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RESEARCH ARTICLE

An analysis of the resource use and costs of febrile neutropenia events in pediatric cancer patients in Australia

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Abstract

Background: Febrile neutropenia (FN) in children with cancer generally requires in-hospital care, but low-risk patients may be successfully managed in an outpatient setting, potentially reducing the overall healthcare costs. Updated data on the costs of FN care are lacking.

Methods: A bottom-up microcosting analysis was conducted from the healthcare system perspective using data collected alongside the Australian PICNICC (Predicting Infectious Complications of Neutropenic sepsis In Children with Cancer) study. Inpatient costs were accessed from hospital administrative records and outpatient costs from Medicare data. Costs were stratified by risk status (low/high risk) according to the PICNICC criteria. Estimated mean costs were obtained through bootstrapping and using a linear model to account for multiple events across individuals and other clinical factors that may impact costs.

Results: The total costs of FN care were significantly higher for FN events classified as high-risk ($17,827, 95% confidence interval [CI]: $17,193–$18,461) compared to low-risk ($10,574, 95% CI: $9818–$11,330). In-hospital costs were significantly higher for high-risk compared to low-risk events, despite no differences in the cost structure, mean cost per day, and pattern of resource use. Hospital length of stay (LOS) was the only modifiable factor significantly associated with total costs of care. Excluding antineoplastics, antimicrobials are the most commonly used medications in the inpatient and outpatient setting for the overall period of analysis.

Conclusion: The FN costs are driven by in-hospital admission and LOS. This suggests that the outpatient management of low-risk patients is likely to reduce the in-hospital cost of treating an FN event. Further research will determine if shifting the cost to the outpatient setting remains cost-effective overall.

Abbreviations: ATC, Anatomical Therapeutic Chemical; CI, confidence interval; FN, febrile neutropenia; GLM, generalized linear model; HITH, hospital in the home; LOS, length of stay; MBS, Medicare Benefits Scheme; PBS, Pharmaceutical Benefits Scheme; PICNICC, Predicting Infectious Complications of Neutropenic sepsis In Children with Cancer.

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1 | INTRODUCTION

Febrile neutropenia (FN) events are a common complication of treatment of childhood cancer. These events are typically managed in-hospital using intravenous antibiotics, with the duration depending on blood culture results, fever resolution, a rising neutrophil count, and underlying cancer treatment status.[1] Available data indicate unplanned admissions due to FN represent a high burden in terms of their impact on patient and caregiver quality of life[2] and an increased use of healthcare resources.[3]

Patients experiencing an FN event, including in the pediatric setting, are heterogeneous and have different risk factors impacting prognosis and outcomes.[1] This has led to the development and validation of several clinical decision rules (CDRs) that identify patients who are at low risk of developing severe infections or complications.[4] Overall, the aim of these CDRs is to reliably guide clinicians to determine whether a patient with FN may be managed at home, thereby reducing hospital length of stay (LOS) or avoiding admission alltogether. This recognizes that hospitalization itself poses a risk for nosocomial infections, that the use of repeated exposure to broad-spectrum antibiotics increases the risk of antibiotic resistance, prolonged illness, and unfavorable outcomes, and ultimately, increases the burden to hospitals in terms of the utilization of resources and overall costs of health care.[5] Accordingly, outpatient management of low-risk FN has been found to be effective and is recommended as part of clinical care.[6]

Previous studies have shown that an increase in hospital LOS is the main driver accounting for the overall cost of managing an FN event.[7] While treating FN in the outpatient setting will reduce some hospital costs, others will be transferred from the inpatient to the outpatient setting, mainly with respect to the use of antibiotics, medical practitioner consultations, and neutrophil monitoring. Of particular interest is the use of antibiotics, a critical component in both the inpatient and outpatient setting, and how costs may differ across patients by the type of antibiotic used, treatment duration, route of administration (oral or intravenous), and delivery mode (inpatient or outpatient). Overall, the magnitude and structure of differences across patients in terms of the composition of healthcare use and the associated costs for the treatment of FN in the inpatient and outpatient settings are unknown.[8]

The objective of this study is to describe the use of healthcare resources and estimate the overall costs associated with FN events in pediatric patients classified as high and low risk for FN.

2 | METHODS

Data on healthcare utilization were collected alongside the Australian Predicting Infectious Complications of Neutropenic sepsis In Children with Cancer (PICNICC) study, a prospective observational study of FN in pediatric patients recruited across eight tertiary hospitals in Australia from December 1, 2016 to January 31, 2018. Detailed methodology is described elsewhere.[7] Data on consecutive episodes of FN in children (age < 18 years) with cancer or hematological malignancy were prospectively collected. Episodes were included if they had a documented fever and neutropenia, and excluded if FN treatment commenced at a non-participating site, the patient had undergone a hematopoietic stem cell transplant within the preceding 3 months or the episode occurred while they were receiving concurrent intravenous or oral antibiotics (excluding prophylaxis).

A formal low-risk FN program was not in use during the study period, and FN episodes were managed according to state-based hospital FN guidelines that were in keeping with international recommendations.[9] Cessation of antibiotics and hospital discharge was typically considered in patients with neutrophil recovery, negative cultures, and at least a 24-hour period of clinical stability and absence of fever. Antibacterial prophylaxis (excluding for *Pneumocystis jirovecii* pneumonia) was not routinely used.

Each FN episode was stratified using the internationally derived[10] and locally validated[4] PICNICC rule. The PICNICC rule uses a series of weighted variables (malignancy type, temperature, clinically "severely unwell," hemoglobin, white cell count, and absolute monocyte count) to estimate the risk of infection, stratified as being low (<.1) and high risk (≥.1).

Inpatient healthcare use was assessed using disaggregated hospital cost data per FN event extracted from the administrative records of hospitals participating in PICNICC. Disaggregated costs were reported using the following categories: pathology, in-hospital services, surgical,

imaging, hospital consultations (i.e., specialist consultations), visit to the emergency department (ED), therapeutics (inpatient pharmaceuticals, prostheses, and blood derivatives), involvement of allied health professionals, and intensive care unit (ICU) use. In-hospital services included the use of surgical and general wards (including nursing services) and the use of theater operating rooms, which also includes the use of anesthesiology services. The mean cost per category and corresponding bias corrected 95% confidence intervals (CIs) for high- and low-risk patients were estimated by bootstrapping the data, with 1000 replications.

Outpatient healthcare use, including medical, diagnostic, and pharmaceutical, was assessed by consenting parents/guardians in PICNICC for access to their child's Medicare data (Australia's administrative claims data) from 30 days before FN onset to 6 months after FN event.[11] Medicare data provide the volume and cost considering the Australian Commonwealth Government reimbursement and patient out-of-pocket payments where applicable for items subsidized via the Medicare Benefits Scheme (MBS; mainly professional attendances, therapeutic procedures, diagnostic procedures and investigations, pathology services, diagnostic imaging), and the Pharmaceutical Benefits Scheme (PBS; outpatient prescription pharmaceuticals). The analysis that assessed the utilization of pharmaceuticals grouped drugs via the Anatomical Therapeutic Chemical (ATC) classification and health services via the MBS item descriptor (for service type) and code.

Outpatient data on healthcare utilization were used to conduct a bottom-up microcosting analysis allowing for an assessment of potential differences in FN events risk classification. Total costs for an FN event comprised the sum of fees to government for medical, pharmaceutical, and hospital services, and out-of-pocket payments to patients for MBS and PBS listed items. Thus, the analysis took a quasi-societal perspective, which does not consider the broader economic impact this may have on families in terms of productive capacity. Costs were attributed to an FN event, if they were incurred from the date of FN diagnosis until the resolution of fever and last observed date of antibiotic use. Healthcare use during the FN event (from FN diagnosis until end of antibiotic therapy) was compared with use prior to the event (30 days prior to the FN diagnosis) and post event (30 days after the end of the FN event). A comparison of utilization of outpatient pharmaceuticals during and 30 days after the end of the event was also explored.

The mean PBS and MBS costs and corresponding bias corrected 95% CIs were estimated by bootstrapping the data, with 1000 replications. A generalized linear model (GLM) was applied to estimate the mean total cost per FN episode, taking into account that individuals may have experienced multiple FN events during the study period. Based on the non-normally distributed nature of the data (being non-negative and positive-skewed), a GLM for a gamma distribution with a logarithmic link function was used.[12,11] The model controlled for gender, age at cancer diagnosis, cancer diagnosis, previous hematopoietic stem cell transplant (HSCT), antibiotic treatment duration, hospital LOS, and FN risk status. Mean costs per low- and high-risk groups were reported using the post-estimation margins command. Finally, outpatients Medicare data were analyzed to assess whether the bulk of its use occurred at a particular time post FN onset. Statistical analyses were undertaken using STATA version 16.[12]

This study has been approved by the Royal Children's Hospital Melbourne Human Research Ethics Committee (RCH HREC 36040A), and an ethics ratification was obtained by the University of Technology Sydney (HREC ETH17-1128). Parents were consented prior to the child's enrolment in the study to allow access to their Medicare data.

3 | RESULTS

The Australian PICNICC study reported 858 FN events occurring in 462 pediatric cancer patients. Overall, 28% of patients experienced one event, 49% experienced two to three events, and the remaining 23% experienced more than four events (range: four to nine). Of all events, 703 (81.9%) and 155 (18.1%) were categorized as high and low risk as per the PICNICC rule, respectively.[10] In-hospital cost data were provided by seven out of eight hospitals for a total of 757 (88%) events corresponding to 416 (90%) patients. The disaggregated in-hospital costs were available for six out of the eight hospitals, and accounted for 710 of the 858 FN events. A small proportion of these events (2.1%) were handled as hospital in the home (HITH), hence the results from this study reflect the management of FN mainly in the hospital setting. Medicare data (MBS and PBS) were available for 429 FN events in 212 (51%) patients.

3.1 | In-hospital utilization of resources and costs

The mean costs of medical services delivered in-hospital, stratified by risk group, is shown in Table 1. Overall, no substantial differences were observed in terms of the pattern of utilization of resources when comparing FN events classified as high and low risk. The cost categories that contributed most to the total hospitalization cost were in-hospital services, mainly including the cost of wards, and hospital consultations (i.e., specialist consultations such as medical oncologist). For both high- and low-risk patients, these two categories contributed most to the total cost, accounting to approximately 70% of the total cost. The cost category that showed the largest difference across high- and low-risk events was therapeutics, accounting for 11.9% and 9.4% of total costs, respectively. Overall, patients classified as high risk had a higher mean therapeutic cost per event compared to low-risk events ($4208 and $1536, respectively).

Statistically significant differences were observed between the two risk groups in terms of LOS where, on average, patients categorized as high risk and low risk remained in hospital for 11 and 6 days, respectively (mean difference of 4.8 days; 95% CI: 2.2–7.3; $p < .0002$). However, this did not translate into a significant difference in mean cost per day between the two risk groups ($2748 vs. $2793 per day for high and low risk, respectively) (Table 1).

Despite no significant differences in the pattern of resource use, results of the GLM analysis for the hospital costs per FN event show that, on average, FN events were associated with statistically

TABLE 1 Costs of managing a febrile neutropenia event considering the in-hospital and outpatient setting.

Method of analysis	Cost category	High risk ($N = 587$)			Low risk ($N = 123$)		
		Mean cost ($AUD)	[95% Confidence interval]		Mean cost ($AUD)	[95% Confidence interval]	
Mean hospital costs per cost category							
Bootstrapping bias corrected	Pathologies	2438	2097	2826	1011	756	1385
	Imaging	689	563	827	353	195	550
	Therapeutics	4208	3495	4943	1536	974	2406
	In-hospital services	12,507	11,127	13,959	5814	4666	7176
	Hospital consultations	11,542	10,134	12,863	5722	4430	7303
	Allied health professionals	1261	1047	1464	713	406	1167
	Surgical	1582	1215	1968	853	373	1719
	ED	457	345	607	401	280	544
	ICU	692	385	1081	–	–	–
Outpatient services							
		High risk ($n = 357$)			Low risk ($n = 72$)		
		Mean cost ($AUD)	[95% Confidence interval]		Mean cost ($AUD)	[95% Confidence interval]	
	Pharmaceutical Benefits Scheme (PBS)						
Bootstrapping bias corrected	30 days pre-FN event	243.2	179.5	305.8	304.2	184.0	463.5
	FN event	28.7	10.2	61.5	17.1	0.3	39.3
	30 days after FN event	286.4	200.1	399.9	206.7	114.6	301.1
	Medicare Benefits Scheme (MBS)						
	30 days pre-FN event	1362.0	1171.5	1549.9	1184.1	835.0	1555.0
	FN event	678.1	444.9	964.4	341.0	156.7	647.3
	30 days after FN event	1258.7	1080.7	1427.7	1344.1	845.7	2132.0
	Medicare (PBS plus MBS)						
	30 days pre-FN event	1605.2	1397.8	1794.7	1488.3	1129.3	1886.5
	FN event	706.8	465.8	1001.1	358.1	169.3	677.2
	30 days after FN event	1545.1	1334.6	1772.0	1550.7	1044.1	2329.7
		High risk ($N = 623$)			Low risk ($N = 134$)		
		Mean cost ($AUD)	[95% Confidence interval]		Mean cost ($AUD)	[95% Confidence interval]	
Hospital and outpatient services (across all three assessed periods pre, post, and during FN event)							
GLM	Cost per hospital day	2748	2652	2845	2793	2609	2977
	Total hospital cost	17,685	17,013	18,356	10,222	9417	11,026
	Total hospital and outpatient cost	17,827	17,193	18,461	10,574	9818	11,330

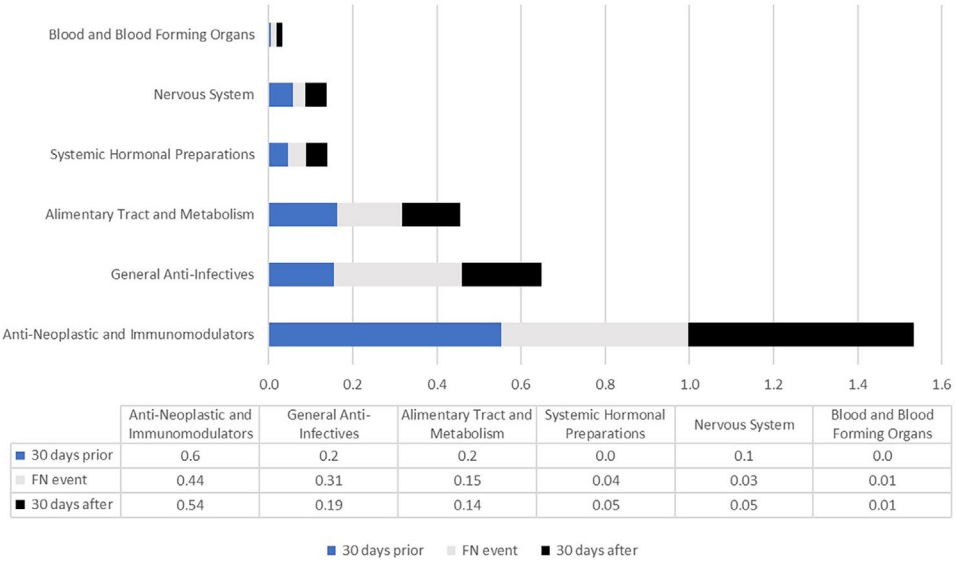
Note: Table shows in-hospital disaggregated costs. Outpatients costs include PBS and MBS for the period of 30 days prior to the event, the period considering the duration of the event (since diagnosis until last antibiotic), and 30 days after the event. A generalized linear model was conducted to estimate the total cost.

Abbreviations: AUD, Australian dollar; ED, emergency department; FN, febrile neutropenia; ICU, intensive care unit; MBS, Medicare Benefits Scheme.

significant higher costs for high-risk compared to low-risk patients ($p < .000$) (Table 1 and Table S1). The mean hospital cost for high-risk events was $17,685 (95% CI: 17,013–18,356) and for low-risk events was $10,222 (95% CI: 9417–11,026). The variables that had a statistically significant impact on the total cost were the risk status, hospital LOS, and duration of the FN event (see Supporting Information).

3.2 | Outpatient resources and costs

MBS and PBS data were available for 429 FN events (of which 357 were classified as high risk and 72 as low risk). For the period from diagnosis with FN and up to 30 days after the end of the FN event, a total of 723 drugs (PBS funded) were prescribed on an outpatient basis



	Anti-Neoplastic and Immunomodulators	General Anti-Infectives	Alimentary Tract and Metabolism	Systemic Hormonal Preparations	Nervous System	Blood and Blood Forming Organs
30 days prior	0.6	0.2	0.2	0.0	0.1	0.0
FN event	0.44	0.31	0.15	0.04	0.03	0.01
30 days after	0.54	0.19	0.14	0.05	0.05	0.01

FIGURE 1 Utilization of pharmaceuticals as per ATC name prior, during, and up to 30 days after the end of the FN event. Figure does not include utilization of drugs classified as dermatologicals, sensory organs, various +, cardiovascular system, respiratory system, musculo-skeletal system, and genito urinary system and sex due to insignificant observations ($n = 14$ observations). The *x*-axis represents the proportion of utilization corresponding to each ATC name. Numbers in the table reflect frequency of utilization (i.e., proportion of use out of total number of drugs prescribed). Small numbers were registered for other types of pharmaceuticals, which are not presented in this figure (dermatological, musculo-skeletal system, genito urinary system and sex, respiratory system, cardiovascular system, and sensory organs). ATC, Anatomical Therapeutic Chemical; FN, febrile neutropenia.

(mean = 1.7 drugs per event) and 19,578 MBS services were delivered (mean = 45.6 services per event). Of these, 72 drugs (less than one per event) and 7289 MBS services (mean per event = 17) were delivered while the event was ongoing, and 651 drugs (mean per event = 1.5) and 12,289 services were delivered after the event had ended (mean per event = 30).

Figure 1 shows the outpatient use of pharmaceuticals classified by ATC during the period prior to the FN diagnosis, during the FN event, and 30 days after the end of the FN event. Across all three periods (pre event, during event, and post event) utilization was dominated by the use of drugs classified as "antineoplasics and immunomodulating" agents, "anti-infectives for systemic use," and "alimentary and tract metabolism." The use of antineoplastics and immunomodulators was dominated by various antineoplastic agents (94%) and some colony-stimulating factors (6%). The use of anti-infectives predominantly included antibiotics (72.0%) and antifungals (27.6%). While there were no substantial differences in the type and use of drugs between events classified as high or low risk, more pathology services were delivered (Table 2). Noting some differences between groups in the proportion of patients receiving cytarabine, cyclophosphamide, doxorubicin, and vincristine were used post FN. No other substantive changes in the pattern of use were observed pre and post FN event, nor between high- and low-risk patients. When we explored the time point as to when the utilization occurred, no differences were observed in any of the service categories analyzed, except for pathology services, where we noticed that the increase in use was concentrated in the fourth (last) week of the 30-day period after the FN event (data not shown).

As can be observed from the results in Table 1, mean total Medicare costs (MBS and PBS costs) did not differ between FN events categorized as high risk and those categorized as low risk, either during 30 days after the end of the FN event. For both risk groups, mean total Medicare costs were higher in 30 days after the event (Table 1).

In the GLM analysis, FN events were associated with significantly higher costs when patients were categorized as high risk compared to low risk for both hospital costs and overall total costs ($p < .000$) (Table 1). The mean overall cost per event (i.e., in-hospital and outpatient costs) in high-risk patients was $17,827 and in low-risk patients was $10,574. For both patient groups, the bulk of the total cost came from the in-hospital setting (99.0%). The variables that had a statistically significant impact on the total cost were the risk status and the hospital LOS (see Supporting Information).

4 | DISCUSSION

Our study provides an in-depth understanding of the cost structure associated with pediatric FN management in Australia and is the first study to incorporate outpatient data in this analysis. Overall, the total cost of FN was due to the use of in-hospital resources (99.0%), and events classified as high-risk are significantly more costly compared to those classified as low risk. Factors significantly impacting total cost were the risk status, hospital LOS, and duration of the FN event. Excluding antineoplastics, antimicrobials are the most commonly used medications in the inpatient and outpatient setting and in the periods before, during, and after the FN event.

TABLE 2 Disaggregated utilization of PBS and MBS services across the three periods studied.

	30 days prior to FN event						FN event (date of diagnosis and AB stop)						30 days after the end of FN event					
	High risk ($n = 357$)			Low risk ($n = 72$)			High risk ($n = 357$)			Low risk ($n = 72$)			High risk ($n = 357$)			Low risk ($n = 72$)		
	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event
PBS																		
General anti-infectives	100 (16)	15,025	42.1	16 (12.7)	2048	28	14 (25.5)	2763	8	8 (47.1)	60	1	102 (19.5)	29,251	82	21 (16.3)	107	1
Antineoplastic and immunomod-ulator	342 (55)	67,104	188.0	73 (57.9)	18,333	255	24 (43.6)	6934	19	8 (47.1)	1080	15	264 (50.6)	65,414	183	85 (65.9)	14,092	196
Nervous system	38 (6)	621	1.7	6 (4.8)	90	1	1 (1.8)	2	0	1 (5.9)			28 (5.4)	555	2	5 (3.9)	108	2
Alimentary tract and metabolism	103 (16)	3142	8.8	20 (15.9)	1325	18	11 (20)	144			90	1	77 (14.8)	2741	8	13 (10.1)	560	8
Dermatologica													3 (0.6)	328	1			
Sensory organs	3 (0.5)	11	0.0	2 (1.6)	17													
Systemic hormonal preparations	27 (4.3)	96	0.3	8 (6.4)	19	0	3 (5.5)	6					29 (5.6)	94	0	5 (3.9)	14	0.2

(Continues)

TABLE 2 (Continued)

	30 days prior to FN event						FN event (date of diagnosis and AB stop)						30 days after the end of FN event					
	High risk ($n = 357$)			Low risk ($n = 72$)			High risk ($n = 357$)			Low risk ($n = 72$)			High risk ($n = 357$)			Low risk ($n = 72$)		
	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event
Various +	4 (0.6)	428	1.2	1 (0.8)	68	1							5 (1)	2316	6			
Cardiovascular system	1 (0.2)	5	0.0										4 (0.8)	22	0			
Respiratory system	2 (0.3)	36	0.1															
Blood and blood forming organs	4 (0.6)	327	0.9				1 (1.8)	392	1				9 (1.7)	1537	4			
Musculo-skeletal system	1 (0.2)	11	0.0				1 (1.8)	3					1 (0.2)	3	0			
Genito urinary system and sex	1 (0.2)	23	0.1															
Total	626 (100)	86,828	243.2	126 (100)	21,899	304	55 (100)	10,244	29	17 (100)	1229	17	522 (100)	102,260	286	129 (100)	14,881	207
MBS																		
Professional attendances	1434 (15.2)	105,520	295.6	243 (15.6)	16,995	236	607 (11)	48,867	137	33 (6.3)	2689	37	1317 (14.4)	93,987	263	237 (14.2)	17,182	239
Diagnostic procedures and investi-gations	96 (1)	8655	24.2	12 (0.8)	1104	15	36 (0.7)	3941	11	4 (0.8)	562	8	100 (1.1)	9730	27	17 (1)	1617	22
Therapeutic procedures	2053 (21.8)	179,467	502.7	367 (23.5)	31,196	433	791 (14.4)	74,398	208	41 (7.8)	3545	49	1856 (20.2)	161,145	451	335 (20)	47,947	666

(Continues)

TABLE 2 (Continued)

	30 days prior to FN event						FN event (date of diagnosis and AB stop)						30 days after the end of FN event					
	High risk ($n = 357$)			Low risk ($n = 72$)			High risk ($n = 357$)			Low risk ($n = 72$)			High risk ($n = 357$)			Low risk ($n = 72$)		
	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event	Freq (%)	Total cost	Mean cost/ event
Diagnostic imaging services	251 (2.7)	62,984	176.4	59 (3.8)	17,606	245	160 (2.9)	26,085	73	34 (6.5)	9165	127	253 (2.8)	64,206	180	44 (2.6)	8343	116
Pathology services	5570 (59.2)	129,35	362.3	880 (56.4)	18,356	255	3906 (71)	88,791	249	411 (78.6)	8592	119	5641 (61.5)	119,85	336	1038 (62)	21,511	299
Miscellaneous services												0	1 (0)	185	1			
Broad type of services	5 (0.1)	248	0.7									0	4 (0)	246	1	4 (0.2)	171	2
Total	**9409 (100)**	**486,229**	**1362.0**	**1561 (100)**	**85,256**	**1184**	**5500 (100)**	**242,081**	**678**	**523 (100)**		**341**	**9172 (100)**		**1259**	**1675 (100)**	**96,772**	**1344**

Abbreviations: AB, antibiotic; FN, febrile neutropenia; Freq, frequency; MBS, Medicare Benefits Scheme; PBS, Pharmaceutical Benefits Scheme.

Our analyses of healthcare resource across the FN event trajectory (30 days prior, during the event, and 30 days post) found, not surprisingly, that during the event, there is a substantial drop in utilization of outpatient pharmaceutical and medical/diagnostic services. When we compared the pattern of use 30 days prior to the event with the period 30 days after the end of FN event, we also observed a slight reduction in most anti-infectives and antineoplastics. A noteworthy exception was the use of amoxicillin/clavulanic acid that showed a trend to increase. Although a formal low-risk FN program was not implemented during the study period, this increase in amoxicillin/clavulanic acid, frequently used to complete FN treatment for lower risk patients, suggests that some centers may have adopted this approach, albeit on an ad hoc basis. Other changes in utilization, such as the reduction in the use of trimethoprim plus sulfamethoxazole, may reflect the practice to wait to neutrophil recovery prior to re-commencement.

The type of drugs (i.e., anti-infectives and antineoplastics) used to manage patients in the inpatient (hospital) setting were not available from the disaggregated hospital cost data. Rather, utilization on the use of inpatient antibiotics was collected as part of the PICNICC study. These data show variation in the use of inpatient antibiotics, which may reflect a lack of consensus in antibiotic treatment in this patient population.[1,13] Of the drugs used in the outpatient setting, anti-infectives accounted for the second highest usage across all periods, after antineoplastics. This represents a previously unrecognised pattern of usage, and highlights the importance of including outpatient anti-infectives in antimicrobial stewardship activities.

Our data further support the hypothesis that implementation of FN care pathways with home-based management of low-risk events may substantially reduce the economic burden of FN to hospitals.[4,14–18] In fact, the studies suggest that the outpatient management is dominant leading to a reduction in costs and an improvement in terms of health outcomes for both patients and carers.[5,8,19] However, none of these studies provide a comprehensive understanding of both in-hospital and outpatient cost structure and the potential for cost-offsets if an intervention that categorizes patients according to risk status is effectively implemented. In general, the available cost studies or cost-effectiveness analyses addressing the different settings where an FN event can be managed have used strong assumptions regarding the outpatient management of FN. For example, one cost-effectiveness analysis that compared inpatient with outpatient management, assumed that all low-risk patients managed in an outpatient setting received the maximum dose of levofloxacin (750 mg/day).[5] Similarly, a cost analysis of FN in adult patients conducted in Australia, assumed all patients were treated with oral antibiotics on that basis that there was a lack of evidence on the use of parenteral antibiotics in the outpatient setting.[8] While these assumptions may be reasonable, it does not reflect the actual use of resources and differential management that these events are likely to have in the outpatient setting. More recently, a cost-effectiveness analysis was conducted to assess the impact of a pilot pediatric low-risk FN program.[20] This program enabled children, identified as low risk using a validated risk stratification tool, to complete FN treatment at home after a brief (<48 hours) inpatient admission. In this study, patients received blood

tests and antibiotics at home via our HITH service. Results showed that home-based FN care by HTIH, as compared to in-hospital management only, was cost-effective from both, a healthcare system and societal perspectives.[21]

Although in our cohort all were cancer patients, only a small part of the outpatient costs were due to the use of drugs. This suggests that the cost of chemotherapy and other cancer drug treatments may be allocated to hospitals, rather than the outpatient setting. The large number of outpatient MBS items identified from FN diagnosis and up to 30 days, largely due to pathology testing, shows that patients undergo close monitoring in this setting. This may increase if the patients FN event is entirely managed from home. Moreover, that we could not find a difference in the time course of when healthcare was being utilized (i.e., first/second/third week after event had ended) is also likely to be explained by the thorough follow-up of FN patients after an event and that in most patients, FN events occur as part of a broader, ongoing course of care. It may also be possible that some costs captured during the 30 days post-FN event period reflect the following chemotherapy cycle rather than being related to the FN event. However, our analysis of the pattern of use of drugs over time showed no difference in the pattern of antineoplastics use.

Home-based care for FN was not routinely used during the PICNICC study period, thus the data in this study cannot be interpreted as indicative of the efficacy, or otherwise, of outpatient management for FN. Thus, the potential impact on healthcare utilization or health outcomes of patients failing to respond to outpatient management requires further investigation. Furthermore, while the analysis of costs does account for multiplicity of events across an individual, it treats each event as independent and does not consider the time interval between events. In addition, while we have provided a detailed accounting of the costs associated with FN care, these are not the only factors to consider with respect to implementing outpatient management programs. Patient and carers' preferences regarding the model of care and out-of-pocket expenses are also relevant for consideration. While an early Canadian study of parental preferences revealed that most parents of children with cancer preferred hospital-based treatment for FN,[22] a more recent study conducted in the United Kingdom suggested some parents would prefer a home-based strategy.[23] This may reflect changes in both patient and clinician acceptance of home-based treatment opportunities for children with cancer over time. Acceptance is likely also influenced by the availability of systems and structures within a healthcare facility to support home-based management, as was identified in an Australian survey of FN practice.[1] Ongoing research in this space is underway as part of a national pediatric FN implementation study (ACTRN12616001440415).

The patterns of healthcare use and costs identified in this study are key in informing resource planning needs with respect to inpatient and outpatient care of pediatric patients with FN. Given the focus on the outpatient management of low-risk patients to reduce the overall cost of treating an FN event, this study shows the importance of ongoing outpatient medical and diagnostic services, such as pathology tests, which are integral to a robust monitoring program to ensure effective FN care. Furthermore, it is also important to consider that there will be a cost shift in health resources from the inpatient to the outpatient setting. Thus, while treatment of low-risk patients may be associated with lower costs, differences in the pattern of healthcare utilization between low- and high-risk patients have implications for access to care where inpatient and outpatient services might rely on different funding sources.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from PICNICC study and Medicare Australia. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the PICNICC study team and/or Medicare Australia.

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REFERENCES

1. Haeusler GM, Slavin MA, Bryant PA, Babl FE, Mechinaud F, Thursky KA. Management of fever and neutropenia in children with cancer: a survey of Australian and New Zealand practice. *J Paediatr Child Health*. 2018;54(7):761-769. doi:10.1111/jpc.13899
2. Crothers A, Haeusler GM, Slavin MA, et al. Examining health-related quality of life in pediatric cancer patients with febrile neutropenia: factors predicting poor recovery in children and their parents. *EClinicalMedicine*. 2021;40:101095. doi:10.1016/j.eclinm.2021.101095
3. Paulus S, Dobson S. Febrile neutropenia in children with cancer. *Adv Exp Med Biol*. 2009;634:185-204. doi:10.1007/978-0-387-79838-7_16
4. Haeusler GM, Thursky KA, Slavin MA, et al. Risk stratification in children with cancer and febrile neutropenia: a national, prospective, multicentre validation of nine clinical decision rules. *EClinicalMedicine*. 2020;18:100220. doi:10.1016/j.eclinm.2019.11.013
5. Bavle A, Grimes A, Zhao S, et al. Cost-effectiveness and improved parent and provider satisfaction with outpatient management of pediatric oncology patients, with low-risk fever and neutropenia. *J Pediatr Hematol Oncol*. 2018;40(7):e415-e420. doi:10.1097/mph.0000000000001084
6. Manji A, Beyene J, Dupuis LL, Phillips R, Lehrnbecher T, Sung L. Outpatient and oral antibiotic management of low-risk febrile neutropenia are effective in children—a systematic review of prospective trials. *Support Care Cancer*. 2012;20(6):1135-1145. doi:10.1007/s00520-012-1425-8
7. Haeusler GM, Thursky KA, Mechinaud F, et al. Predicting Infectious ComplicatioNs in Children with Cancer: an external validation study. *Br J Cancer*. 2017;117(2):171-178. doi:10.1038/bjc.2017.154
8. Lingaratnam S, Worth LJ, Slavin MA, et al. A cost analysis of febrile neutropenia management in Australia: ambulatory *v*. in-hospital treatment. *Aust Health Rev*. 2011;35(4):491-500. doi:10.1071/AH10951
9. Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. *J Clin Oncol*. 2017;35(18):2082-2094. doi:10.1200/jco.2016.71.7017
10. Phillips RS, Sung L, Peek N. Comparison of regression methods for modeling intensive care length of stay. *PLoS One*. 2014;9(10):e109684-e109684. doi:10.1371/journal.pone.0109684
11. Austin PC, Rothwell DM, Tu JV. A comparison of statistical modeling strategies for analyzing length of stay after CABG surgery. *Health Serv Outcomes Res Methodol*. 2002;3(2):107-133. doi:10.1023/A:1024260023851
12. Stata Statistical Software: Release 16. StataCorp LLC; 2019.
13. de Lalla F. Outpatient therapy for febrile neutropenia: clinical and economic implications. *Pharmacoeconomics*. 2003;21(6):397-413. doi:10.2165/00019053-200321060-00004
14. Phillips RS, Lehrnbecher T, Alexander S, Sung L. Updated systematic review and meta-analysis of the performance of risk prediction rules in children and young people with febrile neutropenia. *PLoS One*. 2012;7(5):e38300. doi:10.1371/journal.pone.0038300
15. Miedema KGE, Tissing WJE, Abbink FCH, et al. Risk-adapted approach for fever and neutropenia in paediatric cancer patients—a national multicentre study. *Eur J Cancer*. 2016;53:16-24. doi:10.1016/j.ejca.2015.10.065
16. Delebarre M, Garnier N, Macher E, et al. Which variables are useful for predicting severe infection in children with febrile neutropenia? *J Pediatr Hematol Oncol*. 2015;37(8):e468-e474.
17. Prasad M, Chinnaswamy G, Arora B, Vora T, Hawaldar R, Banavali S. Risk predictors for adverse outcome in pediatric febrile neutropenia: single center experience from a low and middle-income country. *Indian J Cancer*. 2014;51(4):432-437. doi:10.4103/0019-509x.175321
18. Bothra M, Seth R, Kapil A, Dwivedi SN, Bhatnagar S, Xess I. Evaluation of predictors of adverse outcome in febrile neutropenic episodes in pediatric oncology patients. *Indian J Pediatr*. 2013;80(4):297-302. doi:10.1007/s12098-012-0925-3
19. Teuffel O, Amir E, Alibhai SM, Beyene J, Sung L. Cost-effectiveness of outpatient management for febrile neutropenia in children with cancer. *Pediatrics*. 2011;127(2):e279-e286. doi:10.1542/peds.2010-0734
20. Haeusler GM, Gaynor L, Teh B, et al. Home-based care of low-risk febrile neutropenia in children-an implementation study in a tertiary paediatric hospital. *Support Care Cancer*. 2021;29(3):1609-1617. doi:10.1007/s00520-020-05654-z
21. Tew M, De Abreu Lourenco R, Gordon JR, et al. Cost-effectiveness of home-based care of febrile neutropenia in children with cancer. *Pediatr Blood Cancer*. 2022;69(7):e29469. doi:10.1002/pbc.29469
22. Diorio C, Martino J, Boydell KM, et al. Parental perspectives on inpatient versus outpatient management of pediatric febrile neutropenia. *J Pediatr Oncol Nurs*. 2011;28(6):355-362. doi:10.1177/1043454211418665
23. Morgan JE, Phillips B, Stewart LA, Atkin K. Quest for certainty regarding early discharge in paediatric low-risk febrile neutropenia: a multicentre qualitative focus group discussion study involving patients, parents and healthcare professionals in the UK. *BMJ Open*. 2018;8(5):e020324. doi:10.1136/bmjopen-2017-020324

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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