Antibiotics in severely malnourished children: systematic review of efficacy, safety and pharmacokinetics

Marzia Lazzarini & David Tickell

Objective To systemically review the evidence in support of World Health Organization guidelines recommending broad-spectrum antibiotics for children with severe acute malnutrition (SAM).

Methods CENTRAL, MEDLINE, EMBASE, LILACS, POPLINE, CAB Abstracts and ongoing trials registers were searched. Experts were contacted. Conference proceedings and reference lists were manually searched. All study types, except single case reports, were included.

Findings Two randomized controlled trials (RCTs), one before-and-after study and two retrospective reports on clinical efficacy and safety were retrieved, together with 18 pharmacokinetic studies. Trial quality was generally poor and results could not be pooled due to heterogeneity. Oral amoxicillin for 5 days was as effective as intramuscular ceftriaxone for 2 days (1 RCT). For uncomplicated SAM, amoxicillin showed no benefit over placebo (1 retrospective study). The introduction of a standardized regimen using ampicillin and gentamicin significantly reduced mortality in hospitalized children (odds ratio, OR: 4.0; 95% confidence interval, CI: 1.7–9.8; 1 before-and-after study). Oral chloramphenicol was as effective as trimethoprim-sulfamethoxazole in children with pneumonia (1 RCT). Pharmacokinetic data suggest that normal doses of penicillins, cotrimoxazole and gentamicin are safe in malnourished children, while the dose or frequency of chloramphenicol requires adjustment. Existing evidence is not strong enough to further clarify recommendations for antibiotic treatment in children with SAM.

Conclusion Large RCTs are needed to define optimal antibiotic treatment in children with SAM with and without complications. Further research into gentamicin and chloramphenicol toxicity and into the pharmacokinetics of ceftriaxone and ciprofloxacin is also required.

Introduction

Malnutrition is a major health problem in low- and middle-income countries, particularly in children less than 5 years of age. Recent estimates suggest that 3.5% of children worldwide, or nearly 20 million, are severely malnourished.1 Severe acute malnutrition (SAM), characterized by a weight of less than 70% of the median weight for height and/or bipedal oedema, is a life-threatening condition.2 In the absence of appropriate treatment, case-fatality rates in hospitalized children range from 30% to 50%.1,4

In 1999 the World Health Organization (WHO) published Management of severe malnutrition: a manual for physicians and other senior health workers5 to update its 1981 guidelines. A chapter on SAM is also included in the 1995 WHO Pocketbook of hospital care for children.6 Both guidelines focus on hospitalized children. Given recent advances with ready-to-use therapeutic foods, WHO, the United Nations Children’s Fund, the United Nations World Food Programme and the United Nations Standing Committee on Nutrition released a 2007 statement supporting the community treatment of severe malnutrition. The statement focuses on the outpatient management of children with SAM and no medical complications.5 Uncomplicated SAM is defined as a weight of greater than 60% of the median weight for height without marasmic kwashiorkor or severe pitting oedema in children older than 6 months, and without anorexia, fever, hypothermia, vomiting, severe dehydration, severe anaemia, altered consciousness, altered respiration or moderate to severe skin infections.

Since their publication, the WHO guidelines for the hospital treatment of children with SAM have been implemented in many countries worldwide. A recent systematic review highlighted that their implementation has resulted in half of the in-hospital mortality observed with conventional treatment.7

Despite these guidelines, SAM-related mortality remains high in many settings primarily because of operational hindrances to correct guideline implementation8 and because the affected population has changed as a result of the epidemic of human immunodeficiency virus (HIV) in many countries. A recent systematic review of 17 studies (4891 children) reported that, despite treatment for malnutrition, malnourished children who are HIV-positive (HIV+) are significantly more likely to die than malnourished children who are HIV-negative (HIV−) (30.4% versus 8.4%, respectively; P < 0.001; relative risk, RR: 2.81).6 Other factors, such as changing patterns of susceptibility to antibiotics, may also explain the reduced effectiveness of the guidelines in some contexts.

The WHO guidelines for the hospital treatment of children with SAM include a sequence of 10 fundamental steps. We focus this review on WHO’s recommendations for antibiotic treatment (Box 1).2,3

Rationale for antibiotics in severely malnourished children

Several epidemiological studies have documented a high prevalence of pneumonia, bacteraemia and urinary tract infections in children with malnutrition (Table 1).9–23 In this cohort a wide range of both Gram-positive and Gram-negative organisms are

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**Box 1.** Recommendations for antibiotic treatment of children with SAM. 8–9, 11–12

**Step 1.** Treat with amoxicillin for 5 days in children with: pneumonia, bacteraemia, conjunctivitis, gastrointestinal tract infections or para-pneumonic effusion.

**Step 2.** If the child has a focus for infection, consider antibiotics for: meningitis, septicaemia, or urinary tract infections.

**Step 3.** For in-hospital mortality observed with conventional treatment.

**Step 4.** The role of antibiotics in severe acute malnutrition (SAM).

**Step 5.** The importance of screening for HIV in children with SAM.

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**Table 1.** Prevalence of antibiotic-resistant bacteria in children with malnutrition.9–23

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>methicillin-resistant</td>
<td>30–60%</td>
</tr>
<tr>
<td>ampicillin-resistant</td>
<td>10–30%</td>
</tr>
<tr>
<td>ceftriaxone-resistant</td>
<td>0–10%</td>
</tr>
</tbody>
</table>

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frequently isolated,2–23 which supports the recommendation of a broad spectrum antibiotic for these children.2,3

Pathogen prevalence and the risk of infection in children with uncomplicated SAM treated in the community is still not clear. It is also uncertain whether infection rates and types are different in HIV+ and HIV– children.10–13

Patterns of susceptibility to antibiotics vary between countries, although high rates of in vitro resistance to ampicillin and cotrimoxazole, as reported in several African countries, are causing general concern.10–15 High rates of resistance to second-line antibiotics such as chloramphenicol, gentamicin and cephalosporins have also been reported in selected contexts.12–15 While in general, sensitivity to ciprofloxacin remains high (Table 1).2–23 In vitro resistance, however, does not necessarily translate into lack of clinical efficacy.

The objective of this review is to examine studies evaluating the efficacy, safety and pharmacokinetics (PK) of antibiotics in children with severe acute malnutrition (SAM). This review was commissioned by WHO’s Department of Essential Medicines and Pharmaceutical Policies to assess the existing evidence behind current WHO antibiotic recommendations for the management of SAM, allowing further revision of guidelines and recommendations for future research. To our knowledge, no other systematic reviews addressing this specific question have been published.

Methods

Two authors independently reviewed data on pharmacokinetics and clinical efficacy and safety. Both authors collaborated on and cross-checked extracted data, analysis of results and final recommendations.

We wrote a protocol of our methods that was externally reviewed before we searched and summarized the data. Our inclusion criteria were as follows: (i) any study type that reported patient outcomes except single case reports; (ii) for clinical studies, only children under 12 years of age, and for pharmacokinetic studies, adults as well; (iii) as antibiotics, amoxicillin, ampicillin, cotrimoxazole, gentamicin, penicillin G, chloramphenicol, ceftriaxone and ciprofloxacin; as a control in controlled trials, placebo or active treatment; as predefined outcomes, death, recovery, weight gain, prevention of septicaemia and adverse events.

We searched CENTRAL, MEDLINE, EMBASE, LILACS, POPLINE and CAB Abstracts to retrieve relevant studies published between 1951 and September 2010 regardless of language, publication status or study type (Box 2). For ongoing trials, we also accessed the WHO International Clinical Trials Registry Platform, metaRegister of Current Controlled Trials, Clinical trial.gov, the European register of clinical trials on medicines for children and the Lancet’s list of accepted protocols. We contacted experts in the field and manually searched presentations from relevant conferences, reports and the reference lists of the studies identified. We used standard textbooks as references for pharmacokinetic data in eutrophic children.24–25

### Data collection and analysis

We scrutinized every paper to avoid duplication and accessed the full text of all potentially relevant trials. To extract the data we used a predefined form. Study heterogeneity in intervention population and design prevented us from pooling the results. These are shown in tables and in the text. We used Cochrane criteria to assess the risk of bias (quality) in the clinical studies.

### Results

Study selection is reported in Fig. 1. Although we found 2100 studies in broad sensitive searches, only 23 were suitable for inclusion. Studies were excluded because either they lacked relevance to the question, were duplicated, were case reports or animal studies, studied inappropriate populations or had a poor trial design. Table 2 shows the characteristics of clinical studies and the overall risk of bias in each study.21,26–29 Characteristics of pharmacokinetic studies are detailed in Table 3, Table 4 and Table 5.30–48 All included studies refer to children with SAM unless otherwise stated.

#### Amoxicillin

**Clinical safety and efficacy**

Two studies were retrieved: one was a randomized controlled trial (RCT) and the other a retrospective study (n = 458 and n = 2453, respectively). In the RCT, no significant differences in any of the efficacy outcomes were found in children with SAM who received oral amoxicillin for 5 days versus intramuscular ceftriaxone for 2 days. Adverse events were more frequent in the amoxicillin group (eight drug reactions versus two; P = 0.05). No local infections or pain after intramuscular ceftriaxone injection were observed. The costs of treating one child weighing 10 kg were 1.60 United States dollars (US$) for ceftriaxone versus US$ 0.20 for amoxicillin.37

In the retrospective study, which compared oral amoxicillin for 7 days to no antibiotics, children with uncomplicated SAM who received amoxicillin had a lower recovery rate (39.8%) than untreated children (70.8%) (P < 0.001) at 4 weeks but a similar rate of recovery at 12 weeks, and similar rates of death and default.36

One ongoing RCT is exploring the efficacy of amoxicillin versus cefdinir versus no treatment in children with...
### Incidence of bacterial infections in children with severe acute malnutrition

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>No. of children (% HIV+)</th>
<th>Grade of malnutrition</th>
<th>Bacteraemia (%)</th>
<th>LRTI (%)</th>
<th>UTI (%)</th>
<th>Isolated bacteria</th>
<th>Antibiotic resistance in vitro&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>United Republic of Tanzania</td>
<td>781 (19)</td>
<td>Severe</td>
<td>3</td>
<td>17</td>
<td>8</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Kenya</td>
<td>340 (9)</td>
<td>Severe</td>
<td>5</td>
<td>7</td>
<td>–</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Uganda</td>
<td>450 (36)</td>
<td>Severe</td>
<td>17</td>
<td>–</td>
<td>–</td>
<td>Salmonella typhimurium, Staphylococcus aureus, Salmonella enteritidis, Streptococcus pneumoniae</td>
<td>+++  ++  ++</td>
</tr>
<tr>
<td>2006</td>
<td>Uganda</td>
<td>315 (39)</td>
<td>Severe</td>
<td>18</td>
<td>68</td>
<td>26</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Uganda</td>
<td>134 (44)</td>
<td>Severe</td>
<td>22</td>
<td>–</td>
<td>–</td>
<td>Salmonella spp, Escherichia coli</td>
<td>+++  +++  ++  ++</td>
</tr>
<tr>
<td>2005</td>
<td>Kenya</td>
<td>91 (43)</td>
<td>Severe</td>
<td>29</td>
<td>–</td>
<td>–</td>
<td>Coagulase-negative staphylococci</td>
<td>++  ++  ++  ++</td>
</tr>
<tr>
<td>2002</td>
<td>Nigeria</td>
<td>194 (NR)</td>
<td>Severe</td>
<td>–</td>
<td>–</td>
<td>11.3</td>
<td>Escherichia coli, Klebsiella spp, Pseudomonas spp</td>
<td>+++  +++  +  ++/+++</td>
</tr>
<tr>
<td>2001</td>
<td>Congo</td>
<td>Unclear</td>
<td>Severe</td>
<td>13.2</td>
<td>–</td>
<td>–</td>
<td>Enterobacteriaceae</td>
<td>++  ++  ++</td>
</tr>
<tr>
<td>2001</td>
<td>Jamaica</td>
<td>150 (NR)</td>
<td>Mod-severe</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>Coagulase-negative staphylococci</td>
<td>+  +  +</td>
</tr>
<tr>
<td>2000</td>
<td>Malawi</td>
<td>75 (25)</td>
<td>Severe</td>
<td>9</td>
<td>–</td>
<td>17</td>
<td>Streptococcus pneumoniae, Klebsiella spp, Escherichia coli</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Turkey</td>
<td>103 (NR)</td>
<td>All</td>
<td>–</td>
<td>–</td>
<td>31</td>
<td>Escherichia coli, Klebsiella spp, Proteus spp</td>
<td>+++  +  +</td>
</tr>
<tr>
<td>1996</td>
<td>South Africa</td>
<td>323 (NR)</td>
<td>Severe</td>
<td>9.6</td>
<td>–</td>
<td>–</td>
<td>Gram-negative enteric bacilli</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>South Africa</td>
<td>134 (NR)</td>
<td>Severe</td>
<td>–</td>
<td>–</td>
<td>26</td>
<td>Gram-negative enteric bacilli</td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>Gambia</td>
<td>378 (NR)</td>
<td>All</td>
<td>–</td>
<td>28</td>
<td>–</td>
<td>Streptococcus pneumoniae, Haemophilus spp</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>South Africa</td>
<td>134 (NR)</td>
<td>NR</td>
<td>–</td>
<td>–</td>
<td>26</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>United Republic of Tanzania</td>
<td>164 (NR)</td>
<td>Severe</td>
<td>Infections at admission: 92%</td>
<td>Staphylococcus aureus, Escherichia coli, Klebsiella spp, Enterococcus faecalis, Escherichia coli</td>
<td>+++  ++  ++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> + > 20%; ++ > 50%; +++ > 75%.

<sup>b</sup> Children with pneumonia.

Amp, ampicillin; CAF, chloramphenicol; Ceph, cephalosporin (cefotaxime, cefotaxime, ceftriaxone); Cipro, ciprofloxacin; Clavul, amoxicillin and clavulanic acid; Genta, gentamicin; LRTI, lower respiratory tract infection; NR, not reported; spp., species; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.
Systematic reviews
Antibiotics in severely malnourished children
Marzia Lazzerini & David Tickell

uncomplicated SAM (Trial identifier NCT01000298).

**Pharmacokinetics**
Three small studies reported on the pharmacokinetics of oral penicillins (Table 3). The oral bioavailability of penicillin V was the same regardless of nutritional status, although it was significantly reduced when the drug was taken with food. Time to maximum concentration ($C_{max}$) of amoxicillin was significantly longer in children with kwashiorkor and time to $C_{max}$ of penicillin V was longer, though not significantly, in all malnourished groups. However, all malnourished subjects attained high enough serum levels for clinical effect to

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three small studies reported on the pharmacokinetics of oral penicillins.</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
</tr>
<tr>
<td>Three small studies reported on the pharmacokinetics of oral penicillins.</td>
</tr>
<tr>
<td><strong>Table 3</strong></td>
</tr>
<tr>
<td>Three small studies reported on the pharmacokinetics of oral penicillins.</td>
</tr>
</tbody>
</table>

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**Box 2. Search strategy for databases of published studies on the use of antibiotics in children with severe acute malnutrition**

Search strategy* for MEDLINE, adapted for other searches
- Amoxicillin OR ampicillin OR penicillin OR procaine penicillin
- AMOXICILLIN+ OR AMOXICILLIN-POTASSIUM CLAVULANATE COMBINATION OR AMPICILLIN+ OR PENICILLINS+ OR PENICILLIN G+ OR PENICILLIN G, PROCaine
- Gentamicin OR aminoglycoside OR GENTAMICIN+
- Cotrimoxazole OR sulfamethoxazole OR sulfamethoxazole OR trimethoprim OR TRIMETHOPRIM-SULFAMETHOXAZOLE COMBINATION
- Ceftriaxone OR cephalosporin OR CEFTRIAXONE+
- Ciprofloxacin OR quinolone OR fluoroquinolone OR CIPROFLOXACIN+
- Chloramphenicol OR CHLORAMPHENICOL+
- OR/1–7
- Malnutrition OR malnourished OR underweight OR kwashiorkor OR marasmus
- MALNUTRITION OR PROTEIN-ENERGY MALNUTRITION OR CHILD NUTRITION DISORDERS OR INFANT NUTRITION DISORDERS
- OR/9–10
- Pharmacokinetic OR action OR effect OR absorption OR distribution OR clearance OR metabolism
- PHARMACOKINETICS+
- OR/12–13
- 8 AND 11
- 8 AND 11 AND 14 (for pharmacokinetic studies)
- Limit 15 to human (for clinical safety and efficacy trials)

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**Fig. 1. Flowcharts for bibliographic search of studies on the use of antibiotics in children with severe acute malnutrition**

**Clinical and efficacy studies retrieved in electronic databases and ongoing trials:**
- Total retrieved studies: 474
- Included studies: 2 RCTs
  1 before-and-after trial
  2 retrospective reports
- Excluded studies: 469

**Pharmacokinetic studies retrieved in electronic databases and ongoing trials:**
- Total retrieved studies: 2059
- Included studies: 18
- Excluded studies: 2041

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**Additional studies:**
- Writing to experts: 5
- Manual search: 0
- Reference: 5

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**References:**
1. Cox M. et al. (2010) The oral bioavailability of penicillin V was the same regardless of nutritional status, although it was significantly reduced when the drug was taken with food. Time to maximum concentration ($C_{max}$) of amoxicillin was significantly longer in children with kwashiorkor and time to $C_{max}$ of penicillin V was longer, though not significantly, in all malnourished groups. However, all malnourished subjects attained high enough serum levels for clinical effect to
### Table 2. Studies on efficacy and safety of antibiotics in children with severe acute malnutrition

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design (Risk of bias)</th>
<th>Population</th>
<th>Intervention groups</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trehan et al. 2010</td>
<td>Retrospective (high)</td>
<td>(n = 2,453)</td>
<td>1. Amoxicillin 60 mg/kg/day, 7 days</td>
<td>Recovered at 4 weeks: 198 (39.8%), Died at 4 weeks: 10 (2%)</td>
</tr>
<tr>
<td></td>
<td>Setting: Malawi</td>
<td></td>
<td>2. Nothing</td>
<td>135 (70.8%), 26 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Years: 2003–2005</td>
<td></td>
<td></td>
<td>1,673 (85.6%), 39 (7.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>182 (9.3)</td>
</tr>
<tr>
<td>Dubray et al. 2008</td>
<td>RCT (low)</td>
<td>(n = 458)</td>
<td>1. Ceftriaxone 75 mg/kg once daily IM, 2 days</td>
<td>Recovered at 4 weeks: 123 (53.5%), Died: 9 (3.9)</td>
</tr>
<tr>
<td></td>
<td>Setting: Sudan</td>
<td></td>
<td>2. Amoxicillin 40 mg/kg twice daily oral, 5 days</td>
<td>127 (55.7), 43 (18.9)</td>
</tr>
<tr>
<td></td>
<td>Years: 2002–2003</td>
<td></td>
<td></td>
<td>88 (62.9), 2 (0.9)</td>
</tr>
<tr>
<td>Wilkinson et al. 1996</td>
<td>Pre and after study (high)</td>
<td>(n = 300)</td>
<td>1. No standard regimen (Waterlow protocol 1993)</td>
<td>120 (80%): 32 (20%), Died: 8 (6%)</td>
</tr>
<tr>
<td></td>
<td>Setting: South Africa</td>
<td></td>
<td>2. Ampicillin (7 days orally, IV for sick children)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Years: 1992–1993</td>
<td></td>
<td>Gentamicin (5 days IM), Glycaemia controls</td>
<td></td>
</tr>
<tr>
<td>Mulholland et al. 1995</td>
<td>RCT (medium)</td>
<td>(n = 144)</td>
<td>1. Chloramphenicol 25 mg/kg 8-hourly oral</td>
<td>Recovered: 21 (28%), Improved: 19 (27%), Failure: 16 (26%), Died: 4 (5.4)</td>
</tr>
<tr>
<td></td>
<td>Setting: Gambia</td>
<td></td>
<td>2. TMP-SMX 40/200 mg twice daily (&lt; 1 year old), 60/300mg twice daily (&gt; 1 year old)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Years: 1990–1992</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golden et al. 2000</td>
<td>Retrospective (high)</td>
<td>(n unspecified)</td>
<td>Any antibiotic on admission</td>
<td>Negative association (r² = 0.37; P = 0.002) between mortality ratio (observed mortality divided for expected mortality as for Prudhon index) and antibiotic ratio (proportion of children given antibiotics from admission).</td>
</tr>
<tr>
<td></td>
<td>Setting: 9 countries in SSA (unspecified)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Years: 1994–1997</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IM, intramuscular; ITT, intention to treat analysis; PP, per protocol analysis; RCT, randomized controlled trial; SSA, Sub-Saharan Africa; TFC, therapeutic feeding centre; TMP–SMX, trimethoprim–sulfamethoxazole; WG, weight gain; * P < 0.001.
Table 3. Pharmacokinetics of first-line oral antibiotics in children with severe acute malnutrition

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug, dose (per kg)</th>
<th>No. of children</th>
<th>Absorption (%)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml) and T&lt;sub&gt;max&lt;/sub&gt; (min)</th>
<th>Vd (l/kg) protein binding (%)</th>
<th>Clearance (ml/kg/h)</th>
<th>Half life (min)</th>
<th>AUC (μg.min/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Malnourished</td>
<td>Eutrophic</td>
<td>Malnourished</td>
<td>Eutrophic</td>
<td>Malnourished</td>
<td>Eutrophic</td>
</tr>
<tr>
<td>Bolme et al. 1995&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Penicillin V, 20 mg</td>
<td>47</td>
<td>U (f): 35.9*</td>
<td>U (n/f): 29.8*</td>
<td>K (f): 82.6*</td>
<td>K (n/f): 27.1*</td>
<td>U&lt;sub&gt;K&lt;/sub&gt; (f): 9.5*</td>
<td>K&lt;sub&gt;K&lt;/sub&gt; (f): 82.6*</td>
</tr>
<tr>
<td>Bolme et al. 1980&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Penicillin V, 30 000 IU</td>
<td>16</td>
<td>SAM</td>
<td>T&lt;sub&gt;max&lt;/sub&gt;: 120</td>
<td>C&lt;sub&gt;max&lt;/sub&gt;: 5.8</td>
<td>C&lt;sub&gt;f&lt;/sub&gt;: 4.3</td>
<td>U&lt;sub&gt;K&lt;/sub&gt; (f): 40.8*</td>
<td>K&lt;sub&gt;K&lt;/sub&gt; (f): 40.8*</td>
</tr>
<tr>
<td>Buchanan 1977&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Benzyl-penicillin, dose NS</td>
<td>25</td>
<td>Adult serum versus pooled serum of 24 kwashiorkor children</td>
<td>% free drug similar</td>
<td>N: 59.1%, K: 64.0%</td>
<td>% free drug similar</td>
<td>N: 59.1%, K: 64.0%</td>
<td>% free drug similar</td>
</tr>
<tr>
<td>Bravo et al. 1984&lt;sup&gt;34&lt;/sup&gt;</td>
<td>SMX, 22 mg</td>
<td>17</td>
<td>C&lt;sub&gt;max&lt;/sub&gt;: 41.4</td>
<td>T&lt;sub&gt;max&lt;/sub&gt;: 120</td>
<td>C&lt;sub&gt;max&lt;/sub&gt;: 36.8</td>
<td>T&lt;sub&gt;max&lt;/sub&gt;: 150</td>
<td>Vd: 0.529</td>
<td>Vd: 0.529</td>
</tr>
</tbody>
</table>

AUC, area under the plasma concentration time curve; C<sub>max</sub>, maximum concentration; f, fasting; IU, international units; K, kwashiorkor; K<sub>K</sub>, absorption rate constant; M, marasmus; MK, marasmic kwashiorkor; n, normal (controls); nf, non-fasting; NS, not stated; PB, protein binding; SAM, severe acute malnutrition; SMX, sulfamethoxazole; T<sub>max</sub>, time to maximum concentration; TMP, trimethoprim; U, underweight; Vd, volume of distribution; * P < 0.05; ** P-value not specified.
### Table 4. Pharmacokinetics of second-line parenteral antibiotics in children with severe acute malnutrition

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug, dose (per kg), route</th>
<th>No. of children</th>
<th>(C_{\text{max}}) (μg/ml) and (T_{\text{max}}) (min)</th>
<th>Vd (l/kg)</th>
<th>(C_{\text{max}}) (μg/ml) and (T_{\text{max}}) (min)</th>
<th>Clearance (ml/kg/h)</th>
<th>Half life (min)</th>
<th>AUC (μg.min/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>K: 1.18</td>
<td>CL K: 16.9*</td>
<td>K: 1.769.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M: 0.91</td>
<td>CL M: 14.0*</td>
<td>M: 2.138.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MK: 0.93</td>
<td>CL MK: 11.6*</td>
<td>MK: 2594.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
<td></td>
<td>1.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
<td></td>
<td>22.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td>43.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td>177.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td>Same in all groups (no values given)</td>
<td></td>
</tr>
<tr>
<td>Bolme et al. 1980[^32]</td>
<td>Benzylpenicillin, 5000 IU, IV</td>
<td>16</td>
<td>K (C_{\text{max}}) at 2 h: 3.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M (C_{\text{max}}) at 2 h: 4.1</td>
<td>–</td>
<td>–</td>
<td>Trend to slower CL in malnourished</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MK (C_{\text{max}}) at 2 h: 10.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(T_{\text{max}}) same in all groups (30–60 min)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Buchanan et al. 1979[^16]</td>
<td>Penicillin G, 25000 IU, IM</td>
<td>8</td>
<td>–</td>
<td>Day 0: 1.6</td>
<td>Day 21: 1.4</td>
<td>D0: 183*</td>
<td>D0: 57*</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D21: 286*</td>
<td>D21: 32*</td>
<td>–</td>
</tr>
<tr>
<td>Seaton et al. 2007[^26]</td>
<td>Gentamicin, 7.5 mg, IM</td>
<td>34</td>
<td>100% &gt; 8.0 μg/ml at 2 hour</td>
<td>–</td>
<td>0.67</td>
<td>CL 1.67*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>76% &gt; 12.0 μg/ml at 2 hour</td>
<td>–</td>
<td></td>
<td>Trough level: 98% &lt; 1.0 mg/l at 20 h[^a]</td>
<td>84</td>
<td>–</td>
</tr>
<tr>
<td>Samotra et al. 1985[^17]</td>
<td>Gentamicin, 4.0 mg, IM</td>
<td>10</td>
<td>(C_{\text{max}}) 8.9 at 30 min</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>373</td>
<td>199</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(C_{\text{max}}) 10.02 at 30 min</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>22.40</td>
<td>22.32</td>
</tr>
<tr>
<td>Khan et al. 2006[^28]</td>
<td>Gentamicin, 5.0 mg, IM</td>
<td>310</td>
<td>od: (C_{\text{max}}) 11.7 at 60 min*</td>
<td>–</td>
<td>–</td>
<td>Trough level at 24 h: od: 0.29 mg/l*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>tds: (C_{\text{max}}) 4.7 at 60 min*</td>
<td>–</td>
<td>–</td>
<td>tds: 0.48 mg/l*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Bravo et al. 1982[^20]</td>
<td>Gentamicin, 3.5 mg, IV</td>
<td>18</td>
<td>(C_{\text{max}}) 6.31 at 20.67 min*</td>
<td>0.46*</td>
<td>0.39</td>
<td>CL 3.99</td>
<td>82</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(C_{\text{max}}) 8.39 at 24 min</td>
<td>–</td>
<td>–</td>
<td>CL 3.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buchanan et al. 1979[^16]</td>
<td>Gentamicin, 2.4 mg, IV</td>
<td>6</td>
<td>–</td>
<td>D0: 3.9</td>
<td>D21: 4.36*</td>
<td>D0: CL 13.6 ml/kg</td>
<td>D0: 229</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D21: CL 28.7 ml/kg*</td>
<td>D21: 179*</td>
<td>–</td>
</tr>
</tbody>
</table>

\(C_{\text{max}}\), maximum concentration; \(T_{\text{max}}\), time to maximum concentration; D0, day 0 (admission); D21, day 21 (recovery); IM, intramuscular; IU, international units; IV, intravenous; K, kwashiorkor; M, marasmus; MK, marasmic kwashiorkor; N, normal (controls); od, once daily dosing; tds, three times daily dosing; U, underweight; Vd, volume of distribution. *P < 0.05; **P-value not specified.

[^a]: One child who was in shock had a trough level of 5.5 μg/ml; longer clearance was noted in children with hypothermia, high serum creatinine or large base excess.
Table 5. Pharmacokinetics of chloramphenicol in children with severe acute malnutrition

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dose (per kg, route)</th>
<th>No. of children</th>
<th>Absorption constant (per h)</th>
<th>T_{max} (min)</th>
<th>C_{max} (μg/ml) or C_{ss} (μg/ml)</th>
<th>Clearance (ml/kg/h)</th>
<th>Half life (m) or K (per h)</th>
<th>AUC (μg.min/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashton et al. 1993</td>
<td>25 g, IV</td>
<td>34</td>
<td>Malnourished: 1.0</td>
<td>Eutrophic: 1.1</td>
<td>2.1</td>
<td>2.7</td>
<td>M: 4.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Samotra et al. 1986</td>
<td>50 g, oral</td>
<td>12</td>
<td>Malnourished: 1.0</td>
<td>Eutrophic: 1.0</td>
<td>2.1</td>
<td>2.7</td>
<td>M: 4.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Eriksson et al. 1983</td>
<td>25 g, IV/oral</td>
<td>37</td>
<td>Malnourished: 1.0</td>
<td>Eutrophic: 1.0</td>
<td>2.1</td>
<td>2.7</td>
<td>M: 4.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Mehta et al. 1983</td>
<td>25 g, oral</td>
<td>13</td>
<td>Malnourished: 0.045</td>
<td>Eutrophic: 1.0</td>
<td>2.1</td>
<td>2.7</td>
<td>M: 4.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Saini et al. 1981</td>
<td>25 mg, IV</td>
<td>21</td>
<td>Malnourished: 0.045</td>
<td>Eutrophic: 1.0</td>
<td>2.1</td>
<td>2.7</td>
<td>M: 4.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Mehta et al. 1981</td>
<td>25 g x 8 doses, IV/oral</td>
<td>21</td>
<td>Malnourished: 0.045</td>
<td>Eutrophic: 1.0</td>
<td>2.1</td>
<td>2.7</td>
<td>M: 4.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Mehta et al. 1975</td>
<td>25 mg, oral</td>
<td>14</td>
<td>Malnourished: 0.045</td>
<td>Eutrophic: 1.0</td>
<td>2.1</td>
<td>2.7</td>
<td>M: 4.8</td>
<td>5.9</td>
</tr>
</tbody>
</table>

AUC, area under the plasma concentration-time curve; C_{max}, maximum concentration; C_{ss}, steady-state concentration; IV, intravenous; K, kwashiorkor; K, elimination constant; M, marasmus; MK, marasmic kwashiorkor; N, normal (controls); po, per oral; t_{1/2}, half life; T_{max}, time to maximum concentration; U, underweight; * P<0.05.

1 Malnutrition grades were determined using weight for age, not weight for height.
2 Antibiotics in severely malnourished children.
occurred (i.e. the minimum inhibitory concentration [MIC] for common infecting organisms).30-32 Although not reported, the volume of distribution (i.e. the distribution of a drug between plasma and the rest of the body) can be assumed from parenteral models given similar peak concentrations, as described later in the text.

Studies suggest that reduced renal blood flow and glomerular filtration rate in malnutrition lengthen drug half-life and cause slow clearance.30,32,35 However, the side-effects of amoxicillin are predominantly idiosyncratic, with minimal dose-related toxicity.24,25 Therefore, time above MIC is more important to therapeutic efficacy than serum concentrations (*“maximal dose” strategy*).24

**Cotrimoxazole**  
**Clinical safety and efficacy**

No studies were retrieved on cotrimoxazole as a first-line treatment for children with SAM. One ongoing study in Kenya is examining the use of cotrimoxazole as a prophylaxis against infections to reduce mortality in these children (trial identifier NCT00934492).

**Pharmacokinetics**

Two studies, both with a small sample size, were retrieved (Table 3).33,34 Cotrimoxazole has high oral bioavailability22,24 and differences between malnourished and eutrophic children in peak concentrations or in time to C$_{\text{max}}$ were not significant.34 Malnourished and eutrophic children also showed similar volumes of distribution.34

According to limited data on sulfamethoxazole, malnutrition results in prolonged half-life, a larger area under the plasma concentration curve (AUC) and non-significantly slower drug clearance.34 The AUC represents drug bioavailability in terms of plasma concentration as a function of time and indicates the potential for both therapeutic effect and toxicity.

**Amoxicillin and gentamicin**  
**Clinical safety and efficacy**

One before-and-after study ($n = 300$) reported on second-line antibiotics in children with SAM. The introduction of a standardized antibiotic regimen composed of ampicillin and gentamicin, together with an algorithm for hypoglycemia management, reduced the case fatality rate from 20% to 6% (OR = 4; 95% CI: 1.7–9.8).28 Given the design of the study, it is not possible to estimate the relative effect of the introduction of the antibiotic treatment regimen alone.

**Pharmacokinetics**

**Parenteral penicillin**

Three studies were retrieved ($n = 47$, $n = 29$ and $n = 8$ respectively; Table 4).30,32,35 None found a significant difference in C$_{\text{max}}$ when penicillins were delivered intramuscularly to malnourished versus eutrophic individuals.30,32 A trend towards a lower volume of distribution was found in subjects with marasmus and marasmic kwashiorkor,30 with no significant changes noted between admission and recovery.35 There was no appreciable change in protein binding in the presence of malnutrition.24

Significantly slower clearance in all states of malnutrition was seen in one study,30 and a similar trend was seen in another.24 After nutritional rehabilitation a return to a shorter half life and to faster clearance was shown.35

**Gentamicin**

Five studies were retrieved (Table 4).36-40 Gentamicin administered intramuscularly reached similar peak plasma concentrations in malnourished children and eutrophic controls,36,37 but intravenous gentamicin resulted in lower plasma concentrations in malnourished infants (explained by a larger volume of distribution, with more drug moving into non-plasma tissues).37 Two studies showed a higher volume of distribution in malnourished children,39,40 and one found a low to normal volume of distribution on admission and a rise with recovery.40

Gentamicin exhibits concentration-dependent activity and a “post-antibiotic effect” (i.e. persistent bactericidal activity even below the MIC). Thus, one daily dose instead of three can lower toxicity. Compared with traditional three times daily dosing, a single daily dose produced higher peak concentrations and lower 24-hour trough levels in malnourished children,38 with values comparable to those seen in well nourished children.24,49

Gentamicin nephrotoxicity and ototoxicity result from prolonged serum levels > 2 μg/ml.24,25 largely reflecting AUC and clearance, so monitoring serum levels is recommended. However, clearance appears largely unaffected by malnutrition37,50 (except for prolonged clearance in shock and renal impairment),50 although one small study found delayed clearance and half life, which improved with rehabilitation.50 There were no reports of differences in AUC between groups37,50 or of an increase in adverse events with high peak concentrations.24

**Chloramphenicol**  
**Clinical safety and efficacy**

One RCT ($n = 144$) was retrieved. In children with SAM complicated by clinical and radiological pneumonia, the number of children recovering, treatment failures or deaths was the same in children treated with oral chloramphenicol and with cotrimoxazole. This trial was conducted from 1990–92 in a context of low resistance to cotrimoxazole and low HIV prevalence.31

**Pharmacokinetics**

Seven original studies41-47 (Table 5) and one review48 were found. Oral administration studies demonstrate variable absorption and peak concentrations in malnourished subjects.42,44-46 All studies of intravenous administration but one show higher peak concentrations in malnourished subjects than in eutrophic controls43,45,46. No studies looked at intramuscular administration. With multiple oral or intravenous doses, steady-states were significantly higher in malnourished children versus controls.39 Studies found no significant change in volume of distribution44-45 or protein binding42-44 in malnourished subjects.

Several studies show significantly slower clearance and/or a longer half life leading to higher AUC,41,43,44,47 mostly owing to poor hepatic conjugation resulting from malnutrition.41 In contrast, two weaker studies found faster elimination kinetics in malnourished subjects.12,45 Many pharmacokinetic abnormalities resolved with nutritional rehabilitation.44,47 Although some adverse events are idiosyncratic,24 data suggest concentrations > 25–30 μg/ml may precipitate toxicity, including bone marrow suppression.24,25,41

A review therefore concluded that a reduced dose of chloramphenicol would be warranted in malnourished subjects,48 a view supported by multiple studies finding higher drug concentrations42,44,46,47 and delayed elimination in the presence of malnutrition.41,43,44,47

**Ceftriaxone**

No published studies were retrieved for ceftriaxone. One ongoing trial is examining the use of ceftriaxone in children with...
SAM and pneumonia (trial identifier NCT00968370).

Ciprofloxacin
No studies were retrieved for ciprofloxacin. One ongoing trial is looking at oral absorption of ciprofloxacin in children with SAM (trial identifier ISRCTN31079753).

All other antibiotics
**Clinical safety and efficacy**

One personal communication about a retrospective review of case notes was retrieved. In children with SAM admitted to therapeutic feeding centres, a significant association was found between mortality ratio (i.e. observed mortality divided by expected mortality using the Prudhon Index) and the use of an antibiotic upon admission ($r^2 = 0.37; P = 0.002$). Other aspects of care were not controlled for rigorously.

**Discussion**

This review highlights the lack of good quality clinical studies on the use of antibiotics in severely malnourished children. Of the few pharmacokinetic studies that exist, most use single dose kinetics and rarely correlate findings with clinical outcomes, limiting conclusions. Most of them have also excluded severely compromised children, which limits the generalizability of the findings. Given these limitations, the following conclusions can be drawn.

**First-line antibiotics**

Whether antibiotics should be given routinely to children with uncomplicated SAM undergoing outpatient treatment remains undetermined. Epidemiological data on the risk of infection in these children are lacking. The good clinical condition and low case fatality rates reported in these children, together with the findings of one retrospective study, suggest that these children have a low risk of bacterial infections. However, the risk of infection differs in subgroups of children, such as those who are HIV-infected. Data on HIV+ malnourished children, although inconsistent, suggest that they suffer more frequent episodes of severe pneumonia and diarrhoea and have higher rates of death from bacteraemia.

Cotrimoxazole remains questionable as first-line therapy in HIV+ children already receiving the drug for *Pneumocystis jirovecii (carinii)* pneumonia prophylaxis, and efficacy may also be affected by antibiotic resistance patterns in many settings. Amoxicillin remains a valuable option, since it has been proven as efficacious as ceftriaxone but cheaper. Pharmacokinetic studies support the use of oral penicillin in children with SAM at the same doses used for eutrophic children unless severe malabsorption or diarrhoea are present. Taking the drug during fasting can increase absorption.

No further data are available to guide recommendations surrounding the use of first-line antibiotics. Whether first line antibiotics are appropriate for hospitalized children, who by definition have complicated SAM, remains to be determined. An alternative would be to automatically consider these children for a “second-line” regimen.

**Second-line antibiotics**

Based on epidemiological data, recommending broad-spectrum antibiotics for children with complicated SAM appears reasonable. Only one retrospective study reported on the use of ampicillin and gentamicin, whose use led to lower case fatality rates than a previous non-standard protocol. Pharmacokinetic data suggest that parenteral penicillin and gentamicin can be safely given to malnourished children at the doses and intervals recommended for non-malnourished children, unless renal failure or shock are present.

The comparative efficacy and safety of other parenteral antibiotics have not been studied. Moreover, high rates of in vitro resistance to ampicillin and gentamicin have been reported in several African countries (Table 1).

According to discussions with staff members, institutions for the care of malnourished children vary in the degree to which they follow current recommendations. Many institutions are now giving more potent broad-spectrum antibiotics to hospitalized malnourished children guided largely by local in vitro sensitivity data.

**Third-line antibiotics**

Only one small RCT reported equivalent efficacy for cotrimoxazole and oral chloramphenicol in children with pneumonia, albeit with limited generalizability. Moreover, pharmacokinetic studies suggest that oral chloramphenicol is erratically absorbed in malnourished children and that parenteral administration is preferable. Given the risk of accumulation and potential toxicity, adjusting the dose or the frequency is recommended until further data on safety become available.

Other third-line antibiotics often used in practice include ceftriaxone and ciprofloxacin. No studies have been published on the efficacy, safety or pharmacokinetics of these drugs in children with SAM. Ceftriaxone has a broad spectrum, is given in a single daily dose intravenously or intramuscularly and has a wide therapeutic window that increases its likely safety. Reducing its dose or frequency is advisable in children with severe renal compromise. Ciprofloxacin remains a promising treatment considering its broad spectrum, good oral bioavailability and low reported resistance rates. These two drugs are often costly, although their prices have decreased in the recent past, and both are already available and widely used in many low- and middle-income regions. Data on the efficacy and safety of these antibiotics in children with SAM are urgently needed.

**Summary and recommendations**

The use of broad-spectrum antibiotics for children with SAM is supported by epidemiological data demonstrating a high prevalence of infections in these children, but clinical studies are lacking. Evidence supports the use of amoxicillin as a first-line treatment option. However, in children with uncomplicated SAM who are undergoing outpatient management, whether routine antibiotics infer an extra benefit is unclear.

Ampicillin and gentamicin, as recommended by current WHO guidelines, are the only second-line antibiotics that have been studied in controlled trials. There is support from low-quality evidence for their use in hospitalized children with SAM.

Global recommendations for antibiotic treatment in children with malnutrition cannot be further clarified at present because there are few ongoing clinical and pharmacokinetic trials. Local patterns of susceptibility to antibiotics should be taken into account in the choice of an antibiotic.

Well designed RCTs are required to further address doubts surrounding the routine use of antibiotics in uncomplicated SAM, with stratification for HIV status. Also needed are multicentre, multiarm RCTs to further assess the efficacy and safety of different antibiotic regimens for complicated SAM and to
produces many confounding variables. Lack of resources further limits studies. This systematic review has shown that more clinical and pharmacokinetic trials are clearly needed to provide these children with the best available evidence-based care.

Acknowledgements
We thank Vittoria Lutje, Information Specialist, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine.

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Competing interests: None declared.

MLHAB

Antibiotics in severely malnourished children
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compare in vitro sensitivity data with clinical outcomes, with stratification for HIV status. Pharmacokinetic studies on the use of ceftriaxone and ciprofloxacin in malnourished children are also urgently needed given the increased availability and use of these antibiotics in many settings. Admittedly, children with complicated SAM are difficult to study because they often have life-threatening presentations and their multi-faceted management produces many confounding variables. Lack of resources further limits studies. This systematic review has shown that more clinical and pharmacokinetic trials are clearly needed to provide these children with the best available evidence-based care.

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Funding: The original technical report from which this work derives was funded by the WHO, Essential Medicines and Pharmaceutical Policies, Geneva.

Competing interests: None declared.
Antibiotiques chez les enfants gravement dénutris: évaluation systématique de l’efficacité, de la sécurité et de la pharmacocinétique

**Objectif** Évaluer de façon systématique la preuve de l’application des directives de l’Organisation mondiale de la Santé recommandant les antibiotiques à large spectre chez les enfants présentant une malnutrition aiguë sévère (MAS).


**Résultats** Deux essais contrôlés randomisés (ECR), une étude avant/après et deux rapports rétrospectifs sur l’efficacité et la sécurité cliniques ont été récupérés, avec 18 études pharmacocinétiques. La qualité des essais était généralement médiocre et les résultats n’ont pas pu être mis en commun à cause de leur hétérogénéité. L’amoxicilline orale pendant 5 jours était aussi efficace que la ceftriaxone intramusculaire pendant 2 jours (1 ECR). Pour la MAS sans complication, l’amoxicilline n’a montré aucun avantage par rapport à un placebo (1 étude rétrospective). L’introduction d’un régime normalisé utilisant l’amoxicilline et la gentamicine a considérablement réduit la mortalité chez les enfants hospitalisés (rapport des cotes, RC: 4.0; intervalle de confiance de 95%, CI: 1.7–9.8; 1 étude avant/après). Le chloramphénicol oral était aussi efficace que le triméthoprime-sulfaméthoxazole chez les enfants souffrant de pneumonie (1 ECR). Les données pharmacocinétiques suggèrent que des doses normales de pénicilline, de cotrimoxazole et de gentamicine sont sans danger chez les enfants souffrant de malnutrition, alors que la dose ou la fréquence du chloramphénicol nécessite un ajustement. Les preuves existantes ne sont pas assez solides pour clarifier davantage les recommandations.

**Conclusion** De grands ECR sont nécessaires afin de définir le traitement antibiotique optimal chez les enfants souffrant de MAS avec ou sans complications. Des recherches supplémentaires dans la toxicité de la gentamicine et du chloramphénicol et dans la pharmacocinétique de la ceftriaxone et de la ciprofloxacine sont également requises.

**Résumé**

**Prévision des antibiotiques à l’aide de l’administration de la médecine des enfants en danger:**

**Objectif** Évaluer de façon systématique la preuve de l’application des directives de l’Organisation mondiale de la Santé recommandant l’administration d’antibiotiques de large spectre pour les enfants souffrant d’une malnutrition aiguë sévère (MAS).


**Résultats** Deux essais contrôlés randomisés (ECR), une étude avant/après et deux rapports rétrospectifs sur l’efficacité et la sécurité cliniques ont été récupérés, avec 18 études pharmacocinétiques. La qualité des essais était généralement médiocre et les résultats n’ont pas pu être mis en commun à cause de leur hétérogénéité. L’amoxicilline orale pendant 5 jours était aussi efficace que la ceftriaxone intramusculaire pendant 2 jours (1 ECR). Pour la MAS sans complication, l’amoxicilline n’a montré aucun avantage par rapport à un placebo (1 étude rétrospective). L’introduction d’un régime normalisé utilisant l’amoxicilline et la gentamicine a considérablement réduit la mortalité chez les enfants hospitalisés (rapport des cotes, RC: 4.0; intervalle de confiance de 95%, CI: 1.7–9.8; 1 étude avant/après). Le chloramphénicol oral était aussi efficace que le triméthoprime-sulfaméthoxazole chez les enfants souffrant de pneumonie (1 ECR). Les données pharmacocinétiques suggèrent que des doses normales de pénicilline, de cotrimoxazole et de gentamicine sont sans danger chez les enfants souffrant de malnutrition, alors que la dose ou la fréquence du chloramphénicol nécessite un ajustement. Les preuves existantes ne sont pas assez solides pour clarifier davantage les recommandations.

**Conclusion** De grands ECR sont nécessaires afin de définir le traitement antibiotique optimal chez les enfants souffrant de MAS avec ou sans complications. Des recherches supplémentaires dans la toxicité de la gentamicine et du chloramphénicol et dans la pharmacocinétique de la ceftriaxone et de la ciprofloxacine sont également requises.

**Resumen**

**Antibióticos en niños con desnutrición grave: revisión sistemática de su eficacia, seguridad y farmacocinética**

**Objetivo** Revisar sistemáticamente los datos que apoyan las directrices de la Organización Mundial de la Salud que recomiendan la administración de antibióticos de amplio espectro en niños con desnutrición grave (NDG).

**Métodos** Se realizó una búsqueda en los resúmenes CENTRAL, MEDLINE, EMBASE, LILACS, POPLINE, CAB y en los registros de ensayos en marcha. Nos pusimos en contacto con expertos en la materia. Se realizaron búsquedas manuales en listas de referencia y en actas de congresos. Se incluyeron todo tipo de estudios, excepto los informes de casos clínicos individuales.

**Resultados** Se recuperaron dos ensayos controlados aleatorizados (ECA), un estudio comparativo del antes y el después y dos informes retrospectivos sobre eficacia clínica y seguridad, junto con 18 estudios de farmacocinética. La calidad del ensayo fue generalmente baja y los resultados no se pudieron agrupar debido a su heterogeneidad.
tratamiento con amoxicilina por vía oral durante 5 días resultó ser tan efectivo como la ceftriaxona intramuscular durante 2 días (1 ECA). La amoxicilina no superó los beneficios de un placebo para el tratamiento de niños con desnutrición grave que no presentaban otras complicaciones (1 estudio retrospectivo). La introducción de un tratamiento estándarizado con ampicilina y gentamicina redujo de manera significativa la mortalidad entre los niños hospitalizados (oportunidad relativa, OR: 4.0; intervalo de confianza del 95%, IC: 1.7–9.8; 1 estudio comparativo del antes y el después). El tratamiento con cloranfenicol por vía oral resultó ser tan efectivo como la combinación de trimetoprima y sulfametoxazol en el tratamiento de niños con neumonía (1 ECA). Los datos de farmacocinética sugieren que las dosis normales de penicilinas, asociación de trimetoprim y sulfametoxazol y gentamicina resultan seguras en niños malnutridos, mientras que, en el caso del cloranfenicol, debería ajustarse las dosis o la frecuencia de administración. Las evidencias existentes no son lo suficientemente sólidas para aclarar más las recomendaciones sobre tratamientos de antibióticos en niños con desnutrición grave.

**Conclusión** Es necesario realizar amplios ECA para definir el tratamiento óptimo con antibióticos de los niños con desnutrición grave con y sin complicaciones. También es necesario investigar mejor la toxicidad de la gentamicina y el cloranfenicol y la farmacocinética de la deftriaxona y de la ciprofloxacina.

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**References**


