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ORIGINAL ARTICLE

Management of fever and neutropenia in children with cancer

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Abstract
Purpose Febrile neutropenia remains a common, life-threatening complication of chemotherapy in paediatric oncology. Delays in institution of empiric antibiotics have been identified at tertiary and regional centres caring for these patients and associated with decreased survival. Our objective was to reduce the time to administration of empiric antibiotics to less than 60 min from the time of presentation to hospital.
Methods A retrospective study of the records of oncology patients presenting to the emergency department of a tertiary hospital over a 3-month period was performed and time to first antibiotic administration recorded. Potential causes of delay in commencement of antibiotics were identified and an algorithm-based approach to the management of fever in immunocompromised children developed and implemented. Follow-up evaluation data were collected at 12 and 60 months post-intervention. Causes of delay in commencement of antibiotics at regional hospitals that share care with the tertiary hospital were identified through questionnaires, interviews and focus groups, involving patients and medical and nursing staff. The impact of the introduction of the algorithm at one peripheral hospital was evaluated.
Results The mean time to empiric antibiotics was reduced from 148 min (95 % confidence interval (CI) 81–216) at baseline to 76 min (95 % CI 50–101) at 12 months post-intervention and sustained at 65 min (95 % CI 52–77) 5 years after the intervention. At the peripheral hospital, mean time to antibiotic delivery was reduced from 221 min (95 % CI 114–328) to 65 min (95 % CI 42–87) at 12 months after the intervention.
Conclusion The introduction of the guideline, with teaching and support for staff and parents, resulted in an improvement in practice, meeting international guidelines and achieving sustained results at 5 years after introduction at a tertiary hospital. The guideline has been shown to be feasible and effective at a regional hospital.

Keywords Febrile neutropenia · Paediatrics · Oncology

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Introduction

Sepsis is a major cause of morbidity and mortality in paediatric oncology patients, particularly during periods of neutropenia, which is a well-recognised complication of immunosuppressive therapy given to oncology and haematology patients [1]. Physical signs of sepsis in the neutropenic patient may be attenuated due to paucity of inflammatory cells [2]. The empiric use of broad spectrum, intravenous (IV) antibiotics during periods of febrile neutropenia was a major accomplishment in the field of oncology in the 1970s and has since become the standard treatment protocol in most centres worldwide. However, the mortality rate associated with febrile

neutropenia in children as recently as 2005 has been quoted as 3 % [3, 4], although in our experience, mortality has been <1 % over the past decade, despite treating more than 120 new oncology patients each year. Nonetheless, rapid assessment and initiation of empiric antibiotics are essential to prevent complications of bacteremia [5, 6]. This is based on the replication time of common bacteria, as most have a generation time of 30–90 min in animal and in vitro studies [7, 8]. There are as yet no internationally recognised guidelines or criteria that define what constitutes prompt delivery of antibiotics in the febrile neutropenia setting, although within 1 h of presentation is considered a standard safe time frame [9, 10]. Delays have been recorded in centres worldwide [11], Burry et al. [12] reporting on patients in Canada and Gavidia et al. [13] reporting on patients in El Salvador describe cohorts of children with febrile neutropenia receiving empiric antibiotics within an average of 3.5 h after presentation.

The Sydney Children's Hospital, Randwick, is a tertiary referral hospital providing specialist paediatric services to metropolitan Sydney and a wide area of the state of New South Wales, with the Kids Cancer Centre being a specialist haematology and oncology service within the hospital. Based on zip code information, the linear distance between patients' homes and the Sydney Children's Hospital has been calculated using the interactive online referencing tool maintained by the National Mapping Division of Geoscience Australia [14]. Just under 50 % of patients referred to the Kids Cancer Centre at Sydney Children's Hospital live outside of the Sydney Metropolitan area, defined as a distance of less than 55 km and a drive time of less than 1.5 h from the hospital [15] Rural families are defined as living a distance between 56 and 480 km from the referral hospital with a drive time greater than 1.5 h. In New South Wales, a shared care model has been developed with regional hospitals to allow paediatric oncology patients to receive some of their treatment, including management of uncomplicated febrile neutropenia, closer to home.

Emergency physicians and paediatricians play a pivotal role, in collaboration with oncologists, in achieving the aim of timeous initiation of empiric antibiotics in febrile neutropenic paediatric oncology patients, both in the tertiary referral hospital and in the share care regional hospitals. Several barriers to achieving this target have been identified in the literature, both within tertiary hospitals and rural or regional hospital settings, including communication between hospital departments, recognition of the potentially neutropenic febrile patient and rapid clinical assessment [16].

The primary objective of this study was to ensure delivery of empiric antibiotics to all children with fever and suspected neutropenia within 1 h of presentation to a hospital. The secondary objectives of the study were to identify barriers to prompt antibiotic administration and to design appropriate interventions to achieve the primary objective. We describe our experience in improving time to antibiotic administration at the tertiary hospital and the institution of a similar standard of care in a regional hospital involved in the care of childhood cancer patients, which would allow standardised management of febrile neutropenia in the paediatric oncology population regardless of where the patient presents.

Methods

An initial audit by a combined multidisciplinary team from the oncology and emergency departments (ED) at Sydney Children's Hospital (SCH) established that the time to administration of the first dose of antibiotics in children presenting with fever and neutropenia to the ED of the tertiary hospital (SCH) was longer than expected standards, and a project was designed as a collaborative quality improvement plan, using a multimodal approach to identify the scope of the problem, and then determine the barriers to prompt administration of antibiotics, and finally to introduce a practice change to improve the quality of care delivered. At SCH, the study focused on the ED presentation and management of febrile neutropenia. An audit of all oncology patients presenting to the ED at the tertiary hospital over a 3-month period was performed between March–June 2002. Neutropenia was defined as an absolute neutrophil count (ANC) $<1000/\mu L^3$, and fever was defined as a single oral or axillary temperature $\geq$38.0 °C, recorded either at home or after presentation to hospital. Time at presentation to triage was obtained from the ED tracking computer system and time of administration of the first antibiotic from patient medication prescription charts. Age, underlying diagnosis, neutrophil count, clinical findings and haemodynamic parameters were also recorded. Since triage was always within 5–10 min of arrival at the hospital, this was used rather than arrival time.

Analysis of the process identified a number of decision points that caused delay in initiation of antibiotics and a consensus algorithm was developed aimed at speeding up the time to antibiotic initiation. Evaluation of the practice change was planned at a predefined time interval of 12 months after introduction of the algorithm. The practice was reassessed after a further 5 years.

Although the algorithm developed at the tertiary hospital was made available to the share care regional hospitals, anecdotal reports suggested that unacceptable delays were still occurring when febrile neutropenic patients presented to the regional hospitals. An audit of time to initiation of antibiotics at one of the peripheral hospital was recorded from ward notes and medication charts for each patient. At the regional

hospital, parents are advised to present to the paediatric ward at the onset of fever, bypassing the ED, by prior agreements between the paediatricians, paediatric ward nursing staff, parents and the ED staff at this hospital. The regional hospital audited was chosen because it has a larger number of oncology patients presenting with fever and neutropenia than many of the other regional hospitals is one of the closer sites to the tertiary centre, allowing frequent visits and education sessions by nursing staff and a general paediatrician and the nurse unit manager of the paediatric ward at this site were keen to be involved.

In parallel, to improve quality of care of patients at regional hospitals generally, a number of research strategies were introduced in the Kids Cancer Centre, which included questionnaires, interviews and focus groups involving patients and medical and nursing staff at regional centres, with some of the data published [17]. Parents and representatives from each discipline of healthcare professionals involved in the care of paediatric oncology patients in the multiple regional areas completed questionnaires (RJC) were interviewed by research psychologists (CW) and participated in focus groups run by two outreach oncology nurse consultants (KA, WL). To better understand the causes of delay in commencement of antibiotics at regional hospitals that share care of oncology patients with the tertiary hospital, data relevant to delays in initiation of antibiotics, which proved to be a concern for many staff and families were analysed from the data collected from the various projects.

Results

Twenty episodes of febrile neutropenia were included in the initial audit at the tertiary hospital. The mean time from presentation to antibiotic delivery was 2 h and 28 min (range 55–9 h and 55 min). Decision points identified as causing significant delays in administration of empiric IV antibiotics included waiting to be seen by a medical officer who would order a full blood count and blood cultures, followed by further waiting time for results to be obtained and time spent contacting the haematology/oncology specialist team for further advice regarding antibiotics.

The practice change aimed to decrease time to antibiotic delivery was an algorithm (Fig. 1) designed to expedite the identification and management of febrile neutropenic patients in the ED and direct initial clinical

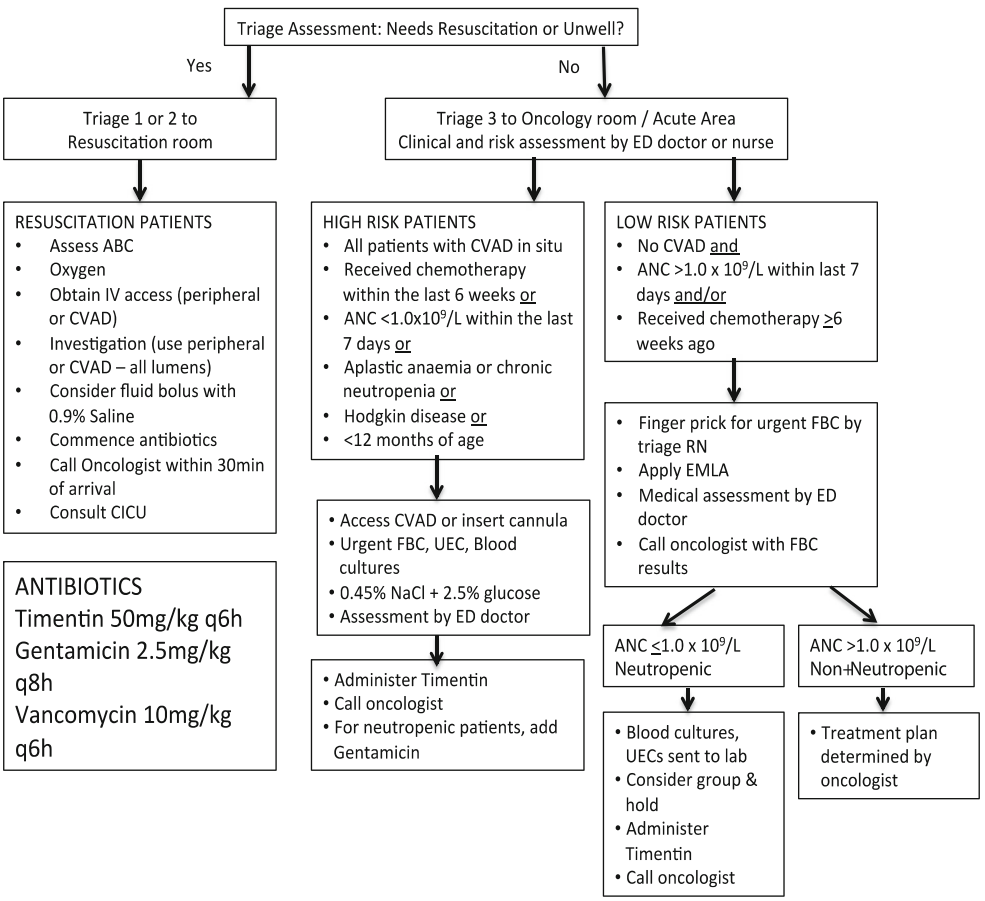

Fig. 1 Febrile neutropenia management algorithm

care. The consensus algorithm proposes that all children receiving chemotherapy may potentially be neutropenic and mandates that all at-risk patients be triaged to category 3, which is defined in the NSW health system as "people who need to be medically assessed within 30 minutes" [18]. Triage is followed by nurse-initiated access of the central venous line, blood being sent for full blood count and culture and after which a clinical review is performed by a member of the ED medical staff. A first dose of empiric antibiotic is then administered prior to consultation with the oncologist and without awaiting full blood count results. The algorithm was designed in collaboration between the multidisciplinary medical and nursing team of oncology, infectious diseases and emergency medicine. Empiric antibiotics complied with the contemporary international consensus on the treatment of febrile neutropenia and incorporated a broad-spectrum beta-lactam, (ticarcillin/clavulanic acid) as first line, with the addition of an aminoglycoside (gentamicin) once neutropenia is proven on blood evaluation. The algorithm was implemented in 2002 at the tertiary hospital and subsequently at the regional hospitals once its success at the primary site had been established.

An educational programme was implemented to prepare medical and nursing staff for the changes in clinical practice:

- Nursing staff were educated in the management of central venous devices by spending sessions in the oncology outpatients unit, providing access to a video and provision of a manikin for education
- The new algorithm was posted in the treatment areas of the ED and on the intranet for quick reference by both medical and nursing staff in the tertiary and peripheral hospital sites
- Senior medical staff were educated on how to access and use the algorithm
- A senior clinical initiatives nurse based in triage identified and fast-tracked patients at risk of neutropenia.
- An article was published in the Kids Cancer Centre oncology patients' "Family newsletter" outlining the change in practice for parents
- Parents were issued with a credit-card-sized alert card identifying their child as being at risk for fever and neutropenia and needing timeous commencement of antibiotics (Fig. 4c)

In the 12 months after initiation of the new triage guidelines and algorithm, no patient was triaged category 2 (critically unwell patient for medical review within 10 min [18]) or above. All identified potentially febrile neutropenic patients were triaged category 3. The time to empiric antibiotics was reduced to 75 min and 12 months after introduction of the algorithm (Table 1 and Fig. 2). A subsequent review of the clinical practice change was undertaken at 5 years post implementation at the tertiary hospital. This showed a sustained improvement in the rapidity of administration of IV antibiotics to febrile neutropenic children, with a mean time of 65 min from triage to delivery of first antibiotic (Table 1 and Fig. 2).

In the regional setting, at the pilot hospital, the baseline audit revealed a mean time to initiation of antibiotics for febrile neutropenic oncology patients of 2 h and 41 min. To better understand the reasons for delay, data identifying issues relating to barriers to prompt antibiotic delivery at presentation of fever and neutropenia at regional hospitals were analysed from the questionnaires, interviews and focus groups referred to in the methods section. Eighty-nine parents and 114

Table 1 Time to antibiotic administration in the tertiary and regional hospitals

	Tertiary hospital			Peripheral hospital	
	Baseline	12 months	60 months	Baseline	12 months
Number of patients	*N*=17	*N*=20	*N*=35	*N*=10	*N*=7
Mean time to first empiric antibiotic	148 min	76 min	65 min	221 min	65 min
95 % CI, α=0.05	81–216	50–101	52–77	114–328	42–87
Proportion receiving antibiotics within 1 h	0 %	35 %	64 %	n/a	n/a
Mean time to medical review (range)	32 min (9–97 min)	17 min (2–41 min)	22 min (10–55 min)	n/a	n/a
Mean time to laboratory results (range)	95 min (30–187 min)	59 min (11–274 min)	n/a	n/a	n/a
Mean time spent in ED	237 min (86–324 min)	177 min (37–304 min)	n/a	Admitted to ward	Admitted to ward

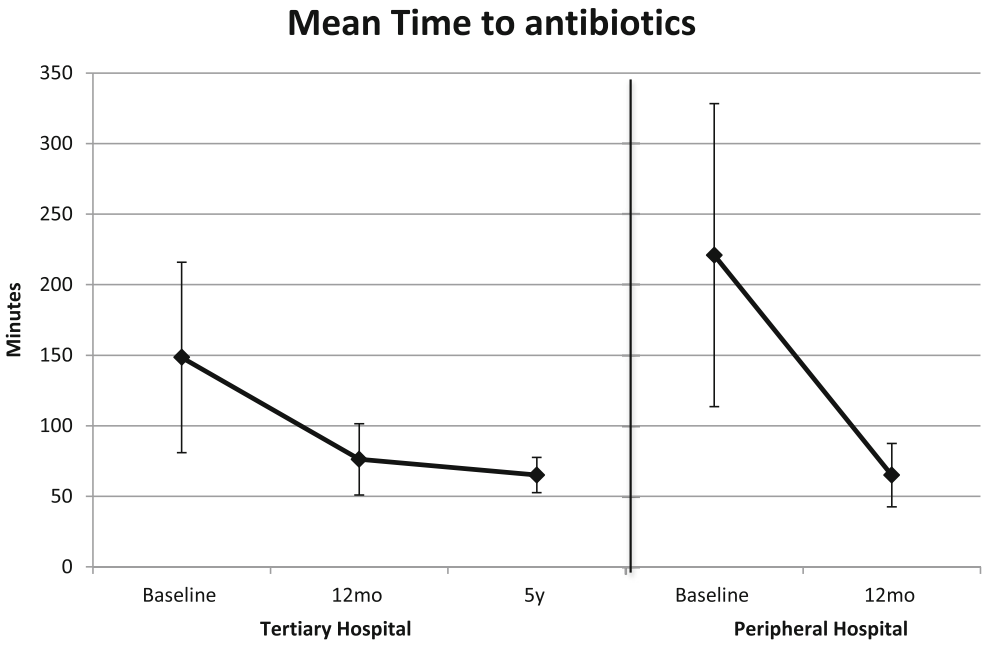

Fig. 2 Mean time to antibiotics with 95 % confidence intervals for each measurement

health professionals from both metropolitan and regional postcodes completed an online- or paper-based questionnaire. Five rural hospitals and 18 multidisciplinary team members were included in the focus groups. Sixty-four family members completed face-to-face qualitative interviews. Factors thought to contribute to delayed antibiotic initiation are summarised in the cause and effect diagram (Fig. 3). In common with the tertiary centre, delays in speaking to the tertiary-based oncologist or the paediatrician at the peripheral site before administering empiric antibiotics were identified, as was difficulty obtaining rapid turnaround times for neutrophil counts. Medical staff identified lacking confidence in managing oncology patients, which slowed their management, an

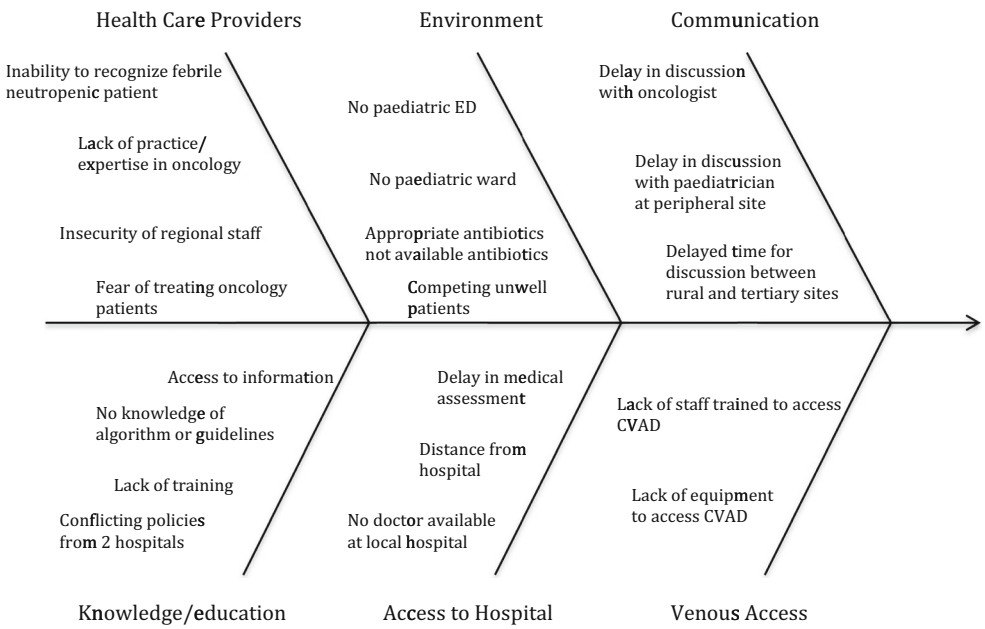

Fig. 3 Cause and effect diagram, delayed antibiotic initiation in a rural setting. *ED* emergency department, *CVAD* central venous access device

observation commented on by parents. Nursing staff identified lack of expertise in accessing central venous access devices (CVAD) as a factor causing delays, despite teaching by outreach nurses from the tertiary hospital, a problem that resulted from frequent turnover of nursing staff at the regional hospital.

At the pilot regional hospital, with the active collaboration of the head of the paediatric department and the senior nurses, an educational programme was implemented to prepare medical and nursing staff for the changes in clinical practice through the implementation of the febrile neutropenic algorithm. To facilitate better implementation of the algorithm, there was intensified education to upskill staff to manage children with fever and neutropenia, provision of a manikin for simulated training in accessing CVADs and use of a video about managing CVADs (Fig. 4a, b). Staff were advised about the "alert card" carried by parents of patients on active therapy with chemotherapy (Fig. 4c). The mean time to administration of the first dose of antibiotic for febrile neutropenic children at the pilot regional hospital was reduced to 65 min when records were audited at 12 months after the concerted upskilling of staff in the use the use of the algorithm.

Discussion

Several factors delaying prompt delivery of empiric antibiotics in potentially neutropenic paediatric oncology

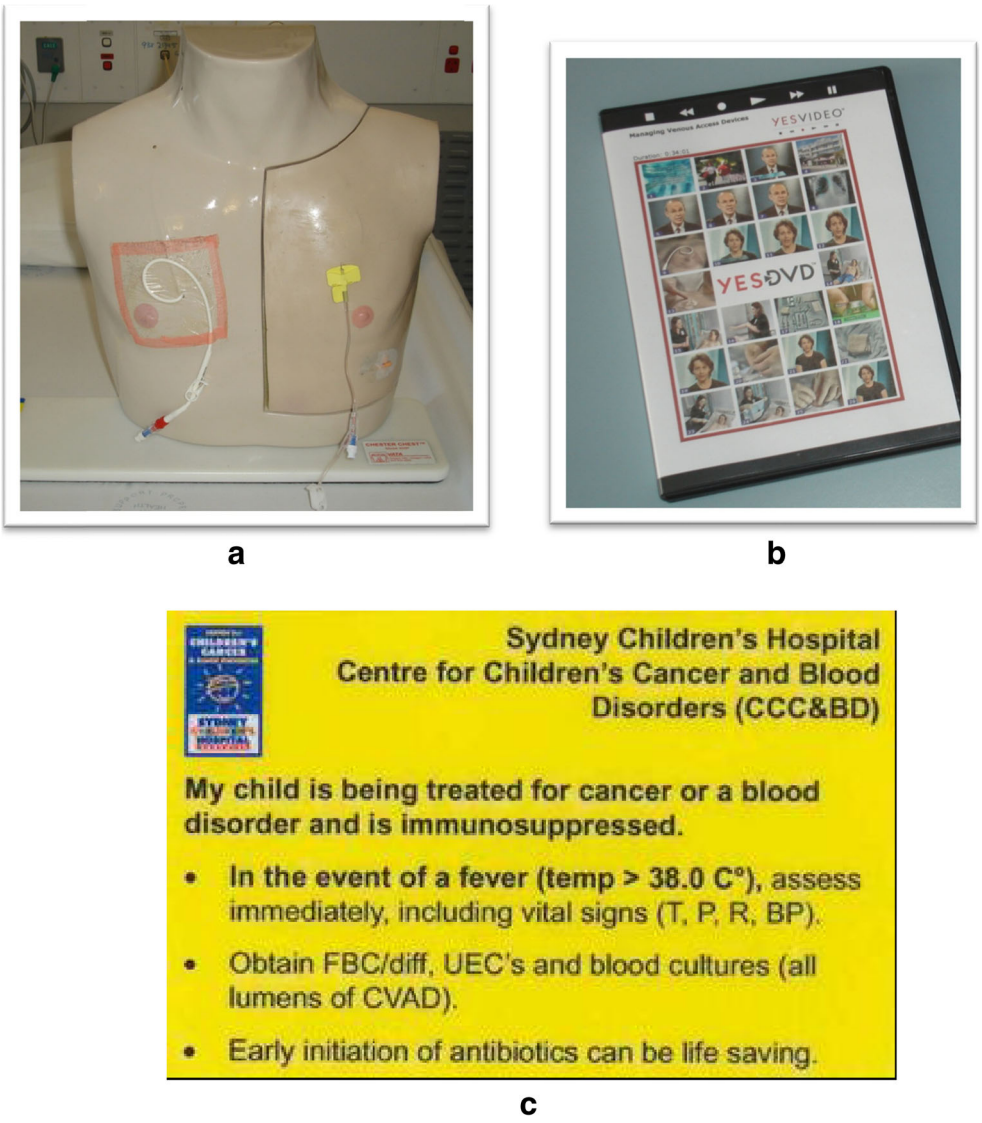

Fig. 4 Educational and supportive materials used during the program. **a** Manikin for teaching central venous access device management. **b** Educational video showing central venous access device management, blood collection and drug administration. **c** Patient held card indicating risk of neutropenia

patients were identified through this analysis, which combined quantitative and qualitative data. These factors were each addressed in turn and interventions to overcome them were incorporated into a simple treatment algorithm, which is accessible to all staff involved in the care of these patients via the hospital treatment guidelines available on the intranet at the tertiary and subsequently at the peripheral sites. Embedded within the new algorithm are strategies to streamline the medical review and management process of a patient identified to be at risk of febrile neutropenia. The interventions are mainly designed to utilise time more efficiently during the process from presentation to treatment by avoiding decision points. The reduced time to initiation of antibiotics was achieved by reorganising the order in which the patients receive their care. The febrile neutropenia management algorithm allows clinical nursing staff autonomy to facilitate blood tests before medical review, in order to utilise the waiting time more efficiently. Furthermore, the ED physicians or junior doctors are no longer required to contact the haematology/oncology physician before commencing empiric antibiotics, which decreased the time to first antibiotic.

Other groups have also observed similarly delays in initiation of empiric antibiotics in the febrile neutropenic paediatric population [13], and streamlining of care in the emergency setting has been trialled to reduce this time and improve the quality of care delivered to affected children. At a Canadian institution, major delays were noted to occur after laboratory reports of neutropenia had been obtained [12]. In contrast, our audit revealed that significant delays occurred while awaiting a confirmation of neutropenia. This delay was overcome by removing the need to await confirmation of neutropenia before antibiotic administration in potentially immunocompromised patients. Our algorithm approach alongside all its support structures, including training and education for all involved health professionals, is a successful intervention with sustained results in the tertiary paediatric setting and promising results in the regional hospital setting. No complications of the protocol driven management have been documented.

Apart from the costs of the educational tools such as the manikin and video, the costs involved in the introduction of the algorithm and its use were no greater than the standard care received by patients. The clinical practice change, did, however, confer many benefits apart from earlier initiation of antibiotic therapy:

- Increased ownership and enthusiasm from staff regarding management of oncology patients
- Greater trust from parents who access the medical system for their febrile neutropenic children, not only in the tertiary centre ED but also regional and peripheral centres, which leads to safe and optimal management of febrile neutropenia in children who would otherwise travel for several hours to attend the tertiary paediatric centre where they are treated for their cancer and place greater trust
- Improved patient flow through the ED

Our future goals are to facilitate this streamlined approach to the management of febrile oncology patients at risk of neutropenia and sepsis to include all peripheral sites that share care for these patients on a regular basis. All stakeholders, multidisciplinary health professionals, and parent consumers supported the principle of improving care for paediatric oncology patients presenting with fever and neutropenia at both tertiary and rural hospitals. Oncologists at the tertiary referral centre also support the algorithm of care. Rural and regional healthcare practitioners have endorsed the approach and shown enthusiasm to "upskill" staff and provide quality care closer to home for patients. Many centres have provided isolation facilities for patients, a previous source of concern for parents and staff alike. The tertiary centre has undertaken ongoing education with recognition that staff turnover resulting in loss of expertise for accessing CVADs is an ongoing risk to the approach. Ongoing auditing of the management of time to antibiotic administration in febrile neutropenic patients has been instituted and is a regular agenda item when outreach nurse consultants visit regional sites. Unique solutions, such as teaching parents to access CVADs and involving primary care physicians and nurse unit managers of rural clinics, in the absence of other resources are being considered to widen expertise to allow treatment closer to home. This approach will allow administration of a first dose of antibiotics where there are no facilities for admission, followed by the safe transfer of the patient to a larger rural centre (Table 2).

Results of this study may be translated to other centres around the world, as similar delays and contributing factors have been identified in developing as well as developed nations [12, 13].

Conflict of interest We declare that we do not have a financial sponsorship for this study. We have full control of all primary data and agree to allow the journal to review the data if requested.

Appendix

Table 2 Timeline of events throughout the study

Audit at the tertiary hospital of time to antibiotic administration in febrile neutropenic patients	April – June 2002
Introduction of algorithm at tertiary hospital combined with education program	2002
12 month re-evaluation of time to antibiotic administration at tertiary hospital	April – June 2003
5 year re-evaluation of time to antibiotic administration at tertiary hospital	April – June 2008
Baseline audit of time to initiation of antibiotics at pilot regional hospital	January – March 2010
Introduction of algorithm and education program to facilitate its use at the pilot regional hospital	June 2010
Re-evaluation of time to antibiotic administration at regional hospital	January – March 2011
Ongoing monitoring of antibiotic delivery to febrile neutropenic children at both sites	

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