

## Managing Febrile Neutropenia in the UK in 2020 Proposed New Management Pathway

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### Disclaimer:

The Children's Cancer and Leukaemia Group (CCLG) does not sponsor nor indemnify the treatment detailed herein. These clinical guidelines are provided by the tumour working group or specialist committee to inform and for use at the sole discretion of treating clinicians who retain professional responsibility for their actions and treatment decisions. Treatment recommendations/modifications are based on current best practice, and in light of the rapidly evolving situation with the COVID-19 pandemic, and not what is necessarily proposed for any forthcoming clinical trial.

The management of febrile neutropenia (FN) is a vital part of Paediatric Oncology/Haematology practice and constitutes a major part of the work of Primary Treatment Centres and POSCUs.

In light of the current coronavirus pandemic and the resultant pressures put on our services, the Supportive Care Group has proposed new guidance over management of one of our most common reasons for admission.

The objectives of this modified febrile neutropenia management process is to:

- Safely reduce the duration of admission
- Safely reduce the duration of (particularly IV) antibiotics

This document is designed to provide a brief background and practical application of a tiered, shortened, admission process. This protocol has been adapted from the paediatric low-risk FN program developed by Gabrielle Haeusler, National Centre for Infections in Cancer, Australia and in collaboration with Jess Morgan and Bob Phillips, University of York, and the CCLG team including Barry Pizer, Sujith Samarasinghe, Richard Grundy and Jessica Bate.

The protocol is not proposed to be a 'one size fits all' for all for PTCs and associated POSCUs. Instead it is recognised that centres should consider whether to adopt the full schema as written or to consider adapting the protocol according to their individual needs and particularly at this time, the effects of the COVID 19 pandemic on services.

Table 1, presents the Australian scoring system but also contains suggested variations to practice that centres may wish to consider for their own circumstances.

Nevertheless, the CCLG Supportive Care Group feels that the protocol is inherently safe and has benefits in respect of reducing hospital admission, exposure to intravenous antibiotics and others.

It is clearly important that there is a mechanism to evaluate such a major change to current practice and even more so to ensure this is carried out in order to ensure patient safety. We would encourage each centre using a version on this protocol to register their protocol with the Supportive Care group, along with ongoing modifications, and evaluate each case which they assess.

The document is not a comprehensive fever/neutropenia protocol. It provides the key elements of a service, but with no local intelligence (such as IV antibiotic choice, location of care or methods of re-assessment). Consider using the 'readiness' checklist to prepare your centres for the move. Each centre, dependent on the pressures they are currently facing, may decide to increase the minimum time recommendations in this tiered response.

### **Background to Fever in Neutropenia (FN)**

Neutropenic patients are at risk of rapidly developing life-threatening sepsis. Neutropenic sepsis is a medical emergency. Failure to recognise and treat this condition appropriately may result in unnecessary morbidity and mortality.

All children undergoing anticancer treatment with a risk of neutropenia who develop a fever ( $\geq 38.0^{\circ}\text{C}$ ) and neutropenia ( $\text{ANC} < 0.5 \times 10^9$  cells/L) should be assessed in hospital and a first dose of antibiotics given within 60 minutes. [11]

Any patient post allogeneic stem cell transplantation (SCT) who is on immunosuppressive drugs, or with severe graft versus host disease that has required treatment with antibody therapy, immunotherapies or high doses of steroids must be treated as febrile neutropenia guidelines irrespective of neutrophil count. Other non-neutropenic allogeneic SCT recipients who are off immunosuppressive drugs and assessed with fever should usually be managed as dictated by their clinical condition.

### **Background to Risk Stratification**

Advancements in supportive care for patients with cancer has seen the risk of death from febrile neutropenia fall from as high as 40% in the 1970s to only 1-3% more recently.

Recognising that many children with FN remain well throughout admission, and that clinically significant infections are rare, much work has been done to attempt to identify patients with "low risk" FN. This is important because management of FN episodes accounts for a considerable percentage of bed usage, which is expensive and inconvenient to patients and their families. A number of strategies designed to reduce the duration of inpatient stay and/or early use of oral antibiotics have been evaluated as non-inferior to existing inpatient intravenous protocols. Seventeen paediatric FN clinical decision rules (CDRs) that risk stratify children with cancer and FN for infection have been derived [2-4]. Validation studies tend to show the rules differentiate between risk groups less well when applied to different datasets [10]. The data from the prospective multisite ( $n=8$ ) Australian-PICNICC study which enrolled 858 FN episodes in children with cancer were used to recalibrate the SPOG (Swiss) rule [1]. This recalibration defined three equally weighted factors (WCC, platelets and chemo intensity). The AUS (Australia-UK-Swiss) rule

was then validated in the 'PICNICC+' dataset, including over 1500 evaluable episodes of FN from the UK, Europe, North and South America. [in submission]

The relationship between AUS score and significant bacterial infection/bacteraemia is shown below:

Australian data:

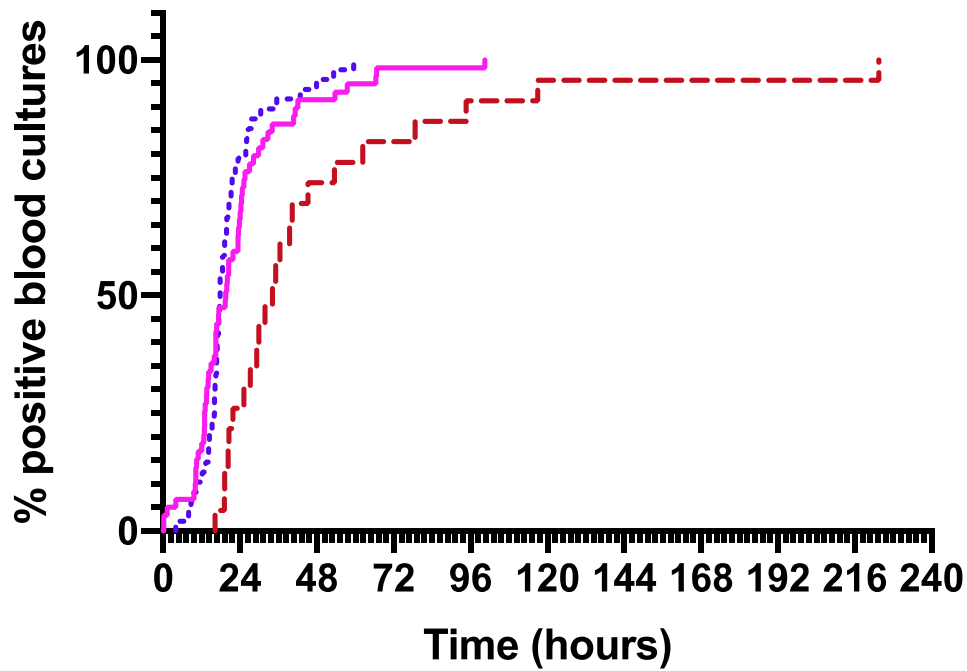
<b>SCORE</b>	<b>0 (n=84)</b>	<b>1 (n=298)</b>	<b>2 (n=284)</b>	<b>3 (n=192)</b>
Bacteraemia	3 (3.6)	22 (7.4)	36 (12.7)	47 (24.5)
Bacterial infection	9 (10.7)	49 (16.4)	66 (23.2)	74 (38.1)
Mortality	0	0	0	1 (0.05%)

PICNICC+ data:

<b>SCORE</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>
No bloodstream infection (BSI)	161	420	441	187
Bloodstream infection	16	69	107	109
% BSI	9.0%	14.1%	19.5%	36.8%
Death (any cause)	1 (0.6%)	1 (0.2%)	1 (0.2%)	3 (1.2%)
ICU	3 (1.7%)	10 (2%)	14 (2%)	10 (3.4%)

\* Deaths in score 1 & 2 were related to disease. Death in score 0 was post-transplant patient with adenoviral reactivation. ICU admissions in this data set came mostly from in-patient episodes, and all were assessed at presentation as 'seriously clinically unwell'.

The 855 case prospective evaluation of FN episodes has demonstrated that by 24 hours, 80% of positive blood cultures will have 'flagged'. [in submission]



— Gram negative   
 ⋯ Gram positive   
 - - - Commensal

The CCLG Supportive Care Group is very encouraged by the data above with respect to the safety of the AUS Clinical Decision Rule and its associated management pathway.

The process has been piloted in Royal Children’s Hospital, Melbourne, where it led to a significant reduction in bed occupancy. In their pilot study 63 children out of 336 children with FN were able to safely receive antibiotics at home. The AUS-rule score, when combined with a safety assessment, can assist clinicians in determining when the patient can be safely discharged to home-based FN care.

## Practical application of the AUS Score

The score can be calculated for each patient when they are recognised as febrile/neutropenic, using counts on admission.

**Table 1:** AUS-rule variables and score

<b>AUS-rule Variables</b>	<b>Yes</b>	<b>No</b>
Preceding chemotherapy more intensive than ALL maintenance*	<input type="checkbox"/> 1	<input type="checkbox"/> 0
Total white cell count < 0.3 x10 <sup>9</sup> /L	<input type="checkbox"/> 1	<input type="checkbox"/> 0
Platelet <50 x10 <sup>9</sup> /L <i>This remains valid despite including patients who may have been transfused</i>	<input type="checkbox"/> 1	<input type="checkbox"/> 0
<b>TOTAL SCORE</b>		
<p><b>Score 0</b> = This patient is <b>very-low risk</b> for a bacterial infection. If they are clinically stable and fulfil the safety-net criteria then <i>discharge home under parental care</i> a <b>minimum of 4-8 hours observation</b> <b>Variations in this group may include an overnight stay for observation</b></p>		
<p><b>Score 1</b> = This patient is <b>low risk</b> for a bacterial infection. If they are clinically stable and fulfil the safety-net criteria then <i>discharge home under parental care</i> <b>more than 4 but within 24 hours observation</b> <b>Variations in this group may include an overnight stay for observation or discharge at 24 hours</b></p>		
<p><b>Score 2</b> = This patient is <b>moderate risk</b> for a bacterial infection. If they are clinically stable and fulfil the safety-net criteria then <i>consider discharge home under parental care</i> <b>after a minimum of 24 hours inpatient observation</b> <b>Variations in this group may include ongoing care until afebrile 24h</b></p>		
<p><b>Score 3</b> = This patient is <b>higher risk</b> for a bacterial infection. If they are clinically stable <b>and</b> fulfil the safety-net criteria then <i>consider discharge home under parental care</i> after a <b>minimum of 48 hrs inpatient care</b> <b>Variations in this group may include ongoing care until afebrile 24h</b></p>		

\* ***This includes: ALL maintenance, LCH maintenance or weekly vinblastine alone (low grade glioma)***

The score alone is insufficient to determine if discharge home/parent-led care is acceptable. Safety and stability criteria need to be fulfilled. These determine is the patient is clinically well, socially safe to be at home, and able to tolerate the **oral antibiotic therapy (variation may include home-based IV antibiotics if resources enable this to occur).**

## Eligibility for home care

All Patients eligible for home care must fulfil all eligibility criteria in Table 2.

**Table 2:** Eligibility criteria for discharge home/parent-led care (must be YES to all to proceed to home care):

Criteria	Eligible	Not eligible
Disease status. Leukaemia/lymphoma in remission (as per last bone marrow aspirate (BMA) or solid tumour stable/responding (as per oncologist)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Low risk disease group: NOT ANY OF - acute lymphoblastic leukaemia (ALL) induction, or acute infant leukaemias, acute myeloid leukaemia (AML), post allogeneic haematopoietic stem cell transplant (HSCT) within 3 months or still on immunosuppression, congenital immunodeficiency, aplastic anaemia, Down Syndrome. <b>Centres may have particular local concerns about other specific diagnosis</b>	<input type="checkbox"/> Yes	<input type="checkbox"/> No
No confirmed focus of infection requiring inpatient care*	<input type="checkbox"/> Yes	<input type="checkbox"/> No
No medical complication requiring inpatient care**	<input type="checkbox"/> Yes	<input type="checkbox"/> No
No severe sepsis at FN presentation***	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Availability of a 24 hour caregiver	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Good education of patient and carer on reportable symptoms	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Availability of a telephone	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Within 1-hour of treating hospital	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Treating team preference	<input type="checkbox"/> Yes	<input type="checkbox"/> No
No previous history of non-compliance with medical care	<input type="checkbox"/> Yes	<input type="checkbox"/> No
<p>*including, <i>but not limited to</i>, central venous access device (CVAD) site infection, cellulitis, perianal cellulitis or pain, significant pneumonia, infection with multi-drug resistant bacteria.  **including, <i>but not limited to</i>, pain requiring intravenous analgesia, poor oral intake or excessive loss requiring intravenous hydration; respiratory distress or oxygen requirement.  ***severe sepsis includes any of (i) altered conscious state, (ii) inotrope requirement, (iii) fluid bolus requirement &gt;40ml/kg or (iv) respiratory support requirement  <b>Variations may consider excluding ANY patient who has received a fluid bolus, or had a past unplanned admission to ICU.</b>  <b>If well, presence of infiltrates on CXR may not be a contraindication to oral antibiotic therapy.</b>  <b>At the time of writing, SARS-CoV2/COVID19 positive swabs should NOT NECESSARILY be a contraindication to home care.</b></p>		

## Managing Patients

Initial assessments and investigations should be as per the Centre's current practice. Note: CRP is not included in the AUS score or assessment, and decisions to admit or discharge are safely made without assessing CRP. Multiple studies and a series of systematic reviews have demonstrated the lack of diagnostic ability of CRP to predict significant illness or bacterial infection [12].

There is almost no data about the value of routine lactate measurement outside of the setting of management of significant sepsis. Notably, lactate may be raised by malignant processes or dexamethasone.

## Antibiotic Treatment

### Every child will start with 1<sup>st</sup> line IV antibiotics

The first dose of an antimicrobial should be administered within one hour of arrival at hospital or development of such symptoms on the ward, ideally immediately after blood cultures are obtained and before any other diagnostic procedures

Discharge home/parent-led care is recommended after a minimum period of in-hospital observation (duration will depend on rule and score)

Prior to discharge home/parent-led care, the patient must:

- be reviewed by a locally approved competent specialist to ensure they are suitable
- receive appropriate education and information leaflet
- have tolerated one dose of oral antibiotics in the hospital

## Antibiotics for home-based management

Home administered antibiotics can be either continuation of intravenous antibiotics or oral antibiotics; such care is preferred by many families [13-15].

Most trials of low-risk (immediate discharge) febrile neutropenia management have used oral antibiotics [5-8]. It is recommended in the SIOP-endorsed international paediatric febrile neutropenia guideline, [16] and been used in Leeds for over a decade. This practice is supported by the CCLG Supportive Care Group.

At present, it is likely that discharge home/parent-led care will be based on oral antibiotics (assuming no mucositis, no vomiting, no significant diarrhoea suggesting reduced absorption),

The suggested antibiotic regimen is a combination of: Oral ciprofloxacin Plus Oral Augmentin. If allergic to penicillin consider clarithromycin instead.

If the above regimen is not feasible consider keeping patient in hospital for IV therapy unless local circumstances allow ambulatory management.

If severe beta lactam allergy or known resistant bacteria present please discuss with local microbiology.

## Duration of Empiric Antibiotics

Antibiotics will be **stopped in any patient with negative blood cultures after being afebrile for at least 24 hours**, if clinically well, unless alternative cause for pyrexia has been found. This approach has been used extensively in Sheffield for over a decade [9], and in other centres in the UK and internationally. NICE guidance is clear in the lack of need for a rising count before stopping antibiotics, and this is supported by data from the recurrent national audits of FN in the UK demonstrating safety [17].

Home antibiotics will be **provided** for 5 days duration, instructions being given to stop when the patient is:

- clinically well, culture negative
- afebrile for >24 hours

If the above criteria have not been met the patient should be reviewed on day 5.

### Medical and nursing staff responsibilities:

- Provide patient education package (inc. patient information)
- Daily phone calls until antibiotics stopped. Ensure families have the correct contact details for the hospital. This is a UK adaptation of the Australian system where a home visit occurs every 24-48 hours.
- Families to take temperature 4-6 hourly during waking hours
- Check blood culture results: antibiotics may need to be changed depending on these results

**Table 4:** Appointments schedule

Day	Appointments / interventions
0 (day of transfer)	Bloods reviewed prior to hospital discharge Telephone appointments arranged Patient information given
1	Observations Telephone follow up Review of blood results and action as required
2 - 4	Observations Telephone follow up Review of blood results and action as required
5	If remains febrile, patient to attend hospital for medical review and decision made for readmission or to continue at home/parent-led care

### Reasons for medical review include:

- Ongoing fever (>72 hours from presentation) or new fever after being afebrile for 24 hours
- Feeling unwell/new symptoms and signs
- Parental concern
- Significant decrease in oral intake or significant increase in output (vomiting and diarrhoea)
- Positive blood culture or new infection identified after transfer home
- Severe or persistent pain
- Chills/rigor/shaking
- Not afebrile by day 5 of home-based care

### Reasons for re-admission include:

- Fever > 38°C beyond **5 days from the start** of the febrile neutropenic episode
- Clinically unwell / unstable
- Infection requiring in-patient care



If readmission needed, follow standard febrile neutropenia management protocol at the appropriate time point i.e. restart iv antibiotics as per empirical regimen but adjusted for sensitivities of any known organisms and consider antifungal therapy once patient is febrile >96 hours from the start of the febrile neutropenic episode.

## Appendix: References

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## **Appendix: Service Evaluation**

To be added when completed