**First Line Antimicrobials in Children with Complicated Severe Acute Malnutrition (FLACSAM)**


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**INTRODUCTION**

- Undernutrition causes 3.1 million deaths.
- SAM causes 0.1 million deaths.
- In Africa, between 15% and 18% of paediatric patients have SAM.
- Children with complicated SAM have a case mortality of between 12 to 20%.

**WHAT IS THE PROBLEM?**

- WHO guidelines for routine antibiotics are based on "low quality evidence".
- High inpatient and post-discharge mortality for SAM despite guidelines.
- Bacterial resistance to the currently recommended first-line antibiotics is an uncertain problem where lab facilities are lacking.
- Some hospitals in Africa are already increasing use of ceftriaxone as a first-line treatment. This is not based on any data that ceftriaxone actually improves outcomes.
- Ceftriaxone use may also lead to increased antimicrobial resistance, including extended spectrum beta lactamase (ESBL) and other classes of resistance.
- No data on efficacy of metronidazole on nutritional recovery.
- Concerns over pharmacokinetics for both drugs in malnourished children. A pharmacokinetic study in 80 malnourished children who received ceftriaxone and metronidazole has recently been concluded.

**CURRENT WHO GUIDELINES FOR SAM**

- If there are complications (hypoglycaemia, hypothermia or the child weak, shallow breathing or crying), give parenteral antibiotics.
  - Intramuscular (IM) 100 mg/kg (IM) every 6 to 12 hours or intravenous (IV) every 6 to 12 hours for 2 days, then oral amoxicillin (25–40 mg/kg every 8 to 12 hours) plus:
    - Gentamicin (7.5 mg/kg IM or IV) once a day for 7 days.
- For enrolment include the completed blood results as follows:
  - Note: Metronidazole 20 mg/kg every 8 h for 3 days may be given in addition to intravenous ceftriaxone in hospitalisations where the drug is available; the efficacy of this treatment has not been established in clinical trials.

**PHARMACOKINETICS**

- Time to peak: Ceftriaxone: 1 h; Metronidazole: 2 h
- Area under the curve: Ceftriaxone: 4000; Metronidazole: 2000
- Half-life: Ceftriaxone: 10 h; Metronidazole: 2000

**RANDOMISED CLINICAL TRIAL**

**Phase 1 (2016)**

- Pharmacokinetics of ceftriaxone & metronidazole
- Faecal carriage of ESBL at admission & discharge
- SAM & non-SAM at 3 hospitals

**Phase 2 (2017-)**

- 2x2 factorial trial: mortality & growth
- Trial participants: 2000 children
- 4 study hospitals: KEMRI, Mombasa, Nairobi and Mbuale (in Uganda)
- 2 treatment interventions:
  - PenGent vs Ceftriaxone
  - Metronidazole vs Placebo
- Sub-studies:
  - Economics: costs, cost effectiveness and costs relating to antimicrobial resistance (AMR)
  - Faecal carriage of ESBL, including non-SAM
  - Further PK work

**Inclusion criteria – clinical trial participants (SAM)**

- Age 2 months to 15 years inclusive
- Severe malnutrition defined as:
  - Kwashiorkor at any age; or
  - for children between 6 to 59 months: MUAC <11.5 cm or weight for length Z score <−3
  - for children aged 2 to 5 months: MUAC <11cm or weight for length Z score <−3
  - for children aged 5 to 13 years: BMI for age-2 z score <−3 or MUAC <11.5cm
- Admitted to hospital and eligible for intravenous antibiotics according to WHO guidelines
- Planning to remain within the hospital catchment area and willing to come for specified visits during the 90 day follow up period
- Informed consent provided by the parents/guardian

**Exclusion criteria – clinical trial participants (SAM)**

- Known allergy or contraindication to penicillin, gentamicin, ceftriaxone or metronidazole
- A specific and documented clinical indication for another class of antibiotic
- Previously enrolled in this study

**FLACSAM Trial Schedule**

- Screening at admission to hospital, information & consent
- Study drug
- Discharge
- Follow up

**FLACSAM Trial Schedule**

- 0% None
- 25% Ak Risk
- 20% Moderate
- 15% Severe
- 10% Kwashiorkor

- Inpatient Case Fatality by Nutritional Status

- Coast General Hospital

- 6 mini
- 26
- 50 min
- 26
- 60 min
- 29
- 2h
- 28
- 2h 24
- 2h 27
- 24h
- 28
- 24h 26
- 24h 29
- 72h
- 28

**CONTACTS**

**FLACSAM Trial Group**


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**METRONIDAZOLE:** 7.5 mg/kg/ds is slow to reach therapeutic levels; td dosing (10-15 mg/kg) is better

**METRONIDAZOLE:** 50 mg/kg/d is too low for malnourished children; 80 mg/kg od is better

**CEFTRIAXONE:** Target ~90% of patients to spend >50% time with levels above 1 to 2 mg/L

**CEFTRIAXONE:** Target ~90% of patients to have an AUC above 70xh on an MIC of ~4 to 8 mg/L