FLACSAM
First Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

Prof. James A Berkley
Inpatient Case Fatality - Pneumonia

MUAC

- >13.5
- 12.5-13.5
- 11.5-12.5
- <11.5
Pneumonia admissions: mortality after discharge
Current WHO guideline for inpatient SAM

- benzylpenicillin (50 000 U/kg IM or IV every 6 h) or ampicillin (50 mg/kg IM or IV every 6 h) for 2 days, then oral amoxicillin (25–40 mg/kg every 8 h for 5 days)
  
  plus
  
  - gentamicin (7.5 mg/kg IM or IV) once a day for 7 days.

These regimens should be adapted to local resistance patterns.

**Note:** Metronidazole 7.5 mg/kg every 8 h for 7 days may be given in addition to broad-spectrum antibiotics; however, the efficacy of this treatment has not been established in clinical trials.
What is the problem?

• High inpatient and post-discharge mortality for SAM despite guidelines
• Deaths apparently from pneumonia, diarrhoea, sepsis
• Apparently better *in vitro* sensitivity to Ceftriaxone than Amp/Gent or Pen/Gent
• Uncontrolled studies suggest improved nutritional recovery with Metronidazole

• Empiric ceftriaxone usage may select resistance without evidence of benefit
• No data on efficacy of metronidazole on nutritional recovery
• Concerns over PK for both drugs in SAM
• Stage 1 (2016-2017)
  • PK ceftriaxone & metronidazole
  • Faecal carriage of ESBL in SAM/non-SAM

• Stage 2 (2017-2019)
  • 2x2 factorial trial → mortality
    • Pen/Gent vs Ceftriaxone
    • Metronidazole vs Placebo
PK in malnutrition

- Malabsorption?
- Reduced plasma proteins – affects drugs that bind?
- Altered volume of distribution – water/fat/muscle?
- Altered hepatic metabolism?
- Altered renal elimination?
PK for Cef & Met

• Ceftriaxone
  • >80% protein bound
  • Renal clearance of unbound fraction
  • Low plasma protein may → more rapid elimination?
  • PK not done in children with malnutrition

• Metronidazole
  • Very highly absorbed in healthy individuals
  • Hepatic metabolism
  • One small study - prolonged elimination in malnutrition?
The diagram illustrates the pharmacokinetics of a drug, focusing on the Absorption Phase and the Elimination Phase. The Absorption Phase is characterized by the peak concentration ($C_{max}$) and the time at which this peak occurs ($t_{max}$). The Elimination Phase is marked by the half-life ($T_{1/2}$) and the area under the curve (AUC).

The AUC is calculated using the integral $AUC = \int_0^\infty Cdt$. The time horizon for the calculation of $AUC$ is from $t$ to $t+\tau$ for the portion of the curve highlighted in blue.

The graph also shows the relationship between the concentration ($C$) and time ($t$), with specific time points indicated for $t_{max}$, $t_{1/2}$, and $\tau$. The concentration values are given in micrograms per milliliter (ug/mL).
PK N=81

<table>
<thead>
<tr>
<th>Time points</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>26</td>
</tr>
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<td>30 min</td>
<td>26</td>
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<tr>
<td>60 min</td>
<td>29</td>
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<td>2h</td>
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<td>4h</td>
<td>24</td>
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<td>8h</td>
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<td>24h</td>
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<tr>
<td>48h</td>
<td>29</td>
</tr>
<tr>
<td>72h</td>
<td>28</td>
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<table>
<thead>
<tr>
<th>Hospital</th>
<th>N</th>
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<tbody>
<tr>
<td>Kilifi County Hospital</td>
<td>28</td>
</tr>
<tr>
<td>Coast General Hospital</td>
<td>25</td>
</tr>
<tr>
<td>Mbagathi Hospital</td>
<td>28</td>
</tr>
</tbody>
</table>
Analysis

• Ceftriaxone
  • Total
  • Free drug

• Metronidazole
  • Total Metronidazole
  • Hydroxy-Metronidazole

• Biochemistry
Ceftriaxone dosage considerations

- 50 mg/kg once daily is too low

- 80 mg/kg once daily (or 50 mg/kg twice daily) are acceptable

- Trial: use WHO dosage of 80mg/kg od
  - Can be increased to 50mg/kg bd if meningitis is subsequently diagnosed
Metronidazole dosage considerations

• Balance efficacy and side effects
• 7.5 mg/kg three times daily takes too long to reach therapeutic levels
• 10 to 15mg/kg twice daily is better, no evidence of accumulation
• Twice daily easier to coordinate on the wards, and parents at home
• Gut concentrations?
• Stage 1 (2016-2017)
  • PK ceftriaxone & metronidazole
  • Faecal carriage of ESBL in SAM/non-SAM

• Stage 2 (2017-2019)
  • 2x2 factorial randomised clinical trial → mortality
    - Pen/Gent vs Ceftriaxone
    - Metronidazole vs Placebo
Factorial Trial

Screening & enrolment

R1: ARM A
R1: ARM B
R1: ARM A
R2: ARM A
R2: ARM A
R2: ARM B
R2: ARM B
R2: ARM B
Factorial Trial

Analysis

- Randomisation 1: A vs B
- Randomisation 2: A vs B

• Does the effect of one randomisation modify the effect of the other?
FLACSAM eligibility

- SAM
- Age 2 months or more
- Requires IV antibiotics according to guidelines
- No documented indication for a different antibiotic
- No documented allergy to study drugs
- Remaining in the area
- Informed consent
FLACSAM
First Line Antimicrobials in Children with Complicated Severe Acute Malnutrition

N=2000
FLACSAM Schedule

Screening at admission to hospital, information & consent

- Study drugs
- Follow up
- Discharge

- d7
- d14
- d45
- d90
ENDPOINTS

• Mortality to 90 days
  • Inpatient, post-discharge
  • Causes

• Grade 4 toxicity

• Readmission & causes

• Growth to 90 days
• Duration of index admission
• Antibiotic usage, days on 1\textsuperscript{st}, 2\textsuperscript{nd} & 3\textsuperscript{rd} line antimicrobials
Sub-studies

• Antimicrobial susceptibility of invasive infections
  • Blood culture at enrolment, deterioration or re-admission

• Faecal carriage of antimicrobial resistance
  • Rectal swabs at admission, discharge and follow up
  • Non-SAM admissions parallel cohort

• Economics
  • Costs to health services and to families
  • Cost/benefit
  • Costs of antimicrobial resistance
<table>
<thead>
<tr>
<th>Date of Enrolment</th>
<th><em><strong>/</strong></em>/___</th>
<th>Complete this record every day during the child's index admission, circle responses</th>
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<tbody>
<tr>
<td><strong>Month ___ ___ Date</strong></td>
<td>___</td>
<td>___</td>
</tr>
<tr>
<td><strong>Seen in morning or afternoon?</strong></td>
<td>am pm</td>
<td>am pm</td>
</tr>
<tr>
<td><strong>Oedema now?</strong></td>
<td>+++ ++ + N</td>
<td>+++ ++ + N</td>
</tr>
<tr>
<td><strong>Oedema improving?</strong></td>
<td>Y N</td>
<td>Y N</td>
</tr>
<tr>
<td><strong>Respiratory distress in last 24h</strong></td>
<td>Y N</td>
<td>Y N</td>
</tr>
<tr>
<td><strong>Cyanosis/ SaO₂ &lt;90% in last 24h</strong></td>
<td>Y N</td>
<td>Y N</td>
</tr>
<tr>
<td><em><em>Shock</em> in last 24h</em>*</td>
<td>Y N</td>
<td>Y N</td>
</tr>
<tr>
<td><em><em>Severe anaemia</em> in last 24h</em>*</td>
<td>Y N</td>
<td>Y N</td>
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<tr>
<td><strong>Convulsion(s) in last 24h</strong></td>
<td>Y N</td>
<td>Y N</td>
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<tr>
<td><strong>Severe Dehydration in last 24h</strong></td>
<td>Y N</td>
<td>Y N</td>
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<tr>
<td><strong>Profuse watery Diarrhoea in last 24h</strong></td>
<td>Y N</td>
<td>Y N</td>
</tr>
<tr>
<td><strong>STUDY-RELATED ANTIMICROBIALS IN LAST 24H (NUMBER OF DOSES)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Penicillin doses</strong></td>
<td>4 3 2 1 0</td>
<td>4 3 2 1 0</td>
</tr>
<tr>
<td><strong>Gentamicin doses</strong></td>
<td>1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0</td>
<td></td>
</tr>
<tr>
<td><strong>Ceftriaxone doses</strong></td>
<td>1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0</td>
<td></td>
</tr>
<tr>
<td><strong>Metronidazole/Placebo doses</strong></td>
<td>3 2 1 0</td>
<td>3 2 1 0</td>
</tr>
<tr>
<td><strong>OTHER IV ANTIMICROBIALS IN LAST 24H</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ampicillin</strong></td>
<td>☐</td>
<td>☐</td>
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<tr>
<td><strong>Amikacin</strong></td>
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<td>☐</td>
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<tr>
<td><strong>Ciprofloxacin</strong></td>
<td>☐</td>
<td>☐</td>
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<tr>
<td><strong>(e.g. augmentin) Co-Amoxiclav</strong></td>
<td>☐</td>
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</tr>
<tr>
<td><strong>Chloramphenicol</strong></td>
<td>☐</td>
<td>☐</td>
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<tr>
<td><strong>Cefotaxime</strong></td>
<td>☐</td>
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<tr>
<td><strong>Ceftazidime</strong></td>
<td>☐</td>
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</tr>
<tr>
<td><strong>Flucloxacillin/Cloxacillin</strong></td>
<td>☐</td>
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<tr>
<td><strong>Meropenem/Imipenem</strong></td>
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KEMRI Centre for Microbiology Research, Nairobi, Kenya: Samuel Kariuki, Gerrishom Angote, Joyce Mukami

creates, Strathmore University, Nairobi, Kenya: Martin Ongas, Bernhards Ogutu

coast General, hospital, Mombasa: Victor Bandika, Jones M Obonyo,

Mbagathi sub-county hospital, Nairobi, Kenya: Christine Manyasi, Pauline Nkirote, Paul Otiku, Faith Waitiri

Mbale Regional Referral Hospital, Uganda: Peter Olupot-Olupot

University College London, UK: Joseph Standing

St George’s Hospital & Analytical Services International Ltd. UK: Karin Kipper

London School of Hygiene & Tropical Medicine: Anna Vassal, Gabriella Gomez