Empirical oral AntibioticS for possible UTI in well appearing Young febrile infants (EASY Study)

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Study Background

- UTIs are the most common serious bacterial infection (SBI) observed in febrile infants (under 3 months of age), accounting for over 90% of all SBIs in this age group.

- In the EASY study we are investigating the use of oral antibiotics prior to the urine culture results are known for infants between 29 and 90 days of age. This may lead to earlier hospital discharge and management at home.

- The EASY study is a randomised controlled, open-label trial, to determine whether oral antibiotics are non-inferior to parenteral antibiotics for the management of suspected urinary tract infection (UTI) in low risk infants.

Trial Overview

Randomised, Non Inferiority Trial

584 participants

18 (minimum) Paediatric Emergency Departments (ED)

Recruitment May 2024

Aims and Objectives

To assess the clinical effectiveness and cost-consequence of early oral antibiotics in infants presenting to hospital with suspected UTI who appear well and are at low risk of complications.

- To determine if the clinical effectiveness of oral antibiotics pending urine culture results is non-inferior to parenteral antibiotics pending urine culture results in terms of treatment failure (i.e. the requirement for additional parenteral antibiotics) and a range of secondary outcomes.
- To evaluate the impact of oral antibiotics on healthcare resource use, costs and selected outcomes via a cost-consequence analysis.

Inclusion Criteria

- 29 to 90 days of age (infants from their 29th day of life to their 90th day of life inclusive. Day of birth is day 1 of life)
- Suspected urinary tract infection (UTI) requiring treatment with antibiotics
- History of fever as defined as temperature ≥38°C measured by any method OR likely fever in last 24 hours including subjective fever reported by caregiver
- Abnormal urinalysis defined as: (1) abnormal urinary dipstick test (leucocyte esterase ≥1+, or nitrite ≥Trace) OR (2) abnormal urine microscopy (≥5 white cells per high-power field in centrifuged urine or ≥10 white cells per mm3 in un-centrifuged urine or bacteriuria with any bacteria per high power field)
- Well on global clinical assessment using the paediatric assessment triangle assessed by a consultant grade doctor

Exclusion Criteria

- Born at <30 weeks gestation
- Discharged from hospital more than 7 days after birth
- Required re-admission to hospital after birth for more than 24 hours
- Known or suspected structural renal abnormality
- Evidence of sepsis and/or meningitis (appear unwell, shock, hypotension, altered mental state, bulging fontanelle, lumbar puncture suggestive of bacterial meningitis)
- Received vaccination within 48 hours of attendance
- Sodium < 128mmol/l on lab or blood gas sample
- Potassium > 6.5 mmol/l on lab sample
- Plasma creatinine > 50 micromol/l
- Inability to tolerate oral medication
- Urine sample was not sent for culture
- Received additional antibiotics (with the exception of the parenteral antibiotic administered within 24 hours of hospital attendance)
- Declined consent for participation

Study Intervention and Comparator

Eligible “low risk” participants will be randomised in a 1:1 ratio to one of two treatment groups.

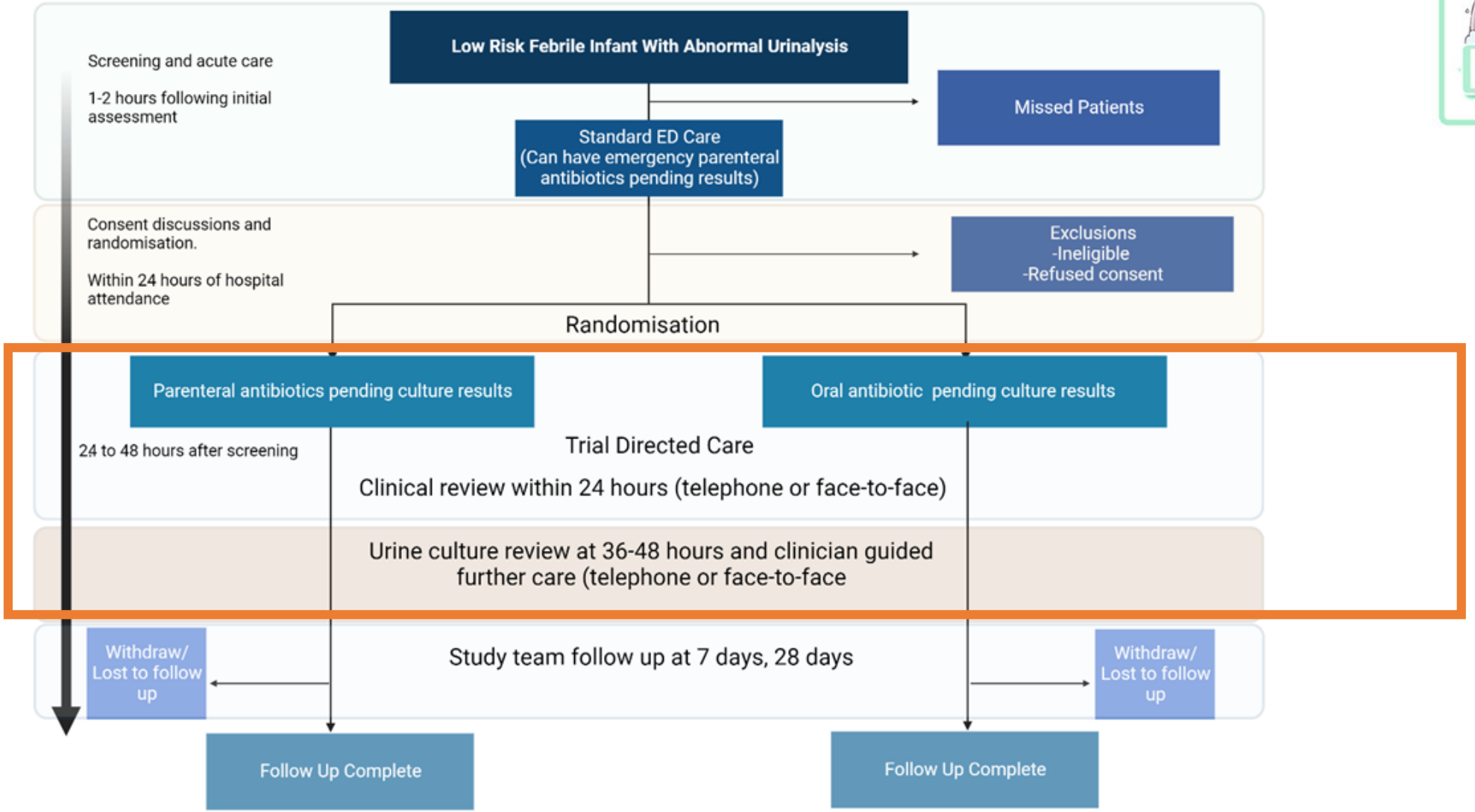
Randomisation must occur with 24 hours of hospital attendance.

Treatment Group	Treatment Description	Study IMP
Intervention	Oral antibiotics and continuation of oral treatment at least until urine culture results are known (typically after 36 to 48 hours).	Cefalexin Co-amoxiclav Trimethoprim
Comparator (standard care)	Continuation of parenteral antibiotics (standard care) at least until urine culture results are known (typically after 36 to 48 hours).	Ceftriaxone Cefotaxime Gentamicin Amoxicillin Cefuroxime Co-amoxiclav

IMP Administration

- Participant enrolment and treatment allocation to be recorded in clinical notes
- Parenteral and Oral antibiotics will be given as per locally determined scheduled prescription
- As in standard clinical practice, if the baby is sick within 30 minutes of administration of any doses of oral cephalexin, co-amoxiclav or trimethoprim, the dose should be repeated. If this occurs after 30 minutes, the dose should not be repeated and the oral antibiotic should be administered at the next scheduled dosing time. If the baby is sick within 30 minutes for 2 consecutive doses, the clinician should consider whether the oral antibiotic cannot be tolerated.

Trial Design



Clinical Reviews

- Within 24 hours of randomisation review clinical progress check symptoms and adherence to medication. If concerned then arrange face-to-face clinical review. Decisions to escalate care or discontinue antibiotics are at discretion of the clinical team.

- At 36 to 48 hours of randomisation review clinical progress check symptoms and adherence to medication. If concerned then arrange face-to-face clinical review. Decisions to escalate care or discontinue antibiotics are at discretion of the clinical team.

- Record review in the clinical record. It may be helpful to combine clinical review with research team review. Please consider informing research nurse (for example) prior to clinical review.

IMP Termination, Adherence and Concomitant Care

- Antibiotic treatment may be ended or switched based on clinical assessment during admission or at dedicated telephone reviews
- The study drug may also be terminated once urine culture results are known and if no longer clinically indicated.
- Study Drug Adherence
  - Full course taken or no more than two missed doses
  - Source document for IMP administration
    - Inpatient administration will be recorded in the hospital prescription chart.
    - Post discharge from hospital, parents/guardians will be verbally asked about adherence at the follow up time points (Participant Review Checklist).
- Paracetamol and ibuprofen can be administered as required to control the infants fever and its associated symptoms. These drugs, and any other prescription medications, will be recorded on the CRF

Pharmacovigilance

- AE reporting period for the trial begins upon consent and ends at day 28 (the last follow up assessment).
- The PI or designee should record all directly observed AEs and all AEs spontaneously reported by the parent/guardian. In addition, the parent/guardian will be asked about AEs as part of the follow up assessments to be completed.
- This paediatric population may experience a range of AEs such as common cold or other common childhood illnesses. Symptoms that are due to an alternative emergent condition do not need to be reported as AEs, unless the event is considered by the PI or designee to be associated with the study drug or unexpectedly severe or frequent.
  - *E.g. upper respiratory tract infection or other viral illness*
- Symptoms associated with UTI, will be captured as part of the **follow up assessments** and do not need to be reported as AEs:
  - *Fever, vomiting, and interference with normal activity*
- Events that are collected as **outcomes** for the EASY study do not need to be reported as AEs:
  - *Treatment failure, deterioration, hospital readmission and fever.*

Pharmacovigilance

- Laboratory confirmed invasive bacterial infections (IBI) including bacterial meningitis and symptomatic bacteraemia should be reported as AEs.
- Complications of peripheral venous access such as extravasation injury, tissued lines and line infections should be reported as AEs.
- All other events should be reported, including new onset of vomiting, diarrhoea, rashes or oral thrush (or a change in severity or frequency of these) which are common side effects of parenteral and oral antibiotics.

Study Team

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