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# Home-based care of low-risk febrile neutropenia in children – an implementation study in a tertiary paediatric hospital.

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| Corresponding Author: | Gabrielle Monique Haeusler, Ph.D.<br>Peter MacCallum Cancer Centre<br>AUSTRALIA |
| Corresponding Author Secondary Information: | |
| Corresponding Author's Institution: | Peter MacCallum Cancer Centre |
| Corresponding Author's Secondary Institution: | |
| First Author: | Gabrielle Monique Haeusler, Ph.D. |
| First Author Secondary Information: | |
| Order of Authors: | Gabrielle Monique Haeusler, Ph.D. |
| | Lynda Gaynor |
| | Benjamin Teh |
| | Franz Babl |
| | Lisa Orme |
| | Ahuva Segal |
| | Francoise Mechinaud |
| | Penelope Bryant |
| | Bob Phillips |
| | Richard De Abreu Lourenco |
| | Monica Slavin |
| | Karin Thursky |
| Order of Authors Secondary Information: | |
| Funding Information: | National Health and Medical Research Council (APP1104527) — Prof. Karin Thursky |
| Abstract: | Background:Home-based management of low-risk febrile neutropenia (FN) is safe, improves quality of life and reduces healthcare expenditure. A formal low-risk paediatric program has not been implemented in Australia. We aimed to describe the implementation process and evaluate the clinical impact.<br>Method:This prospective study incorporated three phases: implementation, intervention and evaluation. A low-risk FN implementation toolkit wasdeveloped, including a care-pathway, patient information, home-based assessment and educational resources. The program had executive-level endorsement, a multidisciplinary committee and a nurse specialist. Children with cancer and low-risk FN were eligible to be transferred home with a nurse visiting daily after an overnight period of observation for intravenous antibiotics. Low-risk patients were identified using a validated decision rule and suitability for home-based care was determined using disease, chemotherapy and patient-level criteria. Plan-Do-Study-Act methodology was used to evaluate clinical |

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| | impact and safety.<br>Results:Over 18 months, 336 children with FN were screened: 130 (39%) were low-risk, of which 63 were transferred to home-based care. Compared to pre-implementation there was a significant reduction in in-hospital median LOS (4.6 to 1.5 days, p<0.001) and 291 in-hospital bed days were saved. Eight (13%) patients needed readmission and there were no adverse outcomes. A key barrier was timely screening of all patients and program improvements, including utilising the electronic medical record for patient identification, are planned.<br>Conclusion: This program significantly reduces in-hospital LOS for children with low-risk FN. Ongoing evaluation will inform sustainability, identify areas for improvement and support national scale up of the program. |
| **Suggested Reviewers:** | Fabianne Carlesse<br>fabiannecarlesse@graacc.org.br<br>Fabianne is a paediatric infectious diseases specialist with clinical and research expertise in managing infections in children with cancer. |
| | Joshua Wolf<br>Joshua.Wolf@STJUDE.ORG<br>Josh is a paediatric infectious diseases physician at St Jude Children's Research Hospital. He has led a number of studies in paediatric FN. |

**Peter MacCallum Cancer Centre**
305 Grattan Street
Melbourne Victoria
3000 Australia

**Postal Address**
Locked Bag 1 A'Beckett Street
Victoria 8006 Australia

**Phone** +61 3 8559 5000
**Fax** +61 3 8559 7379
**ABN** 42 100 504 883

**petermac.org**

**Locations**
Melbourne
Bendigo
Box Hill
Moorabbin
Sunshine


Professor Fred Ashbury
Editor-in-chief
Supportive Care in Cancer

12 February 2020

Dear Prof. Fred Ashbury,

Submission of an Original Article entitled '**Home-based care of low-risk febrile neutropenia in children – an implementation study in a tertiary paediatric hospital**.'

Home-based management of low-risk febrile neutropenia (FN) in children is recommended in international paediatric FN guidelines (Lehrnbecher et al. J Clin Oncol. 2017). Despite this, very few centres have adopted this model of care and there are a paucity of studies describing a framework for implementation.

Our prospective study describes the process for implementing and evaluating a dedicated paediatric low-risk FN program. Over an 18-month period, 63 children with FN were successfully transferred to home-based care. Compared to pre-implementation there was a significant reduction in in-hospital median length of stay (4.6 to 1.5 days, $p<0.001$) and 291 in-hospital bed days were saved. A key program barriers were identified, including timely risk assessment.

Our study should be published in *Supportive Care in Cancer* as it is the largest, prospective paediatric low-risk FN implementation study conducted to date. We have shown the program is safe and significantly impacts length of stay and hospital bed-access. Collectively, our body of research, including the implementation study described in this manuscript, has informed a national scaling study. This national study has received federal funding which will enable the program to be implemented across all eight tertiary paediatric hospitals in Australia.

We believe our study will be of significant interest to your broad academic and clinical. We have reported out study according to the Standards for Reporting Implementation Studies (StaRI) guidelines as recommended by the EQUATOR network.

We look forward to your reply regarding our important study.

Sincerely,

Dr Gabrielle Haeusler
Corresponding author and lead investigator.

# Home-based care of low-risk febrile neutropenia in children – an implementation study in a tertiary paediatric hospital.

Gabrielle M Haeusler,[1-6] Lynda Gaynor,[4,7] Benjamin Teh,[1-3] Franz E Babl,[6,8] Lisa M Orme,[9] Ahuva Segal,[10] Francoise Mechinaud,[11] Penelope A. Bryant,[5,6,7,10] Bob Phillips,[12] Richard De Abreu Lourenco,[13] Monica A. Slavin[1-3, 14,15] and Karin A. Thursky.[1-3, 14-16]

**Affiliations**

1. Department of Infectious Diseases, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

2. NHMRC National Centre for Infections in Cancer, Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia

3. Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia

4. The Paediatric Integrated Cancer Service, Parkville, Victoria State Government, Australia

5. Infection Diseases Unit, Department of General Medicine, Royal Children's Hospital, Parkville, Victoria, Australia

6. Murdoch Children's Research Institute, Parkville, Victoria, Australia

7. Hospital In The Home department, Royal Children's Hospital, Parkville, Victoria, Australia

8. Department of Emergency Medicine, Royal Children's Hospital, Parkville, Victoria, Australia.

9. Children's Cancer Centre, Royal Children's Hospital, Parkville, Victoria, Australia

10. Department of Paediatrics, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Australia.

11. Unité d'hématologie immunologie pédiatrique, Hopital Robert Debré, APHP Nord Université de Paris, France

12. Centre for Reviews and Dissemination, University of York, York, United Kingdom

13. Centre for Health Economics Research and Evaluation, University of Technology Sydney, New South Wales, Australia

14. Department of Medicine, University of Melbourne, Parkville, Victoria, Australia, 3010

15. Victorian Infectious Diseases Service, The Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia

16. NHMRC National Centre for Antimicrobial Stewardship, The Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia

**Corresponding author:** Dr Gabrielle M. Haeusler, Department of Infectious Diseases, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Australia, 3000, P: +61 3 9656 5853 F: +61 3 9656 1185, E: gabrielle.haeusler@petermac.org

## ABSTRACT

**Background:** Home-based management of low-risk febrile neutropenia (FN) is safe, improves quality of life and reduces healthcare expenditure. A formal low-risk paediatric program has not been implemented in Australia. We aimed to describe the implementation process and evaluate the clinical impact.

**Method:** This prospective study incorporated three phases: implementation, intervention and evaluation. A low-risk FN implementation toolkit was developed, including a care-pathway, patient information, home-based assessment and educational resources. The program had executive-level endorsement, a multidisciplinary committee and a nurse specialist. Children with cancer and low-risk FN were eligible to be transferred home with a nurse visiting daily after an overnight period of observation for intravenous antibiotics. Low-risk patients were identified using a validated decision rule and suitability for home-based care was determined using disease, chemotherapy and patient-level criteria. Plan-Do-Study-Act methodology was used to evaluate clinical impact and safety.

**Results:** Over 18 months, 336 children with FN were screened: 130 (39%) were low-risk, of which 63 were transferred to home-based care. Compared to pre-implementation there was a significant reduction in in-hospital median LOS (4.6 to 1.5 days, $p<0.001$) and 291 in-hospital bed days were saved. Eight (13%) patients needed readmission and there were no adverse outcomes. A key barrier was timely screening of all patients and program improvements, including utilising the electronic medical record for patient identification, are planned.

**Conclusion:** This program significantly reduces in-hospital LOS for children with low-risk FN. Ongoing evaluation will inform sustainability, identify areas for improvement and support national scale up of the program.

**Key words:** low-risk, febrile neutropenia, child, implementation, evaluation

## DECLARATIONS

**Funding**: Program implementation was supported by a grant from Better Care Victoria (BCV), Department of Health and Human Services, Victorian State Government. Baseline data collection was supported by a grant from National Health and Medical Research Association (NHMRC) Project Grant (APP1104527).

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**Conflicts of interest/Competing interests:** The authors declare that they have no conflict of interest.

**Ethics**: This study was performed in line with the principles of the Declaration of Helsinki. The study had local Human Research Ethics Committee approval from The Royal Children's Hospital Human Research Ethics Committee (ethics number 36040).

**Consent to participate:** Informed consent was obtained from all individual participants or parent/guardian of patients included in the study.

**Availability of data and material:** Not applicable

**Code Availability**: Not applicable

**Authors' contributions:** All authors contributed to the study conception and design. Data collection were performed by Dr Gabrielle Haeusler and Ms Lynda Gaynor. Analysis was performed by Dr Gabrielle Haeusler, Ms Lynda Gaynor and Prof Karin Thursky. The first draft of the manuscript was written by Dr Gabrielle Haeusler and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

## INTRODUCTION

There are increasing data to support home-based management of children with cancer and febrile neutropenia (FN) who are at low-risk of infection or medical complications. Summarised in two systematic reviews of prospective paediatric FN studies, outpatient and oral antibiotic management appears safe, with low rates of treatment failure.[1,2] In keeping with these data, international paediatric FN guidelines recommend that centres adopt a validated risk stratification program and consider initial or step-down outpatient management if the infrastructure is in place to ensure careful monitoring and follow-up.[3,4] However, despite the evidence and guideline recommendations, survey data from Australia,[5] the United Kingdom,[6] France,[7] and the United States[8] indicate a significant proportion of clinicians continue to opt for traditional in-hospital treatment with intravenous antibiotics for children with low risk FN.

The appropriate selection of children with FN at low-risk of infection is fundamental to the success of home-based care. To date, as many as 27 attempts have been made to derive a rule or set of clinical variables that accurately distinguishes between children at low and high risk of infection with varying results in validation.[9,10] This, together with a paucity of studies describing an approach to implementation or an evaluation of the clinical, economic and quality of life impact of these rules, may, in part, explain the inconsistent uptake of home-based management of low-risk FN.[11]

Over the last few years at our tertiary paediatric hospital, a small proportion of patients with FN have been transferred for home-based management, but decisions have been *ad hoc* and patients have been transferred late in their course.[12] To address this we conducted validation studies to determine the most suitable clinical decision rule to help stratify children with cancer and FN into low- and high-risk for infection or adverse event.[13] Beyond

validation, we showed that in-hospital length of stay (LOS) is the main contributor to overall cost of FN care, and reductions in hospital LOS in patients identified as low risk may translate to healthcare savings of up to AUD $2,000 per day.[14] Finally, a randomised controlled trial at our centre also found significant carer and patient quality of life benefits in favour of home-based care for management of low-risk FN.[15] Based on these and international data we piloted a formal low-risk FN program at our hospital. The program was adapted from an adult low-risk FN program, successfully implemented at a cancer hospital and scaled to other tertiary centres.[16]

The objective of this study was to describe the process of implementing a paediatric low-risk FN program and to prospectively evaluate the clinical impact on LOS and patient safety.

## METHODS

This prospective study incorporated three key phases: implementation, intervention and evaluation. It was conducted at a tertiary paediatric hospital with a 26-bed haematology/oncology and haematopoietic stem cell transplant (HSCT) unit with the majority of patients treated on Children's Oncology Group chemotherapy protocols. Methodology and reporting of results followed the Standards for Reporting Implementation Studies (StaRI) statement.[17] The study had ethics approval from The Royal Children's Hospital Human Research Ethics Committee (ethics number 36040).

**Implementation**. A standardised paediatric low-risk FN implementation toolkit was developed and included an evidence-based care pathway, a patient and staff education package, and an evaluation protocol (available at https://cancerandinfections.org/kids-low-risk-toolkit).[18,19] The pathway incorporates a clinical decision rule (CDR), derived by the Swiss Paediatric Oncology Group (SPOG) and locally validated at our hospital.[13,20] The CDR is

designed to be applied at Day 2 and predicts adverse events using four readily accessible clinical variables (intensity of chemotherapy, haemoglobin, white cell count and platelets). Adverse event was defined as a serious medical complication (death, complication requiring ICU and potentially life-threatening complication as judged by the treating physician) as a result of infection, microbiologically defined infection (positive bacterial or fungal culture from a normally sterile site and detection of a viral antigen by PCR) or radiologically confirmed pneumonia.[20] Additional eligibility or 'safety-net' criteria, for early transfer to HITH, adapted from a local adult low-risk FN program, were also included in the care pathway (Table 1).[16] The pathway was endorsed for state-wide use and made available online.[19]

A multidisciplinary working group comprising key stakeholders from oncology, infectious diseases, emergency medicine, hospital-in-the-home (HITH), pharmacy, quality and safety and the electronic medical record (EMR) team was formed. The group met monthly in the preparation phase, quarterly during implementation and were responsible for overseeing all aspects of the program.

A dedicated clinical nurse consultant was employed (average 0.25 FTE for 18 months) to assist in all phases. Key responsibilities included coordinating steering group meetings, actioning items, updating the EMR, staff and patient education, identifying suitable patients, liaison between relevant medical departments (HITH, oncology and emergency), ensuring appropriate follow up of all patients entered onto the program and clinical data collection. A comprehensive education campaign was conducted in the planning phase targeting all medical and nursing staff from oncology, infectious diseases, HITH and emergency medicine. Nursing bed managers and staff from all medical wards that accept oncology admissions during busy periods were also included in the education.

The hospital EMR (Epic, Epic Systems Corporation) was updated to include a dedicated low-risk FN program patient pathway. The pathway incorporated the SPOG CDR, HITH eligibility criteria (Table 1) and recommended investigations and antibiotics. It enabled a maximum of five days of pathology and antibiotic orders before prompting the user to arrange a medical review to ensure ongoing HITH suitability.

**Intervention.** All children (age ≤18 years) with cancer or leukaemia on active treatment and diagnosis of fever (≥38°C) and neutropenia (absolute neutrophil count ≤1.0 cells/μL) were eligible to be screened for inclusion on the program. Patients who had received a HSCT within the preceding 3 months or who developed FN on concurrent treatment antibiotics were excluded.

All patients received standard empiric FN investigations and treatment on presentation to the emergency department and were admitted to the oncology department. Risk stratification and assessment of HITH eligibility was the responsibility of the treating oncology team. Following identification of suitable patients with low-risk FN, referral to the HITH unit was made with a view to transfer the patient home after a minimum of overnight observation. The patient and family received a program information pamphlet, home-assessment chart to record temperature and other concerns, and education on when and how to contact the hospital. Once home, the patient had a daily clinical review by a HITH nurse, and administration of intravenous antibiotics (piperacillin-tazobactam via a 24-hour infuser), pathology samples (full blood examination plus others as required) and a clinical assessment. The patient was eligible for discharge from the program when all of the following were fulfilled: clinically well, no

documented infection requiring antibiotics, afebrile >24 hours and evidence of marrow recovery including a post-nadir ANC>0.2 cells/mm.[3]

An urgent in-hospital medical review was arranged for the following indications and consideration was given to readmission: recurrent or persistent fever (>48hrs from FN onset) or new fever after being afebrile for 24 hours; new signs and symptoms of infection such as chills, rigors or shaking; significant decrease in oral intake (<50% baseline) or significantly increased fluid losses (vomiting or diarrhoea); positive blood culture result (reported after hospital discharge) or other infection requiring in-hospital care.

**Evaluation**: A prospective cohort design, using Plan-Do-Study-Act (PDSA) methodology, was used to evaluate the clinical impact and safety of the program.[21] Detailed patient demographic, FN episode and outcome data were collected on all low-risk patients using international consensus definitions.[22,23] All deidentified data were entered into an electronic database (REDCap).[24] Key clinical impact indicators included: (i) proportion of eligible patients entered onto program, (ii) reduction in in-hospital LOS and (iii) total number of bed days saved. Safety indicators included (i) number and reason for hospital readmissions and (ii) any adverse events (including but not limited to intensive care unit admission or death). This quantitative information was used to identify key organisations-, healthcare- and patient-level barriers during the 'study' phase of the PDSA cycle.

Post implementation clinical data for FN episodes managed on the low-risk FN program were compared to pre-implementation data from the Australian PICNICC study and matched according to risk status and HITH-eligibility criteria (Table 1).[25] Methodology for the Australian PICNICC study is available elsewhere.[25] Patient demographic, FN episode and

outcome data were collected on consecutive episodes of FN from eight paediatric tertiary FN cancer centres in Australia. There were 304 episodes of outpatient onset FN occurring at our hospital from November 2016 to December 2017 of which 122 and 182 episodes were classified as low and high risk, respectively. Low-risk episodes that had an infection or adverse event known at day 2 (n=11) or who did not fulfil HITH eligibility criteria (n=29) were excluded, leaving 82 low-risk pre-implementation episodes for comparison. Similarly, following exclusion of episodes that had an infection or adverse event known at day 2 (n=23) or who did not fulfil HITH eligibility criteria (n=35) there were 124 high-risk episodes available for comparison.

Progress, including key impact and safety measures, were fed back to the Oncology department (during multi-disciplinary unit meetings) and the Quality and Safety unit (via written reports) on a monthly basis. Additional barriers were identified at the Oncology department meetings and proposed solutions discussed. This qualitative information, together with the quantitative impact and safety data, were fed back to the steering group and the proposed solutions implemented accordingly.

**Statistical analysis:** Continuous data were presented as median and interquartile range. Mann–Whitney U test was used to estimate P-values for continuous data and Fisher's exact test for categorical data. P-value $<0.05$ was considered significant.

## RESULTS

Following a 3-month lead-in preparation phase, the program was launched at our hospital on 8 January 2018.

In the first eighteen months, 336 children with cancer and outpatient onset FN were risk assessed, of which 130 (39%) were low-risk and 44 (34%) were transferred to the program to complete home-based FN care (Table 2). An additional 19 FN episodes, who were assessed as high-risk were also considered appropriate for home-based care by their treating oncologist and were transferred to the program. Of the 86 FN episodes assessed as low risk that were not transferred home, 20 (23.3%) met HITH eligibility criteria and therefore missed opportunities for home-based care (Figure 1).

There was no significant difference in median age, sex and underlying malignancy in the pre and post-implementation cohorts (Table 2). Post implementation episodes transferred to home-based care were significantly more likely to have a fever of unknown cause. For all patients entered on the program, the median time from a documented fever greater than 38.0°C to HITH transfer was 24.0 hours (IQR 12.2-58.8 hours). The median ANC at time of final discharge from the program was 0.33 cells/$mm^3$ (IQR 0.15-0.57 cells/$mm^3$).

During treatment at home, there were 36 in-hospital patient medical reviews required for 32 (50.8%) FN episodes (4 episodes had 2 reviews). Unplanned reasons for in-hospital review included: thrombocytopaenia requiring platelet administration (n=7), CVAD complications (n=6), positive microbiology results (n=3), gastrostomy site complication (n=1), spurious blood result (n=1) and nasogastric tube reinsertion (n=1). Reviews as per protocol included: prolonged (>5 days) neutropenia (n=9) and new or prolonged fever (n=8). Reviews resulted in readmission during eight of 63 (13%) episodes. The median time to readmission was 3.9 days

(IQR 1.2-7.5 days) and median duration of readmission was 7.6 days (IQR 2.6-17.2 days). All re-admitted episodes made full recovery and were discharged without complications.

Compared to pre-implementation data (n=82), there was a significant reduction in median in-hospital LOS for both the low and high-risk FN episodes transferred to the program (4.0 to 1.5 days, $p<0.001$) and a total of 291.2 in-hospital bed days were saved. Considered separately, the reduction in median in-hospital LOS remained significant for episodes identified as low-risk (n=44) but not those identified as high-risk (n=19) (Table 3). However, when compared to pre-implementation high-risk episodes (n=124), there was a significant reduction in median in-hospital LOS for the 19 high-risk episodes transferred to the program (4.8 to 1.9 days, $p=0.01$).

**Program barriers.** Potential barriers to the program were identified during the 'study' phase of the PDSA cycle. They were grouped into organisational, clinical staff, patient identification and infrastructure. Proposed solutions were determined in collaboration with key stakeholders and the program was updated accordingly. Barriers and corresponding solutions, including planned changes, are outlined in Table 4.

An important barrier to ensuring all eligible low-risk FN episodes were entered onto the program was inconsistent risk-stratification of patients by clinical staff, with 16 low-risk FN episodes fulfilling all HITH criteria but not risk stratified (Figure 1). To overcome this, it was agreed that the treating team were responsible for risk-scoring all patients with FN and assessing suitability for the program. The EMR system has also been utilised to improve timely patient identification. A point-of care "best practice" alert (BPA) was developed to appear in the EMR if all the following criteria were met: (i) the most recent documented fever since the start of the admission was ≥38°C; (ii) the most recent neutrophil count in the last 48 hours was

< 1.0 cells/μL; (iii) no previous SPOG score had been documented during that admission and; (iv) the patient had not been admitted more than 5 days. The BPA was targeted to the junior medical officer or consultant assigned to the treating team responsible for the patient. Following implementation, it became apparent that the BPA was not identifying patients with profound neutropenia such that their total white cell count was so low (<0.4 cells/μL) that a differential count was not performed. The BPA was revised in July and August and impact is currently being assessed.

## DISCUSSION

We have shown that implementation of a low-risk FN program, using a structured program incorporating a validated CDR, HITH support and clear criteria for readmission is safe, feasible and significantly reduced in-hospital LOS. Over an 18-month period, over 290 in-hospital bed days were saved, likely contributing to substantial healthcare savings.[14] Of the patients transferred to the program, 13% required readmission for in-hospital care, in keeping with 10% in a recent report of a paediatric low-risk FN program from the USA.[11] A unique aspect of our program was the addition of safety-net criteria (outlined in Table 1) to the validated CDR. These criteria ensured patients who required in-hospital care despite scoring low-risk were not transferred home.

Key components of our low-risk FN program were informed by research conducted locally. The CDR selected for use was validated in the target population and modelling provided estimates of the number of children likely to benefit from home-based FN management.[13] Externally testing the applicability of a CDR prior to implementation is recommended as a key component to the validation process.[26] Furthermore, a systematic review found that studies using well-defined tools to identify children with low-risk FN suitable for home-

based care had significantly lower failure rates of outpatient care compared to studies using less stringent tools (7% versus 19%).[1] These factors, together with the multidisciplinary approach to implementation and provision of monthly feedback on key performance indicators, likely contributed to the success of the program.

Whilst challenging to quantify objectively, the importance of a dedicated clinical nurse consultant supporting all three phases of the program cannot be overstated. The nurse played a crucial role in staff and patient education, patient identification, program evaluation as well as liaison between families on the program and relevant hospital staff. In a systematic review of nurse-led ambulatory programs, clinical outcomes were largely equivalent to physician-led programs, with some areas of health-related quality of life better in the nurse-led models.[27] While high quality economic evaluations are lacking, some studies have shown lower costs in nurse-led programs, largely driven by fewer hospital readmissions and shorter LOS.[27]

Comprehensive evaluation of the program has identified key areas for improvement, in particular ensuring all patients are risk-assessed to avoid missed opportunities for home-based care. Automated identification of all patients with FN and alerting relevant clinicians via the EMR is a potential way to improve case ascertainment. To date, no studies have explored the impact of this approach in the management of low-risk FN. Randomised trials of automated monitoring and alerts in adult patients with sepsis show mixed results ranging from no effect [28] to a significant reduction in LOS and mortality.[29] A key difference between these studies was the lack of accompanying management recommendations in the former study, suggesting that these alerts may not work in isolation and would likely benefit from linking to guidelines and care pathways.

An unintended consequence of the program is the longer total LOS (ie. inclusive of both in-hospital and HITH LOS) in the post-implementation group compared to the pre-implementation group. This may, in part, be explained by clinicians taking a more conservative approach to patients being managed at home. While the median ANC at discharge from the program was 0.33 cells/mm$^3$, one quarter of patients continued to receive antibiotics until ANC was greater than 0.6 cells/mm.[3] Targeted education that earlier discharge and cessation of antibiotics is safe, together with introduction of nurse-led discharge criteria are potential solutions being implemented. Options for oral antibiotics have also been included in the pathway and education regarding the safety and efficacy of this approach is ongoing.[1,2]

A key strength of our study is in the use of prospectively collected pre- and post-implementation data to assess the clinical impact of our program. We have also followed international consensus guidelines for the reporting of implementation studies.[30,31]
We are currently extending our work to investigate the economic and quality of life impacts of this low-risk FN program, adopting similar methodology to a study of an adult low-risk FN program that showed significant cost savings.[16,32] In a baseline economic analysis we identified that the mean cost of standard, in-hospital management of paediatric low-risk FN was $2,200 AUD per day[32]. As the mean costs incurred for home based-care of FN in Australia is AUD $828, the cost benefit of our program is likely to be substantial.

A structured low-risk FN program incorporating risk assessment, regular observation and appropriate safeguards, has enabled children with cancer at our institution to benefit from home-based FN care. By saving 290 in-hospital bed days in 18 months, we have also increased the availability of specialised cancer beds for children requiring in-hospital

chemotherapy and reduced the burden on other speciality wards. This program in currently being scaled nationally, thereby increasing the clinical, economic and quality of life impact of this model of care.

## REFERENCES


1. Morgan JE, Cleminson J, Atkin K, et al. (2016) Systematic review of reduced therapy regimens for children with low risk febrile neutropenia. Support Care Cancer 24:2651-60

2. Manji A, Beyene J, Dupuis LL, et al. (2012) Outpatient and oral antibiotic management of low-risk febrile neutropenia are effective in children--a systematic review of prospective trials. Support Care Cancer 20:1135-45

3. Lehrnbecher T, Phillips R, Alexander S, et al. (2012) Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. J Clin Oncol 30:4427-38

4. Lehrnbecher T, Robinson P, Fisher B, et al. (2017) Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update. J Clin Oncol 35:2082-94

5. Haeusler GM, Slavin MA, Bryant PA, et al. (2018) Management of fever and neutropenia in children with cancer: A survey of Australian and New Zealand practice. J Paediatr Child Health 54:761-69

6. Herd F, Bate J, Chisholm J, et al. (2016) Variation in practice remains in the UK management of paediatric febrile neutropenia. Arch Dis Child 101:410-1

7. Delebarre M, Tiphaine A, Martinot A, et al. (2016) Risk-stratification management of febrile neutropenia in pediatric hematology-oncology patients: Results of a French nationwide survey. Pediatr Blood Cancer 63:2167-72

8. Mueller EL, Walkovich KJ, Yanik GA, et al. (2015) Variation in Management of Fever and Neutropenia Among Pediatric Patients With Cancer: A Survey of Providers in Michigan. Pediatr Hematol Oncol 32:331-40

9. Phillips RS, Lehrnbecher T, Alexander S, et al. (2012) Updated systematic review and meta-analysis of the performance of risk prediction rules in children and young people with febrile neutropenia. PLoS One 7:e38300

10. Phillips B, Wade R, Stewart LA, et al. (2010) Systematic review and meta-analysis of the discriminatory performance of risk prediction rules in febrile neutropaenic episodes in children and young people. Eur J Cancer 46:2950-64

11. Paolino J, Mariani J, Lucas A, et al. (2019) Outcomes of a clinical pathway for primary outpatient management of pediatric patients with low-risk febrile neutropenia. Pediatr Blood Cancer 66:e27679

12. Hodgson KA, Huynh J, Ibrahim LF, et al. (2016) The use, appropriateness and outcomes of outpatient parenteral antimicrobial therapy. Arch Dis Child 101:886-93

13. Haeusler GM, Thursky KA, Slavin MA, et al. (2018) External Validation of Six Pediatric Fever and Neutropenia Clinical Decision Rules. Pediatr Infect Dis J 37:329-35

14. Haeusler GM, Thursky KA, Mechinaud F, et al. (2017) Predicting Infectious ComplicatioNs in Children with Cancer: an external validation study. Br J Cancer 117:171-78

15. Orme LM, Babl FE, Barnes C, et al. (2014) Outpatient versus inpatient IV antibiotic management for pediatric oncology patients with low risk febrile neutropenia: a randomised trial. Pediatr Blood Cancer 61:1427-33

16. Teh BW, Brown C, Joyce T, et al. (2018) Safety and cost benefit of an ambulatory program for patients with low-risk neutropenic fever at an Australian centre. Support Care Cancer 26:997-1003

17. Pinnock H, Barwick M, Carpenter CR, et al. (2017) Standards for Reporting Implementation Studies (StaRI) Statement. BMJ 356:i6795

18. National Centre For Infections in Cancer, Low risk Febrile Neutropenia Toolkit. [updated November 2018. Available from: https://cancerandinfections.org/low-risk-toolkit accessed 02/01/2019.

19. The Royal Children's Hospital, Melbourne, Australia, Clinical Practice Guideline on Fever and suspected or confirmed neutropenia in children with cancer. 2018 [updated November 2018. Available from: https://wwww.rch.org.au/clinicalguide/ accessed 02/01/2019.

20. Ammann RA, Bodmer N, Hirt A, et al. (2010) Predicting adverse events in children with fever and chemotherapy-induced neutropenia: the prospective multicenter SPOG 2003 FN study. J Clin Oncol 28:2008-14

21. Scoville R. 6 Essential Practices for Sustainable Improvement 2017 [Available from: http://www.ihi.org/communities/blogs/six-essential-practices-for-sustainable-improvement accessed 18/01/2019.

22. Haeusler GM, Phillips R, Lehrnbecher T, et al. (2015) Core outcomes and definitions for pediatric fever and neutropenia research: A consensus statement from an international panel. Pediatr Blood Cancer 62:483-9

23. Haeusler GM, Phillips RS, Lehrnbecher T, et al. (2013) The reporting of outcomes in studies of fever and neutropenia in children with cancer: time for consensus. Pediatr Blood Cancer 60:1563-4

24. Harris P, Taylor R, Thielke R, et al. (2009) Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42:377-81

25. Haeusler GM, Thursky KA, Slavin MA, et al. (2019) Risk stratification in children with cancer and febrile neutropenia: a national, prospective, multicentre validation of nine clinical decision rules. EClinicalMedicine 18

26. McGinn T, Guyatt G, Wyer P, et al. (2000) Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. Evidence-Based Medicine Working Group. JAMA 284:79

27. Chan RJ, Marx W, Bradford N, et al. (2018) Clinical and economic outcomes of nurse-led services in the ambulatory care setting: A systematic review. Int J Nurs Stud 81:61-80

28. Hooper MH, Weavind L, Wheeler AP, et al. (2012) Randomized trial of automated, electronic monitoring to facilitate early detection of sepsis in the intensive care unit*. Crit Care Med 40:2096-101

29. Shimabukuro DW, Barton CW, Feldman MD, et al. (2017) Effect of a machine learning-based severe sepsis prediction algorithm on patient survival and hospital length of stay: a randomised clinical trial. BMJ Open Respir Res 4:e000234

30. Pinnock H, Epiphaniou E, Sheikh A, et al. (2015) Developing standards for reporting implementation studies of complex interventions (StaRI): a systematic review and e-Delphi. Implement Sci 10:1-9

31. Hull L, Goulding L, Khadjesari Z, et al. (2019) Designing high-quality implementation research: development, application, feasibility and preliminary evaluation of the implementation science research development (ImpRes) tool and guide. Implement Sci 14:1-20

32. Tew M, Forster D, Teh BW, et al. (2019) National cost savings from an ambulatory program for low-risk febrile neutropenia patients in Australia. Aust Health Rev

**Figure 1**. Primary reasons for the 84 low-risk episodes not being transferred to home-based care

Figure 1

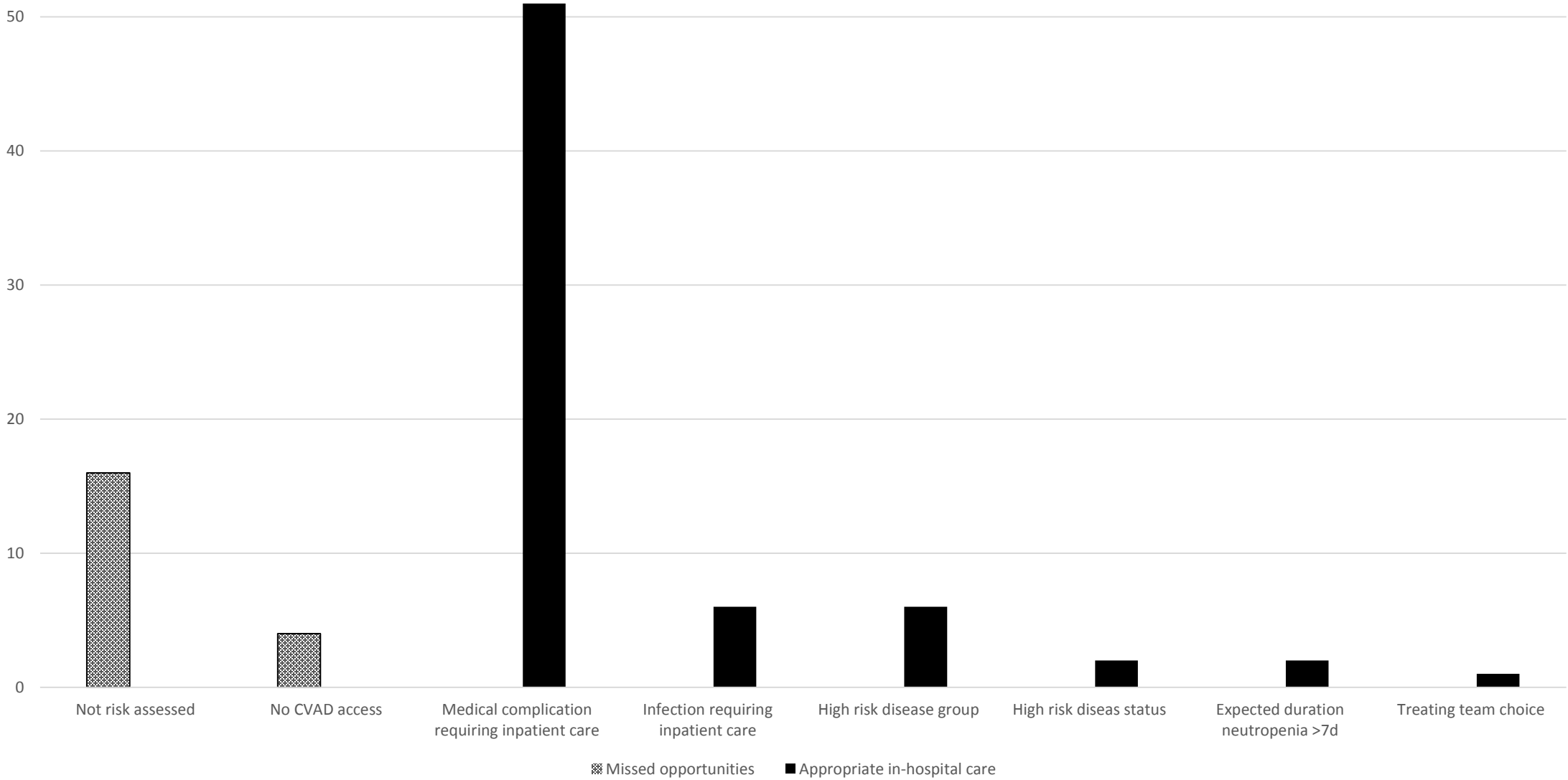
50
40
30
20
10
0
Not risk assessed
No CVAD access
Medical complication requiring inpatient care
Infection requiring inpatient care
High risk disease group
High risk diseas status
Expected duration neutropenia >7d
Treating team choice
Missed opportunities
Appropriate in-hospital care

**Table 1:** Eligibility criteria for early transfer to hospital-in-the-home (must be YES to all to proceed):

| **Criteria** | **Eligible** | **Not eligible** |
|---|---|---|
| Disease status. Leukaemia/lymphoma in remission (as per last BMA) or solid tumour stable/responding (as per oncologist) | ☐ Yes | ☐ No |
| Disease group. Not any of: ALL induction, infant ALL, AML, post HSCT, congenital immunodeficiency, aplastic anaemia | ☐ Yes | ☐ No |
| Expected duration of neutropenia < 7 days | ☐ Yes | ☐ No |
| No confirmed focus of infection requiring inpatient care[a] | ☐ Yes | ☐ No |
| No medical complication requiring inpatient care[b] | ☐ Yes | ☐ No |
| No severe sepsis at FN presentation[c] | ☐ Yes | ☐ No |
| No active infection with multi-drug resistant bacteria | ☐ Yes | ☐ No |
| Availability of a 24 hour caregiver | ☐ Yes | ☐ No |
| Good education of patient and carer on reportable symptoms | ☐ Yes | ☐ No |
| Availability of a telephone (with credit) | ☐ Yes | ☐ No |
| Availability of 24 hour phone advice/emergency department review from treating hospital | ☐ Yes | ☐ No |
| Within 1-hour of an emergency department or treating hospital | ☐ Yes | ☐ No |
| Treating team preference | ☐ Yes | ☐ No |
| No previous history of non-compliance with medical care | ☐ Yes | ☐ No |

BMA is bone marrow aspirate; ALL, acute lymphoblastic leukaemia; AML acute myeloid leukaemia; HSCT, haematopoetic stem cell transplant; FN, febrile neutropenia

[a]including, *but not limited to*, central venous catheter site infection, cellulitis, perianal cellulitis or pain, pneumonia, colitis.

[b]including, *but not limited to*, pain requiring intravenous analgesia, poor oral intake or excessive loss requiring intravenous hydration; respiratory distress or oxygen requirement; pulmonary infiltrates on CXR.

[c]severe sepsis includes any of (i) altered conscious state, (ii) inotrope requirement, (iii) fluid bolus requirement >40ml/kg or (iv) respiratory report requirement

**Table 2.** Demographic and outcome data of pre-implementation FN episodes[25] and post-implementation FN who were transferred to home-based care

| | **Pre-implementation (n=82)** [a] | **Post-implementation (n=63)**[b] | **P value** |
|---|---|---|---|
| Median age, years (IQR) | 5.5 (3.3-8.3) | 7.0 (2.7-9.4) | 0.57 |
| Female, n (%) | 42 (51%) | 33 (52.4) | >0.99 |
| Haematological malignancy, n (%) | 32 (39.0) | 24 (38.1) | >0.99 |
| Cause of fever, n (%) | | | |
| -Bacteraemia | 3 (3.7) | 3 (4.8) | >0.919 |
| -MDI | 14 (17.1) | 1 (1.6) | 0.002 |
| -CDI | 8 (9.7) | 2 (3.2) | 0.19 |
| -fever unknown cause | 57 (69.5) | 57 (90.4) | 0.002 |

IQR is interquartile range; MDI is microbiologically defined infection; CDI is clinically defined infection; [a]restricted to outpatient onset low risk FN who fulfilled HITH criteria and excluding those episodes with AE known at day 2; [b]Includes 19 episodes classified as high risk.

**Table 3.** Clinical impact of low-risk FN program pre and post implementation

| | Pre-implementation (n=82)[a] | Post implementation | | | P value (Column A vs C) |
|---|---|---|---|---|---|
| | | Low risk Not TF to HITH (n=88) | Low risk TF to HITH (n=44) | High risk TF to HITH (n=19) | |
| | **A** | **B** | **C** | **D** | |
| Median in-hospital LOS, d (IQR) | 4.0 (2.4-6.8) | 5.6 (2.7-10.8) | 1.3 (1.0-2.8) | 1.9 (0.9-10.6) | 0.001* |
| Median HITH LOS, d (IQR) | NA | 0 | 3.6 (2.1-5.0) | 4.5 (2.9-6.0) | - |
| Median total LOS, d (IQR) | 4.0 (2.4-6.8) | 5.6 (2.7-10.8) | 5.7 (3.9-7.2) | 8.3 (4.1-15.8) | 0.01[b] |
| Readmissions, n (%) | NA | NA | 6 (13.6) | 2 (10.5) | - |
| ICU admission | 0 | 2 (2.3) | 0 | 0 | - |
| Total bed days saved, n | 0 | 0 | 184.9 | 106.3 | - |

[a]Column A versus D p=0.07; [b]Column A versus D p=0.02

**Table 4**. Program barriers and solutions (italic indicates solutions planned for implementation)

| **Potential barriers** | **Sustainability solutions** |
|---|---|
| **Organisational** | |
| Education and training of all staff | • Standardised education included in all new medical and nursing orientation package<br>• *Update to online paediatric FN learning module to include management of low-risk FN (available at www.eviq.com)* |
| Availability of low-risk nurse lead | • *Formal economic and QOL analysis to inform business case for ongoing support of a dedicated nurse to drive program* |
| **Healthcare staff** | |
| Rotating clinical staff | • All new medical and nursing staff are required to complete orientation package containing information about low-risk FN program<br>• Program education delivered by medical and nursing education leads within the oncology unit |
| Clinician engagement | • Regular (monthly) email communiques to update clinical staff on program progress including patient recruitment, LOS reductions, bed-days saved and readmissions<br>• Low-risk FN nurse attends oncology ward rounds 2-3x/week to promote program |

| | |
|---|---|
| Patient identification | • Clinical role (oncology registrar/fellow), rather than individual person, responsible for risk assessment of all patients with FN<br>• Use of an electronic medical alert to assist in patient identification |
| **Patient** | |
| Accurate risk assessment | • *Recalibrate SPOG clinical decision rule following analysis of prospective Australian PICNICC study data* |
| Prolonged HITH LOS | • *Nurse led HITH discharge criteria*<br>• *Explore use of commercially available WCC and differential point-of-care test* |
| No CVAD access | • Include recommendations for oral antibiotics (amoxicillin-clavulanate and ciprofloxacin in guideline) |
| **Infrastructure** | |
| Monitoring safety and efficiency | • *EMR systems to be updated to assist in automated collection of key outcomes including LOS, number screened, number transferred home and readmissions.* |

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☑ We have no potential conflict of interest.

| Category of disclosure | Description of Interest/Arrangement |
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Corresponding author name Dr Gabrielle Haeusler

Herewith I confirm, on behalf of all authors, that the information provided is accurate.

Author signature G. Haeusler Date 12/02/2020