient oral therapy. Beyond certain thresholds, superiority (most cost-effective) changed from the outpatient IV to the outpatient oral strategy (Table 11). On the contrary, there was no variable identified that changed the preferred strategy from outpatient management (IV or oral) to inpatient treatment or early discharge management, even when we applied extreme ranges. These findings indicate that the model is robust to the finding that outpatient strategies are preferred to inpatient strategies. However, it is sensitive to the question of whether antibiotics should be administered IV or orally in an ambulatory setting.

To further assess the robustness of the model, probabilistic sensitivity analyses were performed. At a willingness-to-pay threshold of $4,000 per QAFNE, IV outpatient treatment was cost-effective in 57 percent of simulations, whereas oral outpatient management was cost-effective in 35 percent of the simulations. The early discharge strategy was cost-effective in 8 percent of simulations; entire inpatient management was cost-effective in <1 percent of simulations. The results of the cost-effectiveness acceptability curve are shown in Figure 4.
Table 11. Summary of one-way sensitivity analyses including threshold values

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Mean</th>
<th>Plausible Range</th>
<th>Threshold</th>
<th>Sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Event Probabilities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>probability of failure for hospital IV</td>
<td>0.043</td>
<td>0.01-0.30</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>probability of failure for early discharge</td>
<td>0.122</td>
<td>0.01-0.30</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>probability of failure for outpatient IV</td>
<td>0.173</td>
<td>0.103-0.246</td>
<td>&gt;0.281</td>
<td>No</td>
</tr>
<tr>
<td>probability of failure for outpatient oral</td>
<td>0.206</td>
<td>0.157-0.30</td>
<td>&lt;0.140</td>
<td>No</td>
</tr>
<tr>
<td>probability of readmission for early discharge*</td>
<td>0.111</td>
<td>0.01-0.30</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>probability of readmission for outpatient IV*</td>
<td>0.195</td>
<td>0.143-0.286</td>
<td>&gt;0.395</td>
<td>No</td>
</tr>
<tr>
<td>probability of readmission for outpatient PO*</td>
<td>0.412</td>
<td>0.273-0.667</td>
<td>&lt;0.241</td>
<td>No</td>
</tr>
<tr>
<td>rate of HCRI</td>
<td>0.005</td>
<td>0.004-0.006</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>relative risk of HCRI for outpatient IV*</td>
<td>0.20</td>
<td>0.15-0.25</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>relative risk of HCRI for outpatient oral*</td>
<td>0.10</td>
<td>0.075-0.125</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td><strong>Utilities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>utility for inpatient IV</td>
<td>0.67</td>
<td>0-1</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>utility for early discharge</td>
<td>0.71</td>
<td>0-1</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>utility for outpatient IV</td>
<td>0.70</td>
<td>0-1</td>
<td>&lt;0.58</td>
<td>Yes</td>
</tr>
<tr>
<td>utility for outpatient oral</td>
<td>0.60</td>
<td>0-1</td>
<td>&gt;0.73</td>
<td>Yes</td>
</tr>
<tr>
<td>utility reduction if failure (factor)</td>
<td>0.80</td>
<td>0.60-1.00</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>utility reduction if HCRI (factor)</td>
<td>0.50</td>
<td>0.375-0.625</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>utility reduction if readmission (factor)</td>
<td>0.50</td>
<td>0.375-0.625</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td><strong>Costs (CAD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>costs per inpatient stay per day</td>
<td>2300</td>
<td>1150-4600</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>costs of initial consultation</td>
<td>500</td>
<td>250-1000</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>costs for outpatient visit</td>
<td>320</td>
<td>160-640</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>costs of home care nurse per visit</td>
<td>90</td>
<td>45-180</td>
<td>&gt;173</td>
<td>Yes</td>
</tr>
<tr>
<td>costs of first-line IV antibiotics per day</td>
<td>14</td>
<td>7-28</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>costs of first-line IV antibiotics per day (home)</td>
<td>19</td>
<td>9.50-38</td>
<td>&gt;116</td>
<td>No</td>
</tr>
<tr>
<td>costs of second-line IV antibiotics per day</td>
<td>74</td>
<td>37-148</td>
<td>&gt;519</td>
<td>No</td>
</tr>
<tr>
<td>costs of oral antibiotics per day</td>
<td>4</td>
<td>2-8</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>increase in costs of antibiotics for HCRI (factor)</td>
<td>1.5</td>
<td>1.125-1.875</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td><strong>Time Parameter (days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>duration of inpatient stay for hospital IV</td>
<td>6</td>
<td>3-12</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>duration of inpatient stay for early discharge</td>
<td>2</td>
<td>1-4</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>duration outpatient treatment early discharge</td>
<td>4</td>
<td>2-8</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>duration of outpatient treatment</td>
<td>6</td>
<td>3-12</td>
<td>&gt;11.1</td>
<td>Yes</td>
</tr>
<tr>
<td>prolongation therapy related to complication‡</td>
<td>6</td>
<td>3-12</td>
<td>&lt;1.4</td>
<td>No</td>
</tr>
<tr>
<td>time to complication</td>
<td>3</td>
<td>1.5-6</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>time to complication early discharge at home</td>
<td>1</td>
<td>0.5-2</td>
<td>-</td>
<td>No</td>
</tr>
</tbody>
</table>

* conditional on failure of therapy; ‡ complication = failure, readmission, healthcare-related infection; IV indicates intravenous, PO oral, HCRI healthcare-related infection, and CAD Canadian dollars. Threshold column indicates values at which outpatient oral therapy is superior to outpatient IV therapy; - indicates no threshold detectable;
Figure 4. This chart presents the cost-effectiveness acceptability curve for the base case. The curves represent the proportion of simulations in which intravenous outpatient therapy (solid line) and oral outpatient therapy (dashed line), respectively, were the cost-effective option at various willingness-to-pay thresholds. For example, at a willingness-to-pay threshold of $4,000 per quality-adjusted febrile neutropenia episode (vertical axis), IV therapy was cost-effective in 57 percent of the simulations (curves for the early discharge strategy and inpatient management are not shown).

To account for uncertainty related to the way the utilities were derived, sensitivity analyses were performed applying the median standard gamble value, the crude mean VAS score, and the crude median VAS score instead of the mean standard gamble value. As outlined in Tables 12A-12C, there were no substantial changes that challenge the overall findings of this cost-utility model. Treatment at home with IV antibiotics remained the most cost-effective option in either analysis, and ranking regarding cost-effectiveness remained also unchanged. However, using the median instead of the mean utility made home IV superior to the early discharge strategy in term of effectiveness.
Table 12. Sensitivity analyses using different approaches to derive utilities

A – Standard gamble median (instead of standard gamble mean)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs</th>
<th>Incremental Cost</th>
<th>Effectiveness</th>
<th>Incremental Effectiveness</th>
<th>C/E</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>HomeIV</td>
<td>$2,732</td>
<td></td>
<td>0.7201</td>
<td></td>
<td></td>
<td>$3,793</td>
</tr>
<tr>
<td>HomePO</td>
<td>$2,757</td>
<td>$26</td>
<td>0.5811</td>
<td>-0.139</td>
<td>$4,745</td>
<td>(Dominated)</td>
</tr>
<tr>
<td>EarlyDC</td>
<td>$5,579</td>
<td>$2,847</td>
<td>0.7131</td>
<td>-0.007</td>
<td>$7,823</td>
<td>(Dominated)</td>
</tr>
<tr>
<td>HospIV</td>
<td>$14,493</td>
<td>$11,761</td>
<td>0.6981</td>
<td>-0.022</td>
<td>$20,760</td>
<td>(Dominated)</td>
</tr>
</tbody>
</table>

B – Visual analog scale mean (instead of standard gamble mean)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs</th>
<th>Incremental Cost</th>
<th>Effectiveness</th>
<th>Incremental Effectiveness</th>
<th>C/E</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>HomeIV</td>
<td>$2,732</td>
<td></td>
<td>0.5401</td>
<td></td>
<td></td>
<td>$5,058</td>
</tr>
<tr>
<td>HomePO</td>
<td>$2,757</td>
<td>$26</td>
<td>0.4427</td>
<td>-0.0973</td>
<td>$6,228</td>
<td>(Dominated)</td>
</tr>
<tr>
<td>EarlyDC</td>
<td>$5,579</td>
<td>$2,847</td>
<td>0.5492</td>
<td>0.0092</td>
<td>$10,157</td>
<td>$310,092</td>
</tr>
<tr>
<td>HospIV</td>
<td>$14,493</td>
<td>$8,914</td>
<td>0.5430</td>
<td>-0.0063</td>
<td>$26,691</td>
<td>(Dominated)</td>
</tr>
</tbody>
</table>

C – Visual analog scale median (instead of standard gamble mean)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs</th>
<th>Incremental Cost</th>
<th>Effectiveness</th>
<th>Incremental Effectiveness</th>
<th>C/E</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>HomeIV</td>
<td>$2,732</td>
<td></td>
<td>0.5590</td>
<td></td>
<td></td>
<td>$4,886</td>
</tr>
<tr>
<td>HomePO</td>
<td>$2,757</td>
<td>$26</td>
<td>0.4243</td>
<td>-0.1347</td>
<td>$6,499</td>
<td>(Dominated)</td>
</tr>
<tr>
<td>EarlyDC</td>
<td>$5,579</td>
<td>$2,847</td>
<td>0.5492</td>
<td>-0.0098</td>
<td>$10,157</td>
<td>(Dominated)</td>
</tr>
<tr>
<td>HospIV</td>
<td>$14,493</td>
<td>$11,761</td>
<td>0.5333</td>
<td>-0.0257</td>
<td>$27,177</td>
<td>(Dominated)</td>
</tr>
</tbody>
</table>

Effectiveness = quality-adjusted febrile neutropenia episode; C/E indicates cost-effectiveness ratio; ICER incremental cost-effectiveness ratio;
Note: All costs are given in Canadian dollars;
HomeIV indicates outpatient management with intravenous antibiotics; HomePO, outpatient management with intravenous antibiotics; Early DC, treatment at home after an initial observation in hospital; HospIV, entire inpatient management;
* Dominated refers to the finding that this strategy is both less effective and more costly than other strategies.
CHAPTER 4 – DISCUSSION

4.1. MAIN STUDY FINDINGS AND INTERPRETATION

To our knowledge, this is the first cost-utility analysis addressing the question of whether low-risk FN in children with cancer is best managed in hospital or in an outpatient setting. The findings of the current study suggest that outpatient management with IV antibiotic treatment is the preferred approach. This strategy was more cost-effective than other strategies including entire inpatient management, treatment at home after an initial observation in hospital, and entire outpatient management with oral antibiotics.

We demonstrated that inpatient care for FN was dominated (i.e. more expensive and less effective) even when tested over a wide range of plausible values in sensitivity analyses. This is important to note since the standard treatment of FN has been inpatient management with broad-spectrum IV antibiotics for all patients for several decades. Modeling the cost-effectiveness of the four proposed treatment strategies indicated that the substantially higher costs of inpatient management could not be justified on the basis of safety and efficacy considerations, or patients’ preferences. Interestingly, health utilities for inpatient management were rated lower as compared to outpatient IV therapy, but higher as compared to the outpatient oral therapy. However, the inter-patient variability regarding preferences was substantial in our study (the health utilities for all 4 treatment strategies ranged from 0 to 1), something that needs to be considered when performing medical decision-making at an individual level.

Whereas the base case analysis favored the outpatient IV management, one-way sensitivity analyses identified several variables that, when tested within the plausible range, could make oral outpatient treatment the superior strategy. Two of those variables were related to health utilities indicating that the overall findings seem to be utility-sensitive. The impression
obtained from one-way sensitivity analyses was consistent with the results of the PSA, which found outpatient oral therapy to be the preferred strategy in more than a third of simulations. From a face validity viewpoint, it appears reasonable that these two outpatient approaches present similar cost-effectiveness ratios. Moreover, having two comparable approaches in terms of cost-effectiveness might allow patients and their families to play a more active role in medical decision making in future, particularly if probabilities of treatment failure are similar between strategies. From a health economic perspective, either outpatient strategy can be considered as an attractive option due to their substantial cost saving potential as compared to inpatient management.

As described in the previous sections, this analysis used a healthcare payer’s perspective considering all direct medical costs. Indirect health costs related to productivity loss of the caregivers, transportation, daycare costs for siblings, and possibly education time for caregivers, were not included into the model. The possible impact of indirect cost factors on the findings of the presented cost-utility analysis remains speculative. However, it can be hypothesized that inclusion of indirect costs would not substantially change the overall result. First, children with cancer admitted to hospital are usually supported constantly by a caregiver, in the majority of cases the mother. It is unlikely that outpatient management would change this setting by ‘utilizing’ more or less caregivers. Thus, indirect costs associated with caregivers’ productivity loss should not differ between inpatient and outpatient management. Second, transportation costs associated with outpatient clinic visits are not relevant for inpatient management. On the contrary, transportation costs related to hospital visitors such as other family members or friends would not be applicable for outpatient strategies. Therefore, costs associated with transportation might be similar between inpatient and outpatient care. Further, management of low-risk FN affects only a short period of time and does not differ between inpatient and outpatient care.
Even in case of a cost-saving effect related to indirect health costs in the inpatient setting, it is very unlikely that such an effect would equal the enormous cost-saving effect that is associated with the reduced direct health costs in an ambulatory setting.

4.2. STUDY LIMITATIONS

This cost-utility analysis has a number of important limitations. First, only limited data were available to estimate the base values in the model leading to uncertainty regarding the precision of the included event probabilities. Only one study each provided data for the inpatient and the early discharge strategies, respectively. However, a recently completed RCT in Europe (SPOG trial NCT00107081) comparing an early discharge strategy (with subsequent oral amoxicillin/clavulanate & ciprofloxacin) with classical inpatient management will provide further data in this regard. In general, the sample size was small in all included studies (between 73 and 199 episodes per study under evaluation) and there were also some methodological limitations related to those studies. For example, none of the studies provided information on allocation concealment, a critical component to avoid selection bias in randomized trials.(66) To minimize this limitation, data were applied across a wide range of values in sensitivity analyses.(58) Whereas the model was not sensitive to event probabilities when changed within the plausible range (one-way sensitivity analysis), it remains possible that parameter uncertainty might impact on the question of whether outpatient IV or outpatient oral is the preferred strategy (as suggested by the PSA).

Second, in pediatrics, proxy respondents are commonly required to obtain HRQL estimates.(42) However, responses from parent proxy-report and child self-report may differ systematically. A systematic review evaluated studies in which parent and child assessments of HRQL were compared.(86) It was found that some studies using the PedQL™ reported higher
parent–child agreement for concrete, observable characteristics such as physical health, whilst other papers also using the same measure found higher levels for psychosocial domains such as social and emotional functioning. Further, little is known about proxy compared to self-report utilities in children. One small study that included children with chronic conditions compared health utilities elicited by standard gamble, time trade-off and HUI in children with at least a grade six education and their parents. In this study, standard gamble utilities were similar between these two respondent types. As a measure of agreement, the intra-class correlation coefficient (ICC) was moderate (0.64, 95% CI 0.30, 0.83). However, child self-report time trade-off utilities were significantly higher than parent proxy time trade-off utilities. The agreement was poor with an ICC of 0.14 (95% CI -0.29 to 0.53). More research has been conducted comparing HUI utilities between parent proxy and child self-report. There was substantial variability regarding agreement within and across different studies with higher levels of agreement for observable phenomena and lower levels of agreements for subjective areas.

It is, however, important to note that multi-attribute utility measures such as HUI or EQ-5D cannot be applied to hypothetical scenarios. If confronted with hypothetical health states as in our project, only direct approaches such as standard gamble, time trade-off, or rating scales can be used. Whereas it would have been desirable to elicit preferences from patients (parents) that were actually experiencing the health state under evaluation, such an approach was not feasible due to the current clinical practice at SickKids, which is not considering outpatient management of FN.

Third, VAS scores were used to derive HRQL estimates. This approach was chosen because standard gamble- or time trade-off scores for outpatient management of FN in children were not available. Further, it has been suggested that conventional standard gamble and time trade-off methods may be inappropriate for eliciting preferences for transient non-fatal health
states (such as low-risk FN) because both require subjects to make trade-offs between a morbid health state and death. On the contrary, VAS are attractive because they are simple, quick to administer, and lend themselves to self-completion. However, cardinal preferences from the VAS are prone to context and end-aversion bias. In addition to biases, the cardinal preferences from VAS do not agree with the cardinal preferences from the classical method of utility measurement, the standard gamble technique. At the aggregate level, however, the relationship can be modeled by a power curve specific to the study in question. We applied a power function suggested by Torrance et al. in the mid-1970s to convert VAS scores to standard gamble values. Sensitivity analyses using converted and non-converted mean and median scores did not indicate substantial variation between the different approaches. Ranking of the strategies in terms of cost-effectiveness remained unchanged. We suggest that our data are robust and plausibly reflect the patients’ preferences. Further, we believe that our findings are more representative than estimations made by physicians or other ‘experts’. Regardless, utility elicitation using VAS remains an important limitation of this study.

The fourth limitation is related to the WTP threshold value. Typically, a cost utility analysis reports an ICER and then justifies that the therapy is cost effective because the ratio is less than a threshold (for example, $50,000 for the gain in one QALY). This assumes that the pot of money available to fund cancer treatment or supportive care is unlimited. This clearly is not the case. Moreover, the ICER reported in our study together with the WTP threshold set at $4,000 are difficult to interpret since FN episodes do not happen twelve times per year (to remember, $4,000 per QAFNE was used as baseline value since this approximates a WTP threshold of $50,000 per QALY). Determining a reasonable ICER threshold for relatively short-term events remains contentious. However, we suggest that an ICER of $130,000 related to a transient episode that might occur on average once or twice a year is not acceptable. Beyond the
discussion about an appropriate ICER threshold, either outpatient strategy might be considered as an attractive option due to its substantial cost-saving potential as compared to inpatient management, the current gold standard for management of low-risk FN in pediatric patients with cancer.

4.3. FURTHER RESEARCH

This study is important since it is the first formal attempt to compare different treatment strategies for low-risk FN in pediatric cancer patients. Results from several RCT included in this cost-utility analysis suggest that outpatient treatment of FN is a safe and efficacious alternative to inpatient management. (22-24, 26-28) These findings are supported by recent findings from a multi-center observational study from the United Kingdom. (34) However, there are several important concerns related to feasibility and patients’ preferences that need to be addressed in future research.

First, accurate risk prediction is crucial to identify low-risk FN episodes in children. In contrast to the MASCC risk index, which is a widely validated tool for adult cancer patients with FN, no such consensus on risk prediction has been reached in children so far. (29) Although several studies of risk prediction have been performed in children, prospective clinical trials are necessary to establish their reliability and validity, and consensus is required to identify one or a limited number of tools to take forward for future research. (30-33) Both a systematic review of the literature and prospective observational studies could be considered for this purpose. (95)

Second, external validity of the established evidence remains a major challenge. Are outpatient strategies feasible in lower-income countries, or are these approaches restricted to prosperous geographic regions that have adequate resources and infrastructure for close patient monitoring? Although 5 of 6 trials analyzed in this thesis have been conducted in lower-income
countries, the external validity of the findings outside the carefully controlled setting of a RCT remains unclear. Further, is outpatient management feasible in rural areas with non-specialized healthcare settings, or can it only be offered in tertiary medical centers? Most of the trials conducted so far have excluded patients that live in rural areas. This is, however, an important issue since many families may not live close to a specialized center.

Third, social barriers to outpatient management have to be taken into account before changing the current standard of care. A recent study indicated that a significant proportion of low-risk patients might not be eligible for outpatient therapy due to social barriers including language, distance of residence from the medical center, and lack of interest. We suggest that large observational studies from a variety of health settings would substantially add information to answer the latter two concerns in the near future.

Fourth, methodological work is needed in order to make progress in health utility assessment in the field of pediatric medicine. Effort needs to be invested in measuring health utilities in younger children and developing methods that take into account the changing cognitive abilities of young children. Such effort will require collaboration between child psychologists, methodologists and clinicians and may involve alternatives to the standard gamble, which do not involve the concept of probabilities or time. An example of such an approach may include trade-offs that involve money, since young children often are exposed to the idea of allowances at a very young age. Similarly, instruments that capture trade-offs with goods that are familiar to children (play time, toys) may be appropriate. Almost certainly, such methods will need to be interviewer administered with extensive use of visual aids.

Finally, we need tools to better understand patients’ preferences with respect to transient health states. Obtaining and interpreting health-state utilities for acute or non-fatal conditions can be problematic. For example, time trade-off techniques with a non-death baseline, or
conjoint analysis to estimate healthy-time equivalents for acute conditions might be promising approaches to consider for future research. A recent study, for example, evaluated the use of conjoint analysis to obtain time trade-off estimates of healthy-year equivalents for clinically relevant durations and severities of acute, self-limiting, or nonfatal conditions. The analysis was performed on 523 women with vasomotor symptoms. The results indicate that this approach may provide an alternative utility-elicitation method when conventional standard gamble and time trade-off methods are inappropriate to the decision context. Whatever technique will be chosen in future, ‘bed-side’ tools that can be used to support the clinical decision making process would be highly desirable.

4.4. CONCLUSIONS
To conclude, this cost-utility model suggests that in pediatric cancer patients with a first episode of low-risk FN, outpatient strategies are preferable to the current standard of care, namely inpatient treatment with IV antibiotics. Uncertainty remains whether IV or oral treatment might be the preferable route of drug administration in an ambulatory setting. However, further research considering different outpatient strategies is required and important practical limitations need to be addressed before outpatient care in children with low-risk FN can be adopted into routine clinical practice.
REFERENCES

1. Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 5 ed: Lippincott Williams & Wilkins; 2005.


85. Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health Econ. 2009 Apr 20.
Appendix A. Definition of treatment failure in the included studies

Santolaya, 2004 (28):
(1) Hemodynamic instability not attributable to volume loss; (2) axillary temperature more than 38°C in two or more daily recordings after day 4; (3) increase in temperature after a 48-hour afebrile period persisting for at least 24 hours; (4) an ascending CRP curve or a nondescending curve over normal limits (a value > 40 mg/L and < 30% decrease from a previous recording) after day 3 persisting for at least 2 consecutive days; (5) isolation of a bacterial pathogen from a significant sample obtained on day 3; and (6) death occurring during the febrile episode attributable to infection.

Mullen, 1999 (22):
Hospitalization for any reason

Paganini, 2003 (24):
No resolution of fever and readmission within 7 days of discharge or a new febrile episode during the same period of neutropenia.

Paganini, 2000 (26):
No resolution of fever and readmission within 7 days of discharge or a new febrile episode during the same period of neutropenia.

Petrilli, 2000 (27):
No survival

Gupta, 2009 (23):
No resolution of the febrile episode and neutropenia without change of regimen or hospitalization. No resolution of fever or any other serious medical complications (with or without resolution of fever) requiring change in therapy or hospitalization.
Appendix B. Outpatient antibiotic treatment for febrile neutropenia in cancer patients: A systematic review and meta-analysis – Data collection sheet

1. Characteristics of trial and intervention:

- Study Number & First Author:

- Year of Publication:

- Study dates (year only): ________ to ________

- Country of study population: _______________

- Publication status:
  - □ Published article
  - □ Conference abstract

- Sponsor of trial:

- Unit of randomization:
  - □ Individual
  - □ Group (comment ________________________________)

- Setting of the trial:
  - □ Inpatient _____ (IV or PO) versus outpatient _____ (IV or PO)
  - □ Inpatient _____ (IV / PO) versus early discharge (after ___hours ) outpatient _____ (IV / PO)
    - If outpatient PO:
      - □ 'Initially oral' antibiotic administration
      - □ 'sequential intravenous to oral' antibiotic administration
  - □ Outpatient IV versus outpatient PO
  - □ Early discharge (after ___hours ) outpatient IV versus early discharge (after ___hours ) outpatient PO
    - For outpatient PO:
      - □ 'Initially oral' antibiotic administration
      - □ 'sequential intravenous to oral' antibiotic administration
- Consistent with:

1) **Objective 1**: To compare the efficacy of outpatient antibiotic treatment versus inpatient antibiotic therapy in febrile neutropenic cancer patients

   - YES
   - NO

2) **Objective 2**: In febrile neutropenic cancer patients treated ambulatory, to compare the efficacy of oral antibiotic/s versus intravenous antibiotic therapy

   - YES
   - NO

3) **neither Objective 1 nor Objective 2** \(\Rightarrow\) **EXCLUSION** (comment: ____________)

- Antibiotic type for outpatient versus inpatient question (**Objective 1**), mode of administration, dose and interval (e.g. Ceftriaxone, IV, 100 mg/kg, q24h):

  Inpatient Group:

  Outpatient Group:

- Antibiotic type for oral versus IV antibiotics for ambulatory patient question (**Objective 2**), mode of administration, dose and interval (e.g. Ceftriaxone, IV, 100 mg/kg, q24h):

  IV Group:

  Oral Group:

- Duration of therapy for outpatient versus inpatient question (**Objective 1**) (median):

  Inpatient Group:

  Outpatient Group:
• Duration of therapy for oral versus IV antibiotics for ambulatory patient question (Objective 2) (median):

IV Group:

PO Group:

• Case definitions:

Inclusion criteria (including definition of low-risk neutropenia):

Exclusion criteria:

• Definition of treatment failure:

2. Characteristics of patients:

• Number of participants and number of episodes in each group:

  Group 1: Number of patients:
  Number of episodes:

  Group 2: Number of patients:
  Number of episodes:

• Age (mean/SD or median/range):

• Main study population:

  □ Adults
□ Children
Do the authors report stratified data for age for any outcome?

□ YES (define outcome: ____________________________________________ )
□ NO

• Source of infection:

Unexplained fever: _____ percent
Documented infection: _____ percent

(documented infection encompasses documented clinical infection and microbiologic infection)

Do the authors report stratified data for source of infection for any outcome?

□ YES (define outcome: ____________________________________________ )
□ NO

• Neutrophil count:

≥100/µL: _____ percent
<100/µL: _____ percent

Do the authors report stratified data for neutrophil counts for any outcome?

□ YES (define outcome: ____________________________________________ )
□ NO

• Underlying disease:

Leukemia: _____ percent
Lymphoma: _____ percent
Solid tumor: _____ percent

Do the authors report stratified data for underlying disease for any outcome?

□ YES (define outcome: ____________________________________________ )
□ NO
3. Characteristics of outcome measures:

- Treatment failure (composite end-point), restricted to 30 days – **per-protocol**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____ of _____ patients</td>
<td>_____ of _____ patients</td>
</tr>
</tbody>
</table>

- Treatment failure (composite end-point), restricted to 30 days – **intention-to-treat** using imputation assuming that all missing participants experienced the adverse event

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____ of _____ patients</td>
<td>_____ of _____ patients</td>
</tr>
</tbody>
</table>

- All cause mortality at 30 days follow-up – **per-protocol**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____ of _____ patients</td>
<td>_____ of _____ patients</td>
</tr>
</tbody>
</table>

- Adverse events requiring discontinuation/modification of therapy – **per-protocol**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____ of _____ patients</td>
<td>_____ of _____ patients</td>
</tr>
</tbody>
</table>
- Readmission to the hospital (applies only to *Objective 2*) – **per-protocol**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____ of _____ patients</td>
<td>_____ of _____ patients</td>
</tr>
</tbody>
</table>

- Incomplete outcome data (number of patients excluded after randomization or lost to follow up (dropouts) before the end of study)

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____ of _____ patients</td>
<td>_____ of _____ patients</td>
</tr>
<tr>
<td>• excluded:</td>
<td>• excluded:</td>
</tr>
<tr>
<td>• lost:</td>
<td>• lost:</td>
</tr>
</tbody>
</table>
4. Validity checklist

1. Was allocation generation appropriate? Specifically must state (eg. stratification not sufficient). If allocation by minimization, can assume allocation generation adequate.
   - Adequate – random number table, random number generator, computer generation, coin-tossing or shuffling
   - Inadequate - alternating patients, alternating blocks of patients, hospital number being odd or even, based on first letter of patient’s name
   - Unclear

2. Was allocation concealment appropriate? Specifically must state
   - Adequate – central randomization, numbered or coded bottles or containers, drugs prepared in pharmacy, serially numbered and sealed opaque envelopes, or other convincing measures
   - Inadequate - alternating patients, alternating blocks of patients, hospital number being odd or even, randomization table posted on bulletin board
   - Unclear

   [If both 1 and 2 are adequate, then add 1 point. If either 1 or 2 are inadequate, subtract 1 point].

3. Was the study double-blinded? A study must be regarded as double-blind if the word double-blind is used.
   - Yes [add 1 point]
   - No  [add 0 points]

4. Was double blinding appropriate?
   - Appropriate – if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.[add 1 point] (as long as use word placebo – mark appropriate)
   - Inadequate [subtract 1 point]
   - Unclear

5. Was there a description of withdrawals and dropouts? (Exclusions after randomization.) Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. As long as all patients are accounted for in this case, then a point can be given. If there were withdrawals and no statement on withdrawals was provided, this item must be given no points. For multiple cycles, also want to see drop-outs by allocation.
   - Yes [add 1 point]
   - No  [add 0 points]

6. Was primary analysis according to ITT? An ITT includes all randomized participants in the group to which they were randomized.
   - Yes [add 1 point]
   - No  [add 0 points]
Appendix C. Definition of exclusion (non low-risk) criteria in the included studies

Santolaya, 2004 (28):

Risk score based on: serum C-reactive protein (CRP) levels of 90 mg/L or greater, presence of hypotension, relapse of leukemia as cancer type, platelet count of 50,000/µL or less, and recent (≤ 7 days) chemotherapy.

Mullen, 1999 (22):

Exclusion criteria: 1) evidence of shock (poor perfusion or hypotension based on age-based blood pressure norms); 2) significant dehydration (>10%); 3) mucositis that prevented adequate oral hydration; 4) identifiable source of infection that would normally require hospitalization and intravenous antibiotics (e.g., perirectal cellulitis, pneumonia, central venous catheter tunnel infection); 5) respiratory distress or other evidence of pneumonia; 6) clinical evidence of typhlitis; 7) bleeding requiring platelet transfusion; 8) residence more than 1 hour from the medical center or unreliable transportation; 9) parents/caretakers deemed by the medical staff to be less than absolutely reliable; 10) patients undergoing leukemia or lymphoma induction therapy; 11) patients undergoing bone marrow/stem cell transplantation; 12) patients with advanced malignant disease refractory to treatment; 13) allergy to ceftazidime or ciprofloxacin; 14) renal insufficiency (estimated glomerular filtration rate (GFR) of <50% normal for age) at the time of the preceding chemotherapy cycle; 15) hepatic dysfunction as evidenced by serum alanine aminotransferase > 4 times normal or bilirubin > 3 mg/dL at the time of the preceding chemotherapy cycle; and 16) infection with microorganisms known to be resistant to ceftazidime or ciprofloxacin.
Paganini, 2003 (24):
Exclusion criteria: 1) severe comorbidity factors (i.e., uncontrolled bleeding, refractory hypoglycemia or hypocalcaemia, hypotension, altered mental status, renal insufficiency [estimated glomerular filtration rate < 50% of the normal level for the patient's age], or hepatic dysfunction [evidenced by a serum alanine aminotransferase level > 4 times normal or bilirubin > 3 mg/dl at the time of the preceding chemotherapy cycle]); 2) respiratory failure; 3) poor clinical condition; 4) fascial, perineal, or catheter-associated cellulitis; 5) evidence of enteritis or severe mucositis; 6) uncontrolled local infection; 7) positive blood cultures within the first 48 hours; 8) neutropenia predicted to last more than 7 days after the onset of fever; 9) parents and/or caretakers deemed by the medical staff to be less than absolutely reliable; 10) infection with microorganisms known as resistant to ceftriaxone or ciprofloxacin; 11) allergy to ceftriaxone or ciprofloxacin; and 12) bone marrow transplantation.

Paganini, 2000 (26):
Exclusion criteria: 1) severe comorbidity factors (i.e., incoercible bleeding, refractory hypoglycemia and hypocalcemia, hypotension, altered mental status, and respiratory failure); 2) poor clinical condition; 3) facial, perineal, or catheter-associated cellulitis; 4) no evidence of enteritis or severe mucositis; 5) uncontrolled local infection; 6) positive blood cultures at 72 hours; 7) persistence of fever longer than 48 hours; and 8) patients undergoing bone marrow transplantation.

Petrilli, 2000 (27):
Leukemia, hemodynamical instability.

Gupta, 2009 (23):
Exclusion criteria: Indications normally requiring hospitalization such as dehydration, severe mucositis, pneumonia, typhlitis, bleeding, and altered mental status; intensive
leukemia/lymphoma treatment except maintenance therapy in acute lymphoblastic leukemia; 
stem cell transplantation; refractory malignancy; renal insufficiency (estimated glomerular 
filtration rate of <50% normal for age) at the time of preceding chemotherapy cycle or at present 
evaluation; severe biochemical derangements such as severe hypoglycemia/hypocalcemia; 
hepatic dysfunction as evidenced by serum alanine aminotransferase >4 times normal or bilirubin 
>3 mg/dL at the time of preceding chemotherapy cycle or at present evaluation; neutropenia 
predicted to last more than 10 days after onset of fever; past history of invasive fungal infections 
and use of prophylactic growth factors.