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A study to compare antibiotics used to treat children with severe acute malnutrition

Submission date
04/05/2017

Recruitment status
No longer recruiting

Registration date
09/05/2017

Overall study status
Completed

Last Edited
23/05/2024

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Children with severe malnutrition who are admitted to hospitals have a high mortality (death rate), usually due to infection. All children with severe malnutrition admitted to hospitals are treated with antibiotics (medication used to kill bacteria). However, the current antibiotics used in hospitals may not be the most effective. It is possible that the antibiotics that are currently used after initial antibiotics should be used first. No studies have been carried out to determine if the current antibiotics used for treating malnourished children are the most appropriate. The aim of this study is to find out if a changed antibiotic system for children with malnutrition is safe, reduces the risk of death and improves nutritional recovery. The study also aims to find out how often children carry bacteria that are resistant to antibiotics in their intestines and the effects of different antibiotics on the ability for bacteria to resist antibiotic treatment and the costs to hospitals and to families of treating malnourished children with the different antibiotics.

Who can participate?
Children aged 2 months to 13 years old with severe malnutrition who are admitted to the hospital.

What does the study involve?
Participants are randomly allocated to receiving one of two intravenous (IV) antibiotic treatments and are randomised again to one of two oral antibiotic treatments. Those who are allocated to the first IV antibiotic treatment group receive ceftriaxone (80 mg/kg) once per day during their hospitalisation. Those in the second group receive the standard antibiotics. Those who are allocated to the first group oral antibiotic treatment group receive metronidazole (10 to 16 mg/kg taken by mouth) for seven days. Those in the second antibiotic treatment group receive a placebo (a dummy medication) which is taken by mouth for seven days. Participants provide blood and faecal samples before they take the antibiotics, while they are taking them and when they leave the hospital. They are followed up for 90 days with three follow up visits which include a health questionnaire, measurements and faecal samples. Parents and carers may be interviewed about the costs of their child's healthcare.

What are the possible benefits and risks of participating?
Participants may benefit from close observation, appropriate nutritional and clinical care.

Communities may benefit from the additional clinical care staff and the additional training about managing severely ill children, antimicrobial usage and infection control. Participants may benefit from the costs of care, consultant and investigation being covered by the study. There are risks with participating in this study. The medications provided have common side effects such as skin rashes, abdominal discomfort, and headache, loss of appetite, nausea and vomiting. There is a risk of drug allergies, therefore history of drug allergies are taken from participants. Participants may experience discomfort from blood tests and rectal swabbing.

Where is the study run from?
This study is being run by the KEMRI/Wellcome Trust Research Programme (Kenya) and takes place in three hospitals in Kenya and one in Uganda.

When is the study starting and how long is it expected to run for?
September 2013 to July 2020

Who is funding the study?
Global Health Trials Scheme [Department for International Development, Medical Research Council & Wellcome Trust] (UK)

Who is the main contact?
Professor James Berkley

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
KEMRI/SERU/CGMR-C/063/3399

Study information

Scientific Title
First Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

Acronym
FLACSAM

Study objectives
Mortality amongst children admitted to hospital with complicated severe acute malnutrition (SAM) is not altered by administration of intravenous ceftriaxone or metronidazole as first line agents compared to penicillin plus gentamicin.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. KEMRI Scientific Ethics Review Unit (SERU), 20/01/2017, ref: KEMRI/SERU/CGMR-C/0063/3399
2. Oxford Tropical Research Ethics Committee (OxTREC), Oxford: 06/02/2017, ref: OxTREC 1-17

Study design
Randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Invasive bacterial infection, Severe acute malnutrition

Interventions
This study is testing two interventions. Participants are randomised to receive either one of two intravenous antimicrobial treatment arms and then are randomised again to one of two oral antimicrobial treatment arms.

Intervention 1:
Participants are randomly allocated to one of two groups:
Arm 1 IV Ceftriaxone: Participants in this group receive 80mg/kg IV ceftriaxone once a day. IV ceftriaxone is given for a minimum of 48 hours and a usual maximum of seven days. If a child receiving IV ceftriaxone is feeding well and no longer has any signs of infection or complications after two days and before seven days, they are prescribed standard care for uncomplicated SAM with oral amoxicillin (40mg/kg every 12 hours) to complete a total of seven days of antibiotics, as per WHO guidance. If a participant has a specific and documented indication to continue ceftriaxone beyond seven days (e.g. proven bacterial meningitis), ceftriaxone is continued beyond those seven days.

Arm 2 IV Benzyl penicillin plus gentamicin (usual care): Participants in this group receive 50 000 U /kg IV benzyl penicillin every six hours. In the usual care arm, as per WHO guidelines, IV benzyl penicillin plus gentamicin is given for a minimum of two days and a maximum of seven days. If a child receiving IV penicillin and gentamicin is feeding well and no longer has any signs of infection or complications after two days and before seven days, they are prescribed standard care for uncomplicated severe acute malnutrition (SAM) with oral amoxicillin (40mg/kg every 12 hours) to complete a total of seven days of antibiotics, as per WHO guidance.

Participants in both treatment arms who are discharged before seven days are prescribed oral amoxicillin to take home to complete a total of seven days of antimicrobial therapy, as per WHO guidance. First line antimicrobial treatment in hospital may be changed on the basis of confirmed antimicrobial susceptibility results from an admission blood culture, this is recorded in the case report form (CRF), along with the reason. Children with specific and documented clinical indications for second or third line antimicrobials, deterioration after at least 48 hours may change antimicrobials for clinical care according to study standard operating procedures aimed at ensuring optimum care. This is recorded in the CRF, along with the reason.

Intervention 2:
Arm 1 Metronidazole: Participants receive 10 to 16 mg/kg oral metronidazole twice a day for seven days.
Arm 2 Placebo: Participants receive a placebo dose to match that for Metronidazole oral twice a day for seven days.

Any early discontinuation of metronidazole or placebo will be recorded in the CRF, along with the reason. Children discharged before seven days will be prescribed oral metronidazole or placebo to complete a total of seven days of therapy.

All participants provide a small volume of blood and a faecal sample in addition to the routine tests for care at admission before antibiotic administration, and again at discharge. Participants

are reviewed daily by the study team, working together with the hospital staff to provide the best care available in the hospital. Participants are followed up for 90 days from enrolment with three scheduled follow up visits which include a health questionnaire, measurements and the collection of a faecal sample at two of the visits. The levels of the antibiotics being used are checked in the blood of 120 participants at Kenyan sites whilst in hospital. Parents and carers of participants at each site may also be interviewed about any costs they have met as a result of the child needing healthcare. If a participant requires readmission to hospital, a small volume of blood is drawn to try and determine the cause. Results of blood tests will be fed back to the clinical team to assist in care. For non-severely malnourished children, a rectal swab will be taken at admission and discharge, and information collected during admission, but with no additional samples or further follow up.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Ceftriaxone, benzyl penicillin, gentamicin and metronidazole

Primary outcome measure
Mortality is measured using source documents from medical records, verbal autopsy, or death or burial certificates in the community from enrolment to 90 days after enrolment.

Secondary outcome measures
1. Grade 4 toxicity events are measured according to the Division of AIDS Tables for Grading the Severity of Adverse Events using medical records from enrolment to end of the study
2. Serious adverse events are measured using inpatient and outpatient medical records from enrolment to 90 days after enrolment
3. Mortality within the first 48 hours after enrolment, by day 7 and until discharge from the index hospitalisation, is measured using inpatient records from enrolment to discharge from hospital
4. Mortality occurring after discharge from the index hospital admission is measured using source documents from inpatient medical records, verbal autopsy, or death or burial certificates in the community from discharge to 90 days after enrolment
5. Causes of death, as determined by an endpoint review committee from enrolment to 90 days after enrolment
6. Re-admission to hospital defined as at least one overnight stay in a hospital or health facility are measured using inpatient records from discharge from the index admission to 90 days after enrolment
7. Causes of re-admission, as determined by the admitting study clinician from discharge from the index admission to 90 days after enrolment
8. Total duration of hospitalisation is measured in days using inpatient records at the start and end of each admission to hospital from enrolment to 90 days after enrolment
9. Total duration of administration of antibiotics in hospital is measured using inpatient records at the start and end of each admission to hospital from enrolment to 90 days after enrolment
10. Change in nutritional status is measured using mid-upper arm circumference, weight-for-length, weight-for-age and length-for-age at enrolment, 14, 45 and 90 days after enrolment
11. Aetiology of invasive infections are measured using microbial culture and sensitivity testing of blood, cerebrospinal fluid, urine or other sterile site samples taken for clinical investigation

from enrolment to 90 days after enrolment
12. Faecal carriage of bacteria expressing Extended Spectrum Lactamase (ESBL) is measured using microbial culture and sensitivity testing of rectal swabs taken at enrolment, discharge from the index admission, day 45 and day 90 after enrolment

Overall study start date
01/09/2013

Completion date
31/07/2020

Eligibility

Key inclusion criteria
1. Age 2 months to 13 years inclusive
2. Severe malnutrition defined as:
2.1. Kwashiorkor at any age
2.2. For children between 6 to 59 months: MUAC <11.5cm or weight-for length Z score <-3
2.3. For children aged 2 to 5 months: MUAC <11cm or weight-for length Z score <-3
2.4. For children aged 5 to 13 years: BMI-for-age Z score <-3 or MUAC <11.5cm
3. Admitted to hospital and eligible for intravenous antibiotics according to WHO guidelines
4. Planning to remain within the hospital catchment area and willing to come for specified visits during the 90 day follow up period
5. Informed consent provided by the parents/guardian

Participant type(s)
Patient

Age group
Child

Lower age limit
2 Months

Upper age limit
13 Years

Sex
Both

Target number of participants
2000

Total final enrolment
1872

Key exclusion criteria
1. Known allergy or contraindication to penicillin, gentamicin, ceftriaxone or metronidazole
2. A specific and documented clinical indication for another class of antibiotic
3. Previously enrolled in this study

Date of first enrolment
20/07/2017

Date of final enrolment
31/03/2020

Locations

Countries of recruitment
Kenya

Uganda

Study participating centre
KEMRI/Wellcome Trust Research Programme
Clinical Trials Facility
PO Box 230-80108
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Study participating centre
Mbale Clinical Research Institute
Mbale Regional Referral Hospital
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Study participating centre
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Sponsor type
University/education

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
Joint Global Health Trials Scheme of the Department for International Development (DFID)

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
30/09/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from: DGC@kemri-wellcome.org

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V1	12/01/2017	11/05/2017	No	Yes
Protocol file	version 1.04	20/03/2019	12/08/2022	No	No