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PAnTher Cub: procalcitonin-guided antibiotic therapy for febrile neutropenia in children and young people with cancer - a single-arm pilot study

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ABSTRACT

Background Febrile neutropenia (FN) is a common complication of cancer treatment in children and young people, and many episodes are over-treated. Procalcitonin, may be an appropriate tool to guide the stopping of antibiotics in those at low risk of serious bacterial infection. Supportive care trials in this population have proven to be difficult to undertake. This single-arm pilot study aimed to evaluate whether a study using a procalcitonin-guided stopping-rule for antibiotics in paediatric FN is possible.

Methods Daily procalcitonin levels were performed during episodes of FN and clear guidance given for antibiotic discontinuation. Episode data and quantitative feasibility data were collected alongside interviews with professionals and ethnographic observations. Analysis was descriptive.

Results Of 32 patients and families approached, 28 patients consented, and 13 had febrile neutropenia. In total, 16 episodes were included in the study. All relevant FN episodes had data captured, with adequate data collection. There were no significant safety events. In 4/8 (50%) of episodes without clear microbiologically documented or clinical infection, antibiotics were reduced in duration or in spectrum. Interviews with professionals revealed the importance of the research, the value of key individuals in the study team, particular challenges of this protocol and suggestions for study improvements.

Conclusions Studies to evaluate procalcitonin-guided approaches to stopping antibiotics in paediatric FN are possible.

What is known about the subject?

- Febrile neutropenia is the most common complication of treatment for children with cancer, and is currently treated with intravenous antibiotics and hospital admission.
- Procalcitonin, an infection biomarker, has been shown to help reduce duration of antibiotics in other populations but has never been studied in immunocompromised patients.
- Previous trials of supportive care interventions in paediatric oncology have struggled with poor recruitment.

What this study adds?

- It is possible to deliver a trial of a procalcitonin-guided antibiotic stopping rule in children and young people with febrile neutropenia.
- Further larger studies to evaluate the safety and efficacy of such an intervention are indicated.

INTRODUCTION

Children and young people (CYP) being treated for cancer are at significant risk of developing sepsis, mainly secondary to chemotherapy. Febrile neutropenia (FN)—fever in the presence of a low neutrophil count—is managed by empirical intravenous antibiotic treatment to avoid potentially life-threatening complications.[1] This approach has led to a reduction in intensive care admission to <5% and mortality to <1% but over-treats most patients.[2] Only 20%–30% of all patients with FN will have a serious bacterial infection.[3] Current practice is to continue antibiotics at least until blood cultures are reported negative, the patient is well and afebrile for at least 24 hours. While service developments in upfront risk stratification in 2020/2021 have shortened average hospitalisation a considerable proportion (75.2%, data from National UK febrile neutropenia service evaluation, Jackson TJ *et al*, 2021) remain in hospital over 72 hours.

Identifying the subgroup of patients who genuinely require antibiotics in this group is challenging. A complimentary approach to upfront risk stratification is using a biomarker to identify the point at which intravenous antibiotics could be stopped. The most widely available infection biomarker currently is C-reactive protein (CRP) but in patients with

FN it discriminates poorly, with a large individual participant data meta-analysis showing it was not significantly associated with microbiologically defined infection.[4]

Procalcitonin (PCT), a biomarker more specific for bacterial infection, peaks at 6 hours and decreases rapidly in response to antibiotic treatment with the additional benefit of being rapid and easy to analyse.[5] Current UK National Institute for Health and Care Excellence guidance on using PCT to diagnose and monitor sepsis concluded there was insufficient evidence to support its routine use in the National Health Service.[6] Further research was recommended. The published studies and all ongoing trials all exclude immunocompromised patients. Systematic reviews support further investigation of its utility in CYP with FN in safely reducing antibiotic use.[7 8]

Although around 60% of paediatric oncology patients are recruited onto cancer treatment clinical trials, there have been few supportive care studies despite patients and families emphasising improving supportive care as vital.[9 10] Many such trials have suffered from poor recruitment rates necessitating early closure.[11 12] Reasons included lack of clinician prioritisation, lack of belief in equipoise of the question or over-complicated eligibility criteria. One challenge in 'reduction of treatment' studies is the 'just in case' principle, for example, where antibiotics are carried on 'just in case' there is an infection.[13] To undertake a large study examining if the use of a PCT-guided approach would be better for patients and families than the current standard, we needed to assess if clinicians and families will agree to this type of management. This single-arm, pilot study aimed to address the question of whether studies of a PCT-guided approach are possible, by exploring why patients and clinicians do, or do not, chose to enter the study, and their views on the value of PCT in altering management.

METHODS

This was a single arm, unblinded pilot study, to assess the 'proof of principle' of serial procalcitonin guided-management for FN with integrated qualitative assessment of the study processes undertaken in the tertiary haematology/oncology centre at Leeds Children's Hospital between November 2020 to April 2021. To be eligible for the study, a patient had to be 18 years old or younger, be treated at the hospital with chemotherapy likely to induce neutropenia, and consent, or their carer consent if unable to do themselves, to inclusion. There were no specific exclusions.

Patient assessment, investigation and antibiotics were hospital standard of care, except for the 'stopping rule' for antibiotics. Briefly, this consisted of admission, if not already in-patient, for a minimum of 8 hours and intravenous broad-spectrum antibiotics (monotherapy with piperacillin/tazobactam preferred) for at least one dose. GCSF (granulocyte colony stimulating factor), for treatment or prophylaxis, was not routinely used.

Procalcitonin was measured at baseline (ideally with initial blood culture samples preantibiotics, or within 8 hours of arrival), then once a day until the patient was discharged. Antibiotics were continued for a minimum of 36 hours.

The 'PCT stopping rule' recommendation was to stop antibiotics when post-baseline PCT was <0.5 ug/L with no growth on blood cultures (minimum 36 hours) and no clinical evidence of severe infection requiring antibiotics, regardless of the patient's temperature (figure 1). The treating clinician was encouraged to document reasons for over-ruling the recommendation. Stopping antibiotics was not necessarily accompanied by hospital discharge.

Episode data collected included daily blood count, CRP, maximum temperature and clinical features of risk stratification; start/stop date and time of intravenous antibiotics; admission/discharge date/time; date/time of resolution of fever; results of infection-related investigations, including blood cultures and clinical determination of any focus of infection. Critical care admissions or death within 7 days of stopping antibiotics, or development of documented/clinically suspected bacterial infection within 72 hours of stopping antibiotics would have led to the study being suspended.

Practicality and feasibility were assessed by evaluating: proportion of eligible patients approached who consented to study inclusion, number of patients enrolled in the study period, proportion of FN episodes treated on study for all FN episodes eligible, proportion of enrolled patients who discontinued or declined intervention, proportion of missing data on primary 'main study' outcome measures and the types of patients recruited. The study also assessed safety and provided data for baseline calculations for further studies, by evaluating the impact of PCT-guided management on antibiotic duration.

A target sample size of 10–20 patients was set, derived from the rate of enrolment we would expect in a Phase 3 trial with 12–15 centres over a 2-year period. A Phase 3 trial would require around 1000 patients to be randomised, or around 125 patients across all centres over 3 months.

Analysis of quantitative data was purely descriptive, using standard methods: continuous data as mean or median as appropriate, and proportions for categorical variables.

Interviews with healthcare professionals were performed following the pilot to explore views and experiences about participating in the study, experiences of recruitment, acceptability of the intervention, practicalities of following the protocol and the use of PCT in decision-making. Interviews were performed in English, using a video-conferencing tool, and audio-recorded. A semi-structured interview guide was used (online supplemental appendix 1). All participants were offered debriefing.

Analysis used a constant comparison approach, aiming for a descriptive thematic level of detail, seeking to provide

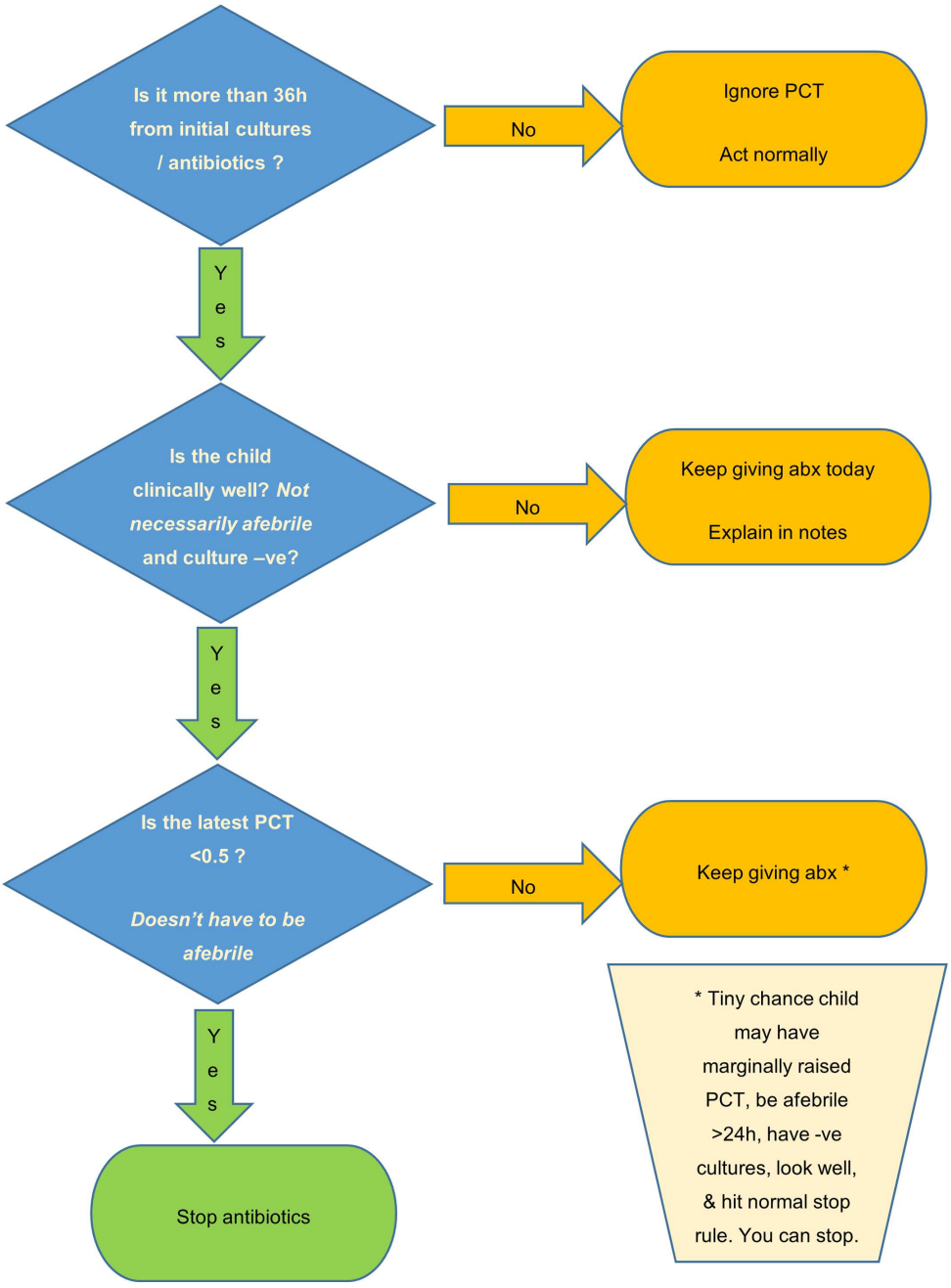

Figure 1 Flowsheet to support clinician decision-making. abx, antibiotics; h, hours; PCT, procalcitonin; -ve, negative.

explanatory information surrounding the delivery of the feasibility study. Regular consultation within the study team allowed for assessment of coding accuracy and consideration of the future research directions.

Initial plans had also included interviews with families participating in the study, but these were precluded by practicalities, including due to the COVID-19 pandemic.

Ethnographic observations were made of the healthcare team by one of the two researcher–clinicians during daily clinical practice, where antimicrobials were under discussion. Records were written as contemporaneously as possible. Staff were made aware of the study through posters and presentations, and an opt-out consent approach used.

Patient and public involvement

Patients and parents were involved in the design of the overarching 'PAnTher' study, for which this study is a pilot. This PPI work has been published.[9]

RESULTS

Quantitative results

Of 32 patients and families approached, 28 patients consented to be part of the study. In total, 16 episodes of FN were included in 13 unique patients (range 1–2). No episode was missed in patients who consented to be part of the study, and none declined. Admission data was collected in full in 12 cases (75%), and subsequent daily

Table 1 Oncological grouping of patients

Tumour/treatment group	Number of patients
Stem cell transplant	2
Solid tumour	6
Brain tumour	1
Leukaemia	2
Lymphoma	2

data completeness was: day 2 11/13 (84%), day 3 8/11 (73%), day 4 7/7 (100%) and day 5 2/5 (40%). Patients were recruited from all major tumour/treatment groups (table 1) including haematological malignancies and stem cell transplant (6/13), all had central lines. The median age was 6 years 5 months (range 8 months to 18 years) and 31% (4/13) were female. The AUS (Australia-UK-Swiss) score ranged from 0 to 3, median 1.[14]

Eight of the 16 episodes had a clinically (2) or microbiologically proven (6) infection. One patient required critical care, within the first day of treatment and while on broad spectrum antibiotics.

In 4/8 (50%) of the cases without clear microbiologically documented or clinical infection, antibiotics were reduced in duration (3 cases, median reduction 2 days, range 1–5) or in spectrum (1 case, switch to co-amoxiclav). The use of procalcitonin may also have supported a change to reduced intensity (oral antibiotic from broad spectrum intravenous therapy) in two patients with clinical lower respiratory tract infection.

PCT levels stayed low or reduced over time in most patients as infections were confirmed absent or brought under control (figure 2). A low PCT (under 0.5 ng/L) alone did not rule out documented infection, emphasising the need to incorporate with clinical features and other investigation results.

Qualitative results

Four healthcare professionals were interviewed: two medical and two nursing, with a range of professional experiences and roles within the study. Interviews lasted 25–30 min. All interviewees were known to the interviewer (JEM). Interviews revealed six key themes:

The importance of this research

Participants spontaneously, and unprompted by the interviewer, commented on the importance of this research programme:

> I just think it's a really good idea, really exciting bit of work that you're doing, to improve… well… patients being at home is ultimately what we want to achieve isn't it but catching the ones that need to actually be in hospital to be safe. (Professional 4)

Participants reflected positively on the potential benefits to antimicrobial stewardship, and on various practical aspects of the study, including patient materials. The study was widely adopted:

> I think the study was taken up well by the whole team. On ward rounds, it was usually a different doctor or ANP who first said, "what is the procalcitonin?" "can we stop?" (ethnographic observation)

Professional experiences of the protocol

Professionals talked about the challenges of reducing antibiotics in this population, including fear and established practice:

> To let someone go home who is febrile and neutropenic is a bit more frightening. (Professional 1)

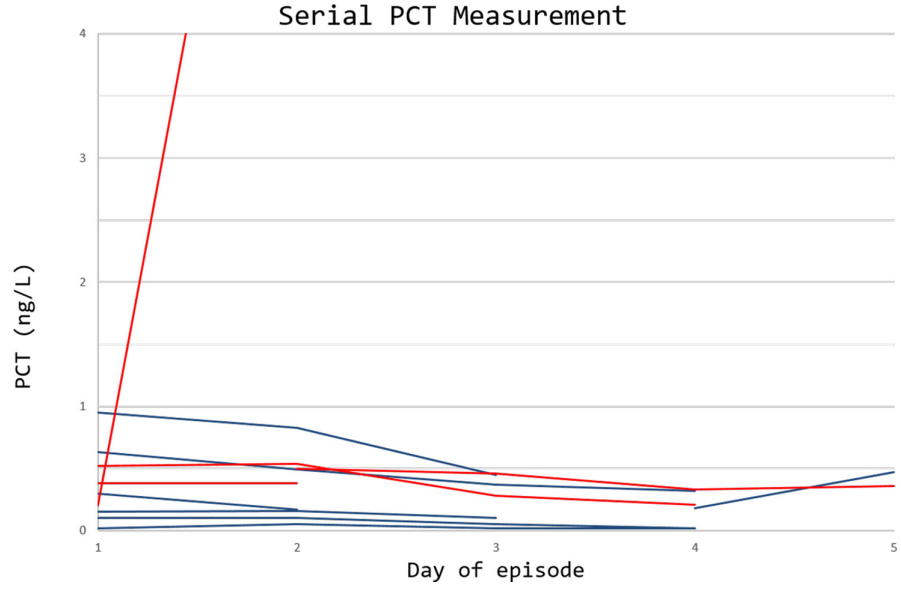

Figure 2 Serial PCT measurements in individual patients. Red: Cases with documented infection. Blue-grey: Cases with no documented infection. PCT, procalcitonin.

I'd like to think I would do things rationally but I think the scenario might be that if they're still spiking its just kind of engrained that you keep going… (Professional 3)

The 'key individual' factor

Participants clearly associated PAnTherCub with core members of the study team, reflecting on seeing them deliver the study, considering study team approaches in their decision-making, and speaking with the study team about FN:

In our daily rounds we saw Dr Phillips and you [JEM] consenting patients about the study… you people were asking our opinions about the study. (Professional 2)

In one meeting, a professional referred to the influence of a key professional on the success of the research as 'the Bob Phillips factor' (ethnographic observation). Future implementation of a large study at multiple sites would need to consider the identification of such 'key individuals' and how they play a role in the success of study delivery.

Particular challenges of the study

Recruitment

Participants spoke of some challenges to recruitment, including finding the time to speak with families about PAnTherCub, and the relatively brief recruitment period before the pilot closed.

Timing

The commencement of PAnTherCub coincided with other changes in FN policy related to the COVID-19 pandemic, where location of patient care, up-front risk stratification and timing of discharge for low-risk patients were amended. During the interviews, it became clear that some participants struggled to separate the different changes:

There was a lot of changes all happening all at once. (Professional 4)

This is unlikely to be a particular challenge in a future larger study, but maintaining stability in local FN policy may help study sites when delivering this research.

Identification of enrolled patients

One challenge recognised by professionals was in identifying patients as PAnTherCub participants and therefore remembering to perform PCT tests. This was helped by parental prompting 'I do remember some parents saying we're on the PAnTherCub study as like a reminder' (Professional 4) and participants stated this would become a less significant issue in a larger trial as professionals became more familiar with study processes.

Perceptions of parental experiences

Participants reported that PAnTherCub was generally well received by families:

'I think they thought it was great… (Professional 1)

Though they anticipated some parents may have concerns about reducing antibiotics:

I think the families saw that using antibiotics is something reassuring them, maybe patient is febrile and he is on broad spectrum antibiotics this is a good thing and about the study, to stop antibiotics even if the patient is febrile is something create anxiety for the families but I think we need to alleviate the anxiety by reassuring… (Professional 2)

Suggestions for study improvements

Participants suggested the following key developments moving forwards:

- Increased promotion and awareness within professional teams, particularly for nursing and junior medical staff, familiarising them with the protocol and possible roles within the study (eg, recruitment)
- Clarification of elements of the protocol relating to children undergoing stem cell transplantation, including both eligibility and analysis.
- Consideration of site-specific practices to increase recruitment, for example, targeting certain clinics or prior to planned prolonged admissions.
- Identifying site-specific techniques for identifying enrolled patients at presentation with FN, including markers on patients' paper notes, flags on electronic systems, 'prescribing' blood tests, addition of PCT to standard order sets and posters close to initial blood taking equipment.

DISCUSSION

PAnTherCub has demonstrated that studies to evaluate a PCT-guided approach to paediatric FN are possible, and welcomed by the paediatric haematology/oncology community. There were no concerning safety events. Preliminary outcome data and qualitative data relating to implementation have been provided to inform future study designs.

No previous studies in this setting have evaluated biomarker-driven stopping rules for FN. However, previous studies in paediatric supportive care have struggled with recruitment.[11 12] PAnTherCub appears to have successfully overcome these challenges. The recruitment of key individuals to study teams and a site-specific approach to implementation are likely to be key elements in supporting larger studies of stopping-rule trials.

PAnTherCub's strengths included the engagement of professionals and families in the delivery of the intervention, and in the high quality of data collected. This was facilitated by the single centre design focusing on

one team. Future work will need to evaluate the ability to translate this to other centres. Furthermore, the brief duration of the PAnTherCub study means we have been unable to establish whether these successes could be sustained over a longer period and potentially lead to further improvements as a study became embedded in a unit's practice. In addition, we have not yet tested whether patients are happy to be randomised between this intervention and standard care, though the acceptability of the intervention in PAnTherCub suggests this is likely.

As a single-arm pilot study, PAnTherCub is the first step in developing research to evaluate the use of PCT-guided FN management in paediatric haematology/oncology. The next phase of research will include a feasibility study exploring issues relating to multiple study sites, patient randomisation (to a control group) and confirming required sample sizes for a definitive study. The final stage will be a larger randomised controlled trial to assess the use of procalcitonin-guided approaches.

PAnTherCub has shown that it is possible to deliver a trial of a procalcitonin-guided febrile neutropenia management intervention in paediatric haematology/oncology. Further larger studies to evaluate the safety and efficacy of such an intervention are indicated.

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Contributors JEM was involved in protocol development, collecting data, analysis and drafting of the manuscript. BP conceptualised the research and developed the protocol. He was also involved in collecting data, analysis and drafting of the manuscript. Both authors have approved the final draft of the manuscript. BP is the guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the West Midlands – Black Country Research Ethics Committee (Ref 20/WM/0205). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data for this study contains the following elements, which when combined would make the patients identifiable given the rarity of childhood cancer in the identified geographical area and time of this study: # Demographic data: (ii) episode date; (iii) age; (iv) cancer diagnosis & treatment;# FN episode data: (i) inpatient or outpatient onset; (ii) time of start of temperature; (iii) time of presentation;A reduced data-set taking out all items to produce sufficient anonymity (for sensitive data; childhood cancer) would severely limit their utility for researchers.The patients and families who took part in this study, and the Research Ethics Committee who granted permission for it, agreed the data should be available for sharing in ethically approved secondary use projects. Such studies are typically individual participant data meta-analysis collaboratives. Anyone who has such an approved project, investigating aspects of paediatric febrile neutropenia and biomarker profiles, is encouraged to approach bob.phillips@york.ac.uk <mailto:bob.phillips@york.ac.uk> for access to the data set.

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REFERENCES

1 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;35:2082–94.
2 Orudjev E, Lange BJ. Evolving concepts of management of febrile neutropenia in children with cancer. *Med Pediatr Oncol* 2002;39:77–85.
3 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.
4 Phillips R, Stewart L, PICNICC C. Meta-Analytic validation of the PICNICC prediction model for the risk of microbiologically defined infection in febrile neutropenic episodes. *Pediatr Blood Cancer* 2017;64:e26772.
5 van der Galiën HT, Loeffen EAH, Miedema KGE, *et al*. Predictive value of PCT and IL-6 for bacterial infection in children with cancer and febrile neutropenia. *Support Care Cancer* 2018;26:3819–26.
6 National Institute for Health and Care Excellence (NICE). CG151 neutropenic sepsis: prevention and management in people with cancer. full guideline, 2012. Available: https://www.nice.org.uk/guidance/cg151
7 Carrol ED, Thomson APJ, Hart CA. Procalcitonin as a marker of sepsis. *Int J Antimicrob Agents* 2002;20:1–9.
8 Haeusler GM, Carlesse F, Phillips RS. An updated systematic review and meta-analysis of the predictive value of serum biomarkers in the assessment of fever during neutropenia in children with cancer. *Pediatr Infect Dis J* 2013;32:e390–6.
9 Phillips B, Depani S, Morgan J. What do families want to improve in the management of paediatric febrile neutropenia during anti-cancer treatment? report of a patient/public involvement group. *BMJ Paediatr Open* 2019;3:e000398.
10 Aldiss S, Fern L, Phillips B. Top 10 research priorities for teenage and young adult cancer in the United Kingdom: prioritising need for psychosocial research. *Pediatr Blood Cancer* 2018;65:e27455.
11 Bate J, Baker S, Breuer J, *et al*. PEPtalk2: results of a pilot randomised controlled trial to compare VZIG and aciclovir as postexposure prophylaxis (PEP) against chickenpox in children with cancer. *Arch Dis Child* 2019;104:25–9.
12 Marshall E, Steven N, Billingham L. Difficulties in running a phase III trial to investigate the optimal management of patients with low-risk neutropenic fever. in: NCRI cancer conference Abstracts., 2009. Available: https://abstracts.ncri.org.uk/abstract/difficulties-in-running-a-phase-iii-trial-to-investigate-the-optimal-management-of-patients-with-low-risk-neutropenic-fever/ [Accessed 26 Oct 2021].
13 Charani E, Ahmad R, Rawson TM, *et al*. The differences in antibiotic decision-making between acute surgical and acute medical teams: an ethnographic study of culture and team dynamics. *Clin Infect Dis* 2019;69:12–20.
14 Haeusler GM, Phillips R, Slavin MA, *et al*. Re-evaluating and recalibrating predictors of bacterial infection in children with cancer and febrile neutropenia. *EClinicalMedicine* 2020;23:100394.