ORIGINAL ARTICLE

Variation in policies for the management of febrile neutropenia in United Kingdom Children's Cancer Study Group centres

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Arch Dis Child 2007;**92**:495–498. doi: 10.1136/adc.2006.102699

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Accepted 22 January 2007
Published Online First 6 February 2007

Objective: To assess the variation in the current UK management strategies for the treatment of febrile neutropenia in childhood.

Design and setting: A postal survey of all 21 United Kingdom Children's Cancer Study Group (UKCCSG) centres assessing and collating local policies, protocols or guidelines relating to the management of febrile neutropenia. Further direct contact was undertaken to clarify any uncertainties.

Results: All 21 centres provided information. The policies used to manage febrile neutropenia in the centres around the UK vary in almost every aspect of management. Definitions of fever ranged from a persistent temperature of >37.5˚C to a single reading of >39˚C. Neutropenia was inconsistently defined as an absolute neutrophil count of $<1\times10^9$, $<0.75\times10^9$ or $<0.5\times10^9$. Choices of antibiotic approaches, empirical modifications and antistaphylococcal treatment were different in each protocol. The use of risk stratification was undertaken in 11 centres, with six using a policy of reduced intensity therapy in low risk cases. Empirical antifungal treatment was very poorly described and varied even more widely.

Conclusions: There was a great deal of variation in definitions and treatment of febrile neutropenia in the UKCCSG children's cancer treatment centres. A degree of variation as a result of local microbiological differences is to be expected, but beyond this we should seek to standardise the core of our approach to defining fever and neutropenia, risk stratification and duration of empirical therapy in a way that maintains safety, minimises resource utilisation and maximises quality of life.

Febrile neutropenia (FNP) is the second most common reason for hospital admission among children with cancer, with approximately 4000 episodes of FNP occurring annually in the UK. It is a cause of significant morbidity in children and young adults treated for cancer, accounts for a substantial use of resources and remains fatal in some instances.

With the advent of aggressive management of FNP, the outcome of episodes in children has improved dramatically. Mortality fell from 30% in the 1970s to 1% in the late 1990s.[1] Intensive care management is required in less than 5% of cases, although a substantial proportion of children have complications which require specialised care.[2] There remain many episodes of FNP, possibly two thirds or more, in which this aggressive management strategy is excessive.[2]

A significant challenge is to accurately assess the risk of each episode. In the high risk group, an aggressive approach to therapy is warranted, while in the low risk group tailoring therapy to maintain safety while maximising quality of life with sensible use of resources should be undertaken. A multinational scoring system for risk prediction is available for use with adults[3] and there are a number of pan-European studies on the management of adult FNP.[4] Despite excellent collaborative approaches to chemotherapy treatment protocols in children across the UK, Europe and North America, few large-scale studies of supportive care in children have been performed.

In the UK, paediatric oncology is delivered in 21 United Kingdom Children's Cancer Study Group (UKCCSG) centres, often in collaboration with a patient's local hospital (shared care centres). The extent of involvement of shared care centres varies around the UK but usually involves the treatment of FNP. Much supportive care management remains rooted in the individual oncology centres' histories and experiences, influenced to varying degrees by published evidence. The National Institute for Clinical Excellence (NICE) guidance document[5] *Improving outcomes with children and young people with cancer*, which has been recently published in the UK, calls for a ''national policy for the management of FNP'' (p 54). We determined to assess how varied the current management strategies were for the childhood cancer population.

METHODS

A postal survey of all 21 UKCCSG centres was carried out in 2005 (via the Royal College of Nursing Paediatric Oncology Nurses Forum (PONF) link nurse), requesting copies of local policies, protocols or guidelines relating to the management of FNP at the tertiary centre. Further direct contact was made to clarify any uncertainties.

From each document, information was sought on:

- the definitions of fever and neutropenia,
- the nature of any risk stratification,
- the choice of empirical antibiotics,
- guidance on the nature and timing of empirical additional or alternative therapies and
- the choice of empirical antifungals and the timing of commencement.

Abbreviations: CVC, central venous catheter; FNP, febrile neutropenia; NICE, National Institute for Clinical Excellence; UKCCSG, United Kingdom Children's Cancer Study Group

Table 1 Definitions of febrile

Temperature (primary/secondary and time*)	Number of policies
39°C/38°C (time unspecified)	1
38.5°C/38°C over 4 h	1
38.5°C/38°C within 4 h	2
38.5°C/38°C over 1 h	2
38.5°C/38°C within 1 h	4
38.5°C/38°C within 12 h	2
38.5°C/38°C (time unspecified)	2
38.5°C	2
38°C	3
38°C/37.5°C (time unspecified)	1

*If no secondary temperature is given, only a single definition is used.

RESULTS

Response rates

All centres provided information. There were 20 different policies in use. The two centres in London have combined to use a common policy covering London and the South-East of England.

Definitions of febrile

Febrile is defined in nearly all centres as either a single temperature greater than a ''peak'' (the primary definition) or a prolonged fever of lower intensity (the secondary definition). Nine different definitions are currently used. The most common is ''peak recorded temperature >38.5°C or two readings >38°C over the course of 1 h'' (table 1).

Most policies indicate strongly the need to start broad spectrum antibiotics in a significantly unwell child on treatment for malignant disease, regardless of the recorded temperature or neutrophil count.

Definitions of neutropenia

Neutropenia is defined more consistently, with 14 centres using an absolute neutrophil count of $<1.0\times10^9$/l, one using 0.75×10^9/l, three using $<0.5\times10^9$/l and two using ''$<0.5\times10^9$/l or less than 1.0×10^9/l and falling''.

Initial choice of antibiotics

Initial treatment is by two broad spectrum antibiotics in 16/20 policies (table 2). This is most commonly an aminoglycoside/piperacillin-based combination (in 7/20) or aminoglycoside/cephalosporin (in 6/20). Four policies use single agent meropenem.

Aminoglycosides

Fourteen centres use aminoglycosides in their initial therapy. In 13 cases this is administered on a once daily basis, but one protocol uses a split daily schedule.

Certain protocols use other measures in addition to monitoring drug levels to reduce potential toxicities. Aminoglycosides are discontinued in five policies at 48 h (in one policy at 72 h) unless specifically required. Two policies exclude those who have or are about to receive cisplatin chemotherapy, while a further two request intensive drug level monitoring in these patients.

Table 2 Empirical therapy antibiotic combinations

Initial therapy	Number of policies
Aminoglycoside*/piperacillin-based	7
Aminoglycoside*/cephalosporin†	6
Aminoglycoside*/carbapenem	1
Cefuroxime/flucloxacillin	1
Ciprofloxacin or ceftazadime/vancomycin	1
Carbapenem	4

*Gentamicin in 13, tobramycin in one centre; †ceftazidime in four, ceftriaxone or cefuroxime in one each.

Empirical alterations in antibacterial treatment

All units acknowledge the need to direct antibiotics as indicated by positive culture results. There are three ways in which empirical changes in antibacterial treatments are built into protocols:

1. increased intensity for significantly unwell patients (eg, additional aminoglycosides with a single-agent carbapenem),
2. planned progressive therapy (ie, switching antibiotics at a specific point in time) and
3. empirical therapy directed against coagulase negative staphylococci.

The indication for empirical switching of antibiotics in the six policies which describe this is continuing fever after 24–96 h. The most common is from a piperacillin-based antibiotic to meropenem. One centre switches their initial empirical anti-staphylococcal treatment from flucloxacillin to vancomycin at 48 h according to a ''planned progressive'' programme.

Empirical anti-coagulase-negative-staphylococcal therapy is commenced at the outset in two centres, and started later in eight more. All centres commence specific anti-staphylococcal therapy if there are clinical or microbiolgical signs suggestive of central venous catheter (CVC) infection.

Duration of therapy

The minimum duration of therapy varies from 2 to 5 days. Most policies (12, 70%), which defined stopping rules were based on the absence of fever, negative 48 h blood culture results and benign clinical features. Five policies suggest a minimum of 5 days of therapy. Nearly all policies require a minimum period without fever before discontinuing antibiotics (table 3), usually ''48 h afebrile''.

Risk stratification

Fourteen policies use risk stratification based on a combination of clinical features, aspects of therapy and neutrophil counts. The stratification highlights individuals at greatest risk or defines a group which have the potential for early discharge (''low risk FNP'').

The five policies that define a higher risk stratum add another empirical antibiotic to the treatment regimen for these patients. In four policies, this is the addition of an aminoglycoside to monotherapy, while the fifth adds a glycopeptide.

Six policies define low risk FNP. The centres rely on the child being clinically well, having negative blood cultures (for at least 48 h), and most refer to the severity of bone marrow suppression (requiring neutrophil counts of $>0.1\times10^9$/l or ''evidence of neutrophil recovery''). The child is then discharged on oral antibiotics for a period of time.

Antibiotic treatment of low risk FNP

Low risk patients are initially treated as inpatients for 48 h. Five policies use initial intravenous antibiotics and one uses initial oral antibiotics. For continuation therapy, oral β lactam, cephalosporins or quinolones were used either alone or in combination. The duration of treatment was to ''complete 5 days therapy'' or ''until afebrile 48 h''. Only one policy did not require children to be afebrile before discharge on oral antibiotics.

Table 3 Duration afebrile before discontinuing antibiotics

Duration afebrile	Number of policies
24 h	1
48 h	13
72 h	1
Undefined	2
No stopping rule	3

Empirical antifungal treatment

Empirical antifungal therapy is commenced between day 3 and 6 of continuing fever (median day 4) with standard or liposomal amphotericin-B (eight centres standard, nine liposomal, three not specified). The duration of therapy was extremely unclear, with only four policies making specific recommendations for duration or stopping rules.

DISCUSSION

The policies used to manage FNP in the centres around the UK vary in almost every aspect of management from the definitions of fever and neutropenia, choice of antibiotic approaches, empirical modifications, antistaphylococcal treatment and the use of risk stratification to empirical antifungal treatment.

Conventionally, it is assumed that the wide variation between policies arises from unchangeable local factors, such as variation in flora and resistance patterns. However, having now reviewed the UKCCSG Centre policies, it would appear that the variations exist largely as a result of tradition and history, there being only scanty research and few facts on which to base consensus therapy management. Similar variability has been reported in the treatment of adult FNP in the UK.[6]

Such variation may reflect some centres undertreating episodes of FNP but is more likely to reflect a broader overtreatment of the problem. It is impossible to compare therapeutic outcomes between protocols as the overall recordable adverse event rates (PICU admission <5%, mortality 1%)[2] are very low and we did not attempt to assess compliance with protocol. The less tangible costs of psychological morbidity, disruption to family/school life and resource issues although important are often ignored when such comparisons of protocols are being made as they are difficult to quantify.

Protocol differences between UKCCSG Centres appear to cause confusion and concern for families when they are treated away from their home centre (eg, when on holidays). This can undermine the confidence that patients have in their care and adds significantly to the stress associated with treatment. To reduce these problems it should be possible, within the UK, to standardise key elements of care such as definitions of fever and neutropenia, initial risk stratification and duration of empirical treatment. It is acknowledged that the choice of antibiotics used will vary according to local microbiological environments, but treatment approaches should be standardised and where possible follow the most beneficial practices (eg, using single-agent empirical antibiotics[7] and once daily aminoglycosides if necessary[8]).

One area which could lead to immediate and important gains in health quality and resource utilisation is in the identification of a group of patients with low risk febrile neutropenia and development of a specific treatment strategy for this group.[1 9–11] The NICE guidance *Improving outcomes with children and young people with cancer*[5] recognises this (p 54), and stated that ''national research is required for:

- ''the development of robust methods of risk stratification in the management of FNP'' and
- ''the exploration of the safe introduction of shorter periods of inpatient admission and/or community-based therapy for low risk episodes''.

This strategy is currently being explored by the UKCCSG/PONF Supportive Care Group, which is developing a *Framework guideline for the management of low risk FNP* through a consensus process. Further work by this group is ongoing in the diagnosis and treatment of CVC-associated infections, in the rationalisation of antifungal therapies and the further refinement of the management of low risk FNP.

What is known on this topic

- Febrile neutropenia is a common, resource-intensive and clinically important complication of treatment for malignant disease in childhood.
- Various approaches to the management of this condition have been studied.
- The management of febrile neutropenia varies considerably across adult oncology units in the UK.

What this study adds

- All United Kingdom Children's Cancer Study Group centres have policies to treat febrile neutropenia.
- The policies vary in almost all aspects, from the definitions of ''febrile'' and ''neutropenic'' to their use of risk stratification and duration of antibiotic therapy.

CONCLUSIONS

There is a great deal of variation in definitions and treatment of febrile neutropenia among the UKCCSG children's cancer treatment centres. We expect a degree of variation as a result of local microbiological differences allied to the adaptation of standard approaches to an individual patient's circumstances. However, in order to provide the most appropriate care for our patients and their families, we should seek to standardise the core of our approach to defining fever and neutropenia, risk stratification and duration of empirical therapy in a way that maintains safety, minimises resource utilisation and maximises quality of life.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the assistance of all the PONF link nurses and UKCCSG centre co-ordinators in supplying their policies and answering queries.

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Funding: None.

Competing interests: None.

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IMAGES IN PAEDIATRICS

doi: 10.1136/adc.2007.118687

Spinal extradural haematoma due to haemophilia A

A 4 month old boy was admitted to our hospital because of irritability and incomplete left limb paralysis. He was born at term at another hospital by spontaneous vaginal delivery to a 26 year old primipara Filipino woman. He had a productive cough, rhinorrhea and was irritable for 1 week before admission. The left hemisphere incomplete paralysis began at that time. He had no trauma and no skin lesions, such as petechiae or purpura. The neurological examination revealed mild muscle weakness and decreased deep tendon reflexes on his left side. Spinal magnetic resonance imaging (MRI) revealed an extradural haemorrhage extending from C4 to S1 (figs 1 and 2). A detailed interview revealed a history of bleeding on the maternal side, and he was diagnosed with haemophilia A.[1 2] His clinical condition improved promptly and fully following treatment with clotting factor. At the age of 2 years, he is developing normally; no neurological abnormalities have been detected and there has been no spinal recurrence.

Unless the neurological deficiency progresses rapidly, as in this case, non-surgical, conservative management is safe for a spinal extradural haematoma in patients with haemophilia, rather than attempting high-risk surgical management with inappropriate coagulation status.[3 4]

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Competing interests: None declared.

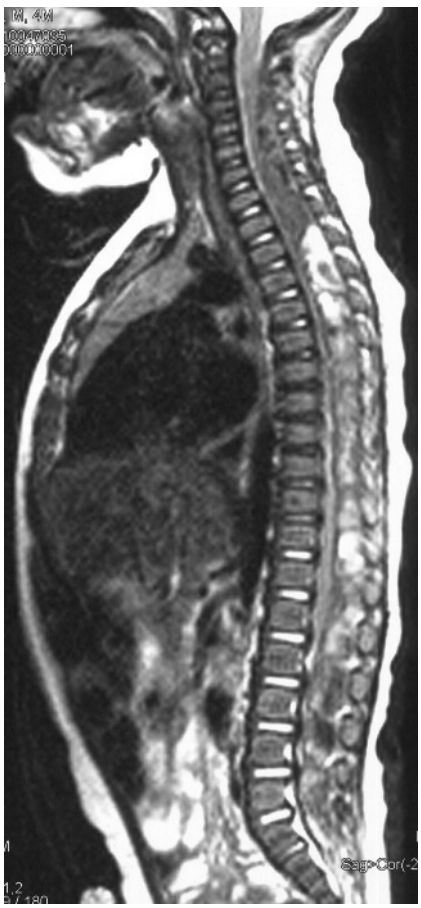

Figure 1 MRI of the spine showing coexisting old and new haemorrhages.

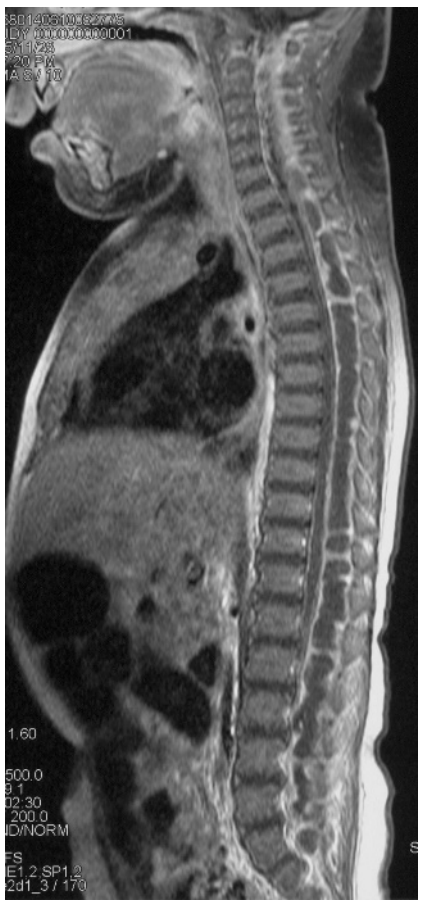

Figure 2 Enhanced MRI of the spine showing an extradural haemorrhage extending from C4 to S1.

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