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Procalcitonin-guided Antibiotic Therapy for febrile neutropenia in children and young people with cancer. A single-arm pilot study

Summary of the Study

Treatment for childhood cancer can make children at increased risk of life-threatening infections, and when a fever occurs, children need to be admitted to hospital for antibiotics urgently to get on top of any severe infections quickly. This approach to treating 'febrile neutropenia' (FN) is very safe, meaning nearly all severe infections can be cured, but it also means that well children, who may just have a cold, get stuck in hospital for days until their temperature settles.

We have previously shown in our research that a blood test called procalcitonin (PCT) can help to show who has a severe infection. We'd now like to show that it's safe to use this test to shorten the amount of time children spend on antibiotics.

Ideally we need to undertake a very large 'supertanker' of a study, with hundreds of children, half getting the PCT-test management and half not getting it, to test if this really makes a difference. In order to do this though, we need to firstly check that it is possible – that the patients, families and doctors will be prepared to take part in such a study. This is what this application is for; to undertake a pilot study, to make sure that the big 'supertanker' is feasible.

Our pilot study will work with 10-20 families who agree to have their FN managed this way. We will see if it possible to do the blood tests quickly, act on the results, and send children home. We will discuss with doctors, nurses, ANP (advanced nurse practitioners) and the families to hear about and understand their views on this way of managing infections. We will also look to see what proportion of people who might have been able to take part in the study agreed to do so. These findings will be used to work out whether the supertanker study is possible and how to do it well.

Background and Rationale

Children and young people being treated for cancers are at significant risk of developing sepsis, mainly secondary to chemotherapy. FN - fever in the presence of a low neutrophil count – is managed in the UK by immediate admission to hospital and empirical intravenous (IV) antibiotic treatment to avoid potentially life-threatening complications.(1) Each cancer patient will experience a median of two unexpected hospitalisations for FN during their treatment, an estimated 3,000 admissions/year in the UK and around 250/year in Leeds Children's Hospital.(2) Families are advised to attend hospital immediately if unwell or febrile for the prompt assessment and treatment of presumed sepsis.

This approach has led to a reduction in intensive care admission to <5% and mortality to <1% (3) but over-treats a majority of patients. Only 20-30% of all patients with FN will have a serious bacterial infection (4). Other causes of fever include viral or fungal infections, mucositis, drug (chemotherapy) effects, blood transfusions or the malignancy.(5) 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. Patients generally remain inpatients for a minimum of 48 hours and the median hospital stay for FN is 4 days (range 1-19 days) (6-8).

Identifying the sub-group who genuinely require antibiotics in this patient group is challenging as clinical manifestations are often subtle and non-specific. Patients at low-risk for SBI can be safely treated with upfront or early stepdown to oral antibiotics(9-14); this is recommended by NICE guidelines on the management of FN (15). Unlike adults, there is no single validated risk prediction tool in CYP and current tools over-estimate the risk of individual episodes(16) resulting in around 80% of patients being deemed 'high-risk'(6). Local Leeds audits have shown similar figures; with only 10-20% of patients being 'low risk' and suitable for early discharge. Safe, rapid, discharge from hospital is identified as a key patient-important outcome in trials of FN management. (17)

A complimentary approach to up-front risk stratification is using a biomarker to identify the point in every FN episode at which intravenous antibiotics could be stopped and reduce the length of hospital stay. The most widely available infection biomarker currently is CRP but in FN patients it poorly discriminates between different types of inflammation(18), with a very large individual participant data meta-analysis showing it was not significantly associated with microbiologically defined infection.(19)

Procalcitonin (PCT), a biomarker more specific for bacterial infection, peaks at 6 hours and decreases rapidly in response to antibiotic treatment with the additional benefits of being widely available, easy to analyse and rapid.(20) PCT has been studied in several patient groups to diagnose sepsis and monitor response to treatment. An HTA commissioned systematic review (SR) and cost-effectiveness analysis (36) informed NICE guidance (co-applicant BP was a panel member) on the use of PCT in diagnosing and monitoring sepsis; it concluded there was insufficient evidence to support its routine use in the NHS (31). Further research was recommended. Subsequent to this, two large (>1500 patients) RCTs with pragmatic study design examining PCT-guided decision-making in neonates with suspected infection (NeoPIns) and critically ill adults on ICU (SAPS) found significant reductions in antibiotic duration in the PCT arm.(39, 40) and two HTA-commissioned trials have been funded (37, 40). The published studies, the review 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.(18, 21)

More judicious use of antimicrobials is linked to reduction in adverse events for patients, healthcare resource reduction and positive impact on antibiotic resistance. It is a key part of the NICE antimicrobial stewardship guidance and Public Health England's Stay Smart Then Focus toolkit.(32-34) The proposed study supports the UK 5-year Antimicrobial Resistance Strategy (35, 36) to protect effectiveness of available antibiotics, and NICE guidance which recommends valid decision-support systems as an antibiotic stewardship intervention, for example biomarker-guided antibiotic duration algorithms.

Although around 60% of paediatric oncology patients are recruited onto cancer treatment clinical trials, there have been very few supportive care studies in either paediatric or adult oncology despite patients and families emphasising to us that improving supportive care is a vital aspect of the cancer experience.(17, 22) Many have suffered from poor recruitment rates necessitating early closure.(23, 24) Reasons included lack of clinician prioritisation, lack of belief in clinical equipoise of the question, or over-complicated eligibility criteria. One of the challenges with 'reduction of treatment' studies is the 'just in case' principle, for example where antibiotics are carried on 'just in case' there is an infection, which has been shown to drive continued prescriptions in hospital.(25) To undertake a large study examining if the use of a PCT guided approach really would be better for patients and families than the current standard, we need to demonstrate a clinicians and families will agree to this type of management. This proof of principle study proposes to address the question of if a PCT guided approach is 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.

Project Aims and Hypotheses

This study aims to answer the question “Is it practical to perform a study to manage antibiotic delivery in febrile neutropenia for children and young people undergoing treatment with anti-cancer drugs with the routine serial use of PCT measurements?”

The hypothesis is serial procalcitonin will indicate more rapidly than fever which children and young people do not have a serious bacterial infection and in whom their antibiotics can be stopped, and that parents and clinical teams will be happy to undertake such a study to see (in a larger trial) if it is clinically and cost-effective.

Methodology

This is a single arm, unblinded cohort study, supporting or refuting the “proof of principle” of procalcitonin guided-management for febrile neutropenia patients with integrated qualitative assessment of the study processes to enrich understanding for future studies; the Quintet Recruitment Intervention (QRI) method.(25)

- Intervention

Daily, serial, procalcitonin-guided decision making for duration of antibiotic therapy

Patient assessment, investigation and antibiotics used will be as current Leeds Children’s Hospital guidelines, with the exception of the ‘stopping rule’.

Procalcitonin will be measured at baseline (with initial blood culture samples pre-antibiotics), then once a day along with routine blood tests until the patient is discharged. The test is currently used in clinical practice in critical care sites in Leeds Children’s

Antibiotics will be continued for a minimum of 36 hours

There will be a recommendation to stop antibiotics when post-baseline PCT is <0.5ug/L with no growth on blood cultures (minimum 36 hours) and no clinical evidence of severe infection requiring antibiotics, regardless of the patient’s body temperature.

The treating clinician will be free to continue antibiotic therapy (e.g. on the basis of clinical symptoms or other investigations) but clear reasons of why the recommendation is being overruled must should be given.

The treating clinician will also be free to decide when the patient is safe for discharge and may keep the patient admitted for observation even if antibiotics are stopped.

Primary objective:

- To assess the feasibility of a PCT-guided antibiotic management of FN antibiotic management in CYP with cancer.

Secondary objectives:

- Acceptability of the study to patients, families and treating clinicians
- Challenges in recruitment, data capture and retention in the study
- Adherence to advised stopping rule
- Provide data for a formal randomised feasibility trial

Primary outcomes:

- Recruitment rate: proportion of eligible patients approached who consent to study inclusion

Secondary outcomes:

- Discontinuation adherence: proportion of episodes where antibiotics stopped according to PCT-guided recommendation over 6 months
- Safety: number potentially infection related admissions to critical care after discontinuation of antibiotics over 6 months
- Recruitment strategy: proportion of potentially eligible patients who were approached to consent over 6 months
- Attrition: proportion of enrolled patients who then discontinued or declined intervention over 6 months
- Data quality: proportion of missing data on primary outcome measures over 6 months

- Impact on PCT on clinical decision making and reasons for adherence and non-adherence (qualitative data)
- Patient, parent and clinician attitudes to study (qualitative data) including the outcomes important to CYP/families

Quantitative Data

We will log patients screened, found eligible, approached for consent and reasons for declining study entry and whether all FN episodes seen were treated on study or not. These data will support the 'QRI' element of the study.

Baseline clinical data for each patient who attends and consents with FN will be collected. Episode data will include blood count, CRP, maximum temperature and clinical features of risk stratification at diagnosis and daily; start/stop date and time of intravenous antibiotics; admission/discharge date and time; date/time of resolution of fever; results of infection-related investigations, including blood cultures and clinical determination of focus of infection if identified. The PCT levels and time point taken will be documented together with reasons of non-adherence to stopping recommendation if applicable. Any PICU admission or death within 7 days of stopping antibiotics, or development of documented/clinically suspected bacterial infection within 72 hours of stopping antibiotics will be considered SAEs and the study suspended. These data provide the clinical outcomes of the study.

Qualitative Data

The qualitative information explores the views and experience of clinicians and patients/families about participating in study – particularly recruitment, acceptability, practicalities and impacts on shared-decision-making.

The qualitative data will be drawn from three sources; ethnographic observation of antimicrobial decision making discussions, interviews with clinician-researchers and interviews with participating parents / patients. These will be combined with quantitative data in a mixed-method analysis to improved recruitment, and also to understand the nature of the antibiotic decisions.

Ethnographic observations will be made of the health care team by one of the two researcher-clinicians during daily clinical practice, where starting and stopping antimicrobials

are under discussion. The focus will be largely on the decision to stop or de-escalate (move to a 'less powerful' antibiotics), but observations on all deliberations will be recorded. The records will be handwritten as contemporaneously as possible. Presentations and posters will be present to make staff aware of the study and an opt-out consent approach used as is common in ethnographies.

Clinician interviews will have two reasons: to explore recruitment issues, and adherence with the PCT-guided strategy. We will interview 4 clinicians. The interviews will explore views and experiences of health professionals about participating in study, experiences of recruitment (including rationales for not approach and challenges of consent), acceptability of intervention, practicalities of following study protocol and use of PCT in decision-making, including their understanding/interpretation of the research protocol and treatment recommendations and how the views of patient/family impacted on decision-making.

Interviews with up to 4 parents/2 patients to address experiences of recruitment, understanding and acceptability of the intervention, and view of their impact on any shared-decision making.

Each interview will last a maximum 60 minutes, and for parents, performed within 3-4 weeks after an admission for FN to minimise recollection challenges or contamination with other events.

Interviews will take place face-to-face wherever possible, with an option for telephone or videoconference (zoom/skype/facetime) interviews at participant request. Interviews will be held at a location and time that is convenient for the participant. All audio-recording will use an encrypted digital recorder. A research diary will be kept by the to record general observations, analytical thoughts and factors relevant to the research aims. The field notes within this diary will form part of the data analysed within the study.

We will aim for diversity within the patient and parent participants in terms of age, gender, oncological diagnosis of the child, socioeconomic circumstances and experience of febrile neutropenia, whilst recognising the challenges of achieving this experienced in previous research in this field.(31)

When analysing the qualitative material, this study will use a constant comparison approach, in which repeated comparing of the different individuals and groups allows parallel and contrasting themes to be identified and explored. The analysis will be mostly at a descriptive

thematic level but there is potential for greater depth, which will be decided iteratively dependent upon the data acquired, but will seek to provide explanatory information surrounding the challenges of the feasibility study. The team's previous experience of qualitative research in this area ensures knowledge of the existing literature which allows contextualisation of new findings.

Analysis of the qualitative data will take place simultaneous to the data collection phase to impact upon the performance of the study; informing approaches to recruitment and improving adherence. Regular consultation within the study team will allow for assessment of coding accuracy and for consideration of the future directions of the research.

- Sample size

We hope to enrol 10-20 patients. This is derived from the rate of enrolment we would expect to require to undertake a Phase 3 trial with 12-15 centres over a 2 year study period. A Phase 3 trial will require around 1000 patients to be randomised, so around 125 patients over 3 months. From this, in a single centre, we would aim to enrol 10-20 patients.

- Eligibility

Children aged birth to 18 years old who have cancer or a cancer-like condition and are currently undergoing treatment under the care of the paediatric oncology and haematology department at Leeds Teaching Hospitals, admitted to Leeds with febrile neutropenia.

(* Includes all patients who have received a stem cell transplant, who have Langerhans cell histiocytosis, severe aplastic anaemia or haemophagocytic lymphohistiocytosis and receive cytotoxic chemotherapy)

- Statistical methods

The analysis will be primarily descriptive and no formal statistical comparison is planned. The data will be summarised using standard methods: continuous data will summarised as mean or median as appropriate, and proportions for categorical variables.

Project planning, management and timelines

We anticipate the study to run over 9 months: the study will open to recruitment within 3 months of the grant award. This period will include finalising the study protocol, creation of patient-information and consent forms, obtaining research ethics committee and local approvals and opening the site. There will be a 4 month recruitment period with 1 month

lead-in time to full recruitment rate. The final 2 months are allocated for analysis of the data and initial dissemination of results. Some expenses may need to be deferred beyond this period, for example, the payment of an 'open access' charge to ensure the study information is available as widely as possible will only become payable on acceptance in an academic journal (often around 3 months following the initial submission of the paper).

Co-Investigator Roles

Bob Phillips is an Honorary Consultant in Paediatric Oncology and international research leader in supportive care interventions in children's cancer. He will be Chief Investigator and oversee the project, governance and data analysis.

Jess Morgan is a Clinical Lecturer / higher specialist trainee in paediatric oncology. She has extensive experience in mixed methods research, integrating qualitative and quantitative components. She has developed this project alongside Bob Phillips and lead the qualitative research.

Outputs and Outcomes

The study will produce a small 'proof of principle' cohort which will support or refute the practicality of using such an approach in a major randomised trial. It will begin to produce insights into the drivers which facilitate or barriers which stop participation, and the beliefs which affect choices to follow or deviate from the PCT-guided algorithm.

These will be measured in the production of a layered series of dissemination summaries; for young people and parents, clinical teams, and academic audiences. The work will feed into larger funding bids for a trial should it prove practical to undertake.

Capacity building and sustainability

The study supports the research team in submitting a bid to a major funder (suggested to be NIHR RfPB or HTA programmes), and promotes the Candlelighters plan of developing researchers who will undertake applicable, high quality, supportive care research. The undertaking of research will develop the ward staff further in undertaking research. The use of a QRI approach, integrating qualitative and quantitative data to understand study process barriers will be developmental and further improve the chances of success in later applications, and enhance the study team in applying this specific technique.

Justification of costs

(See appendix)

Procalcitonin tests; required to determine if effective in altering management on FN.

Encrypted digital recorder: the department doesn't yet own a secure digital recording device, and is essential for recording the consultations

Open Access Fee; this is to publish the results in an academic journal. Open access means the results of the study are available to anyone who wants to read it, and increases the transparency associated with the research.

Jess Morgan is zero costed as her research time is fully funded by the NIHR Clinical Lecturer role

Bob Phillips: one half-day per week (on average) to run the study, oversee governance and data quality, undertake analysis and lead the study write-up and dissemination.

Printing costs and 'panther' beads: These are to make sure the documentation is available and the participants have a 'bead of courage' to show they are part of the study.

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