

**SEVERE ACUTE MALNUTRITION UPDATE:**  
**CURRENT WHO GUIDELINES AND THE WHO ESSENTIAL MEDICINE LIST FOR CHILDREN**

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# 1. Introduction

In 2007, the Better Medicines for Children (BMC) initiative of the World Health Organisation (WHO) was developed in response to World Health Assembly (WHA) resolution 60.20, which cited overwhelming evidence that nearly 50% of children under 5 years of age were dying of preventable diseases for which effective medicines existed. In recognition of the need to improve access to evidence-based paediatric formulations which may be utilised in an optimal manner, an Essential Medicines List for children (EMLc) was created, alongside a children’s formulary.<sup>1</sup>

This document was prepared in response to a need to review and potentially update the current recommendations for the antibiotic treatment of both inpatient and outpatient management of severe acute malnutrition (SAM). The current recommendations (Table 1) are based on guidelines published in 2013 in the WHO Pocketbook for Hospital Care for Children, and the 2013 update on SAM (outpatient management).<sup>2,3</sup> The global threat of increasing antimicrobial resistance and new data on efficacy and safety profiles requires a re-review of the current evidence to ensure recommendations are the most appropriate. The evidence base for the use of antibiotics in children presenting with uncomplicated SAM has been recently enlarged.

Condition	Recommendation	Evidence base <sup>a</sup>	Year updated
Uncomplicated SAM <sup>4</sup>	<b>Oral Amoxicillin</b> Dosage and time frame not specified	Conditional recommendation, low quality evidence	2013
Complicated SAM <sup>3,4</sup>	<b>IV Benzylpenicillin</b> 50,000U/kg IM/IV every 6 hours for two days OR <b>IV Ampicillin</b> 50mg/kg IM/IV every 6 hours for two days THEN <b>Oral Amoxicillin</b> <u>25-40mg/kg/dose every 8 hours</u> for 5 days (total 7 day course)  AND <b>IV/IM Gentamicin</b> 7.5mg/kg IM/IV once daily for 7 days	Weak recommendation, low quality evidence	2012
Complicated SAM <sup>3,4</sup>	<b>“Oral Metronidazole</b> 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”.	None	2013

<sup>a</sup> at the time of the recommendation

**Table 1: Current WHO inpatient and outpatient management guidelines for SAM**

## 2. Information Supporting Public Health Relevance

### 2.1. Epidemiology and classification of SAM

SAM affects nearly twenty million children under 5 years, causing up to 1 million deaths each year by increasing susceptibility to death from severe infection.<sup>5</sup> The most susceptible age for malnutrition is 6 to 18 months, (when growth velocity and brain development are especially high); however, with many low-income settings introducing solids to children as young as two months, it is increasingly recognised that SAM may occur in infants aged <6 months.<sup>6</sup> SAM is defined by two distinct clinical entities:<sup>3,4,7</sup>

- i. **Severe wasting** (marasmus; defined as middle upper arm circumference [MUAC]<115mm in children 6-59 months, or a weight-for-height/length <-3 Z scores according to the 2006 WHO growth standards) in children aged 0 to 59 months;
- ii. **Nutritional oedema** (kwashiorkor; defined as bilateral pitting oedema).

Children with SAM are classified according to the absence or presence of medical complications:<sup>3</sup>

- i. **Uncomplicated SAM:** children who are clinically well without signs of infection or other indication for hospital admission, with a retained appetite ('passed an appetite test'). Retained appetite is regarded to indicate the absence of severe metabolic disturbance. These patients are deemed to be most appropriately managed as outpatients, with ready-to-use therapeutic foods.
- ii. **Complicated SAM:** children who have clinical features of infection, metabolic disturbance, severe oedema, hypothermia, vomiting, severe dehydration, severe anaemia or a lack of appetite, requiring inpatient treatment initially with low-protein milk-based feeds. Children are discharged to continue nutritional management as an outpatient is recommended when complications have resolved.

### 2.2. Treatment of SAM

Typically, children treated in the community with uncomplicated SAM have a case fatality of less than 5%, whilst children treated as inpatients because of complicated SAM – usually because of severe infections including pneumonia, diarrhoea, sepsis or HIV, have a reported case fatality of 10 to 40%.<sup>8</sup> It is also clear that children with complicated SAM have a high ongoing risk of mortality after discharge from hospital.<sup>9-11</sup>

Previously, all children with SAM were managed as inpatients with empiric broad-spectrum parenteral antibiotics, regardless of whether or not clinical features of infection (or other complications) were present.<sup>12</sup> However, in the past decade, the advent of clinically effective ready-to-use therapeutic foods (RUTF) has resulted in recommendations for children with uncomplicated SAM (>80% of paediatric SAM cases) being treated as outpatients, following the WHO-UNICEF community-based model for the management of malnutrition.<sup>7,12</sup> This has occurred simultaneously with changes to the nutritional and clinical profile of children diagnosed with (and treated for) SAM following the publication of the 2006 WHO Child Growth Standards and increasing use of mid-upper arm circumference (MUAC) for diagnosis, which resulted in significant changes to the measurement of nutritional status, and a subsequent increase in the number of children classified as having SAM in some areas.<sup>13,14</sup>

### **2.3. Rationale for antimicrobial use in SAM**

The rationale behind antibiotic treatment for all children with SAM lies in the observation that malnourished children may not show signs of clinical infection,<sup>15</sup> and their elevated mortality compared to well-nourished children. Some older clinical trials have suggested evidence for improved growth and decreased mortality in malnourished children treated with antibiotics.<sup>16</sup> The mechanism behind this clinical improvement has been postulated to be secondary to the treatment of underlying covert infection, prevention of colonising pathogens, minimisation of nutrient diversion by dampening inflammatory responses, treatment of small intestinal bacterial overgrowth and a reduction in enteropathy via alterations in the gut microbiome.<sup>16,17</sup> Indeed, several epidemiological studies have documented a high prevalence of covert pneumonia, bacteraemia and urinary tract infections in children with malnutrition caused by a variety of both Gram-positive and Gram-negative organisms, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella* spp, *Salmonella* spp, and other Enterobacteriaceae.<sup>18-23</sup>

With the majority of SAM treatment shifting to the outpatient setting, broad-spectrum oral antibiotic administration continues to be recommended by the WHO and UNICEF for uncomplicated SAM. For complicated SAM, intravenous antibiotic therapy followed by oral therapy (including a prolonged course of an aminoglycoside) is recommended, however, these recommendations are based on weak evidence.<sup>3,8,24</sup> Increasing antibiotic resistance is an issue of international concern,<sup>25</sup> as well as cost and logistical considerations of continuing antimicrobial treatment and possible side effects of therapy, this review was conducted to assess recent international evidence of the clinical efficacy of antibiotic treatment in children with SAM. High rates of non-susceptibility have been documented in several epidemiological studies in children with SAM, including both first- and second-line therapies.<sup>18,19,21,26-30</sup> Furthermore, the need for a routine course of oral antibiotics in children with uncomplicated SAM has been questioned, with some resource-constrained clinics choosing not to prioritise their administration.<sup>15,31</sup>

## **3. Review of Current Evidence on Treatment Options**

### **3.1. Methods**

#### *3.1.1. Search strategy*

Extensive systematic reviews were conducted in 2011 to address the appropriate management of children with SAM was used to inform the recent WHO guidelines and update the EMLc,<sup>32</sup> and independently of the EMLc process.<sup>33</sup> To ensure correspondence with the 2011 research, the search strategy was replicated in this review. A systematic search for systematic reviews, meta-analyses, multi-centre studies and randomised controlled trials was conducted using the search terms outlined in Table 2. The databases EMBASE, Cochrane database of systematic review and Pubmed were searched. Trials were limited to those conducted within humans and published since 2010 in English or French language, to update the information previously retrieved.<sup>32</sup>

1) Amoxicillin OR Ampicillin OR penicillin OR Procaine Penicillin
2) Amoxicillin+ OR Amoxicillin Clavulanate Combination OR Ampicillin+Penicillins+ OR Penicillin G+ OR Penicillin G,Procaine
3) Gentamicin OR aminoglycoside OR GENTAMICINS+
4) Cotrimoxazole OR sulfamethoxazole OR sufamethoxazole OR Trimethoprim OR Trimethoprim-Sulfamethoxazole Combination
5) Ceftriaxone OR cephalosporin OR Ceftriaxone+
6) Ciprofloxacin OR quinolone OR fluoroquinolone OR Ciprofloxacin+
7) Chloramphenicol OR Chloramphenicol+
8) OR 1-7
9) Malnutrition OR malnourished OR underweight OR kwashiorkor OR marasmus
10) Malnutrition Or Protein-Energy Malnutrition or Child Nutrition Disorders Or Infant Nutrition Disorders
11) OR 9-10
12) 8 AND 11
13) Limit 12 to human (for clinical safety and efficacy trials) AND published between 2010-2016

**Table 2: Search terms used in search strategy**

International clinical practice guidelines were also reviewed, including the Infectious Diseases Society of America (IDSA), the European Society for Clinical Medicine (ESCMID), BMJ Clinical Evidence, the American Academy of Paediatrics, Therapeutic Guidelines (Australia), Action Contre le Faim, Medicines Sans Frontiers, Valid International, and national guidelines in high-burden countries in Asia and Africa.

Clinical trial registries including [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and <http://www.who.int/ictrp/en/> were searched for ongoing trials relevant to antibiotic treatment in SAM.

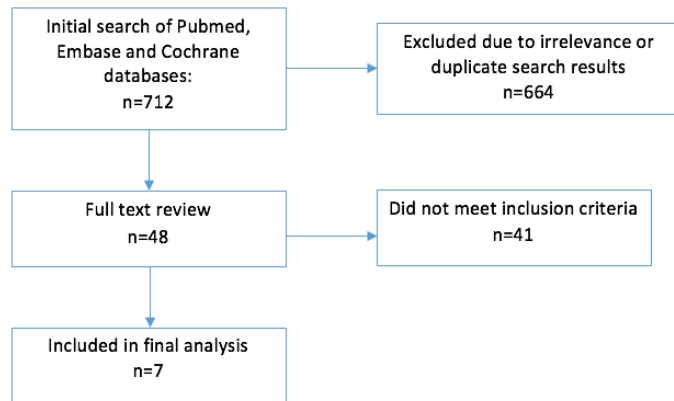
### 3.1.2. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> <li>• Systematic review, randomised controlled trial or multi-centre study investigating antibiotic therapy in children with complicated or uncomplicated SAM</li> <li>• Where resistance patterns were investigated, information on antimicrobial testing methodologies documented</li> </ul>	<ul style="list-style-type: none"> <li>• Published before 2010</li> <li>• Not pertaining to treatment in humans (unless informing pharmacokinetics)</li> <li>• Data pertaining to carriage rates only</li> <li>• Irrelevant to clinical question</li> <li>• Duplicates</li> <li>• Correspondence</li> <li>• Case reports or epidemiological studies</li> </ul>

**Table 3: Inclusion and exclusion criteria**

## 3.2. Results

The initial search produced 712 papers (Figure 1) of which 48 qualified for full text review. Ultimately, 7 studies met the inclusion criteria (Table 3), which were abstracted and are detailed in Appendix A. Quality assessment of the studies was performed as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.<sup>34</sup>



**Figure 1: Search Results**

### 3.2.1. Characteristics of Included Studies

Since 2010, four studies were systematic reviews and/or meta-analyses (conducted across an international setting),<sup>32,33,35,36</sup> and three papers were double-blind, placebo controlled trials, conducted in Malawi,<sup>37</sup> Niger,<sup>31</sup> and Kenya.<sup>9</sup> All papers assessed children aged 6-59 months, aside from one recent RCT which extended the intervention group to severely malnourished children aged 2 months and above.<sup>9</sup> There was consistency across all the studies in the definition of complicated and uncomplicated SAM.

The one meta-analysis was classified as high-quality evidence; with the remaining systematic reviews and RCTs classified as Grade Level B (moderate-quality evidence; see Appendix A). Study heterogeneity in interventions and populations prevent further pooling of the results for this review. There was one further review of pharmacokinetics in children with SAM.<sup>38</sup>

### 3.2.2. Choices of antibiotics

Ideally, the choice of antibiotic should be dictated by local resistance patterns and common pathogens, a point which continues to be highlighted in the most recent WHO guidelines.<sup>4</sup> However, in regions where malnutrition is common, microbiological data is rarely unavailable and may be misleading where laboratories are not externally quality controlled. The choices of antibiotic are influenced by cost, availability and the ease of administration.<sup>16</sup> Where choices are limited and there are significant mortality risks, the overall risk-benefit of the available antibiotic choices is likely to be very different from that in a developed country setting.

### 3.2.3. Evidence for current guidelines in uncomplicated SAM

Prior to the most recent update, previous WHO guidelines<sup>12</sup> recommended co-trimoxazole administration for treatment of children with SAM in the community, which was changed to amoxicillin in the 2013 guidelines due to concerns regarding the inferior efficacy of co-trimoxazole in treating small intestinal bacterial overgrowth, which may have been unfounded,<sup>39,40</sup> although neither are as effective as agents such as amoxicillin-clavulanic acid or metronidazole for this condition.<sup>16,41</sup>

Lazzerini's systematic review, which informed the 2013 WHO guidelines update, documented evidence from two studies assessing the clinical efficacy of amoxicillin in children with uncomplicated SAM.<sup>32</sup> The first was an un-blinded RCT conducted in Sudan (n=458) which indicated oral amoxicillin (40mg/kg/day twice daily) for 5 days was as effective as IM ceftriaxone for two days.<sup>42</sup> Intention-to-treat analysis in this study revealed that 53.5% (123/230) in the amoxicillin group and 55.7% (127/228, difference 2.2%, 95% CI -6.9-11.3) in the ceftriaxone group had a weight gain of at least 10g/kg/day during a 14-day period. Recovery rate was not significantly different [70% (161/230) in the amoxicillin group and 74.6% (170/228) in the ceftriaxone group (p=0.27)], nor were the case fatality rates [3.9% (9/230) and 3.1% (7/228), respectively (p=0.67)]; with most deaths occurring in the first two weeks of admission.<sup>43</sup>

A retrospective study in Malawi, discussed in Lazzerini's review, compared oral amoxicillin (60mg/kg/day; n=498) for 7 days to no antibiotics (n=1,955) in two nutrition programmes, suggesting a poorer recovery rate for children receiving amoxicillin at 4 weeks (39.8% vs 70.8%; p<0.001), but a similar rate of recovery at 12 weeks, and similar rates of death and default.<sup>44</sup> However, this research was acknowledged to be at risk of strong bias, not just due to its retrospective data collection, but because different district locations of the two cohorts of patients, who were also not stratified by risk of HIV status (with a high burden among the study population).<sup>45</sup>

The current search revealed two further systematic reviews<sup>33,35</sup> and two RCTs<sup>13,46</sup> assessing the efficacy of amoxicillin in SAM, as well as a meta-analysis combining their results.<sup>36</sup> While excluded from the inclusion criteria, three relevant observational studies were also noted in the literature, and for the provision of their epidemiological data, these studies are described in Appendix B.<sup>20,47,48</sup>

Picot's systematic review<sup>35</sup> did not reveal any interventional studies beyond those already documented in the Lazzerini review. Alcoba's systematic review and-meta-analysis (of observational data only)<sup>33</sup> favoured amoxicillin over co-trimoxazole for *in vitro* susceptibility [medians: 42% (IQR 27–55%) versus 22% (IQR 17 to 23%); population-weighted-means 52.9% (IQR 23 to 57%) versus 35.4% (IQR 6.7 to 42%)], yet the authors point out that the evidence from intervention studies (discussed below) revealed conflicting results over the efficacy of amoxicillin in children with SAM, which is especially difficult to interpret when patients are not stratified by HIV status.

Trehan et. al.'s double-blind three-armed RCT<sup>49</sup> (GRADE level B) compared a third-generation oral cephalosporin, cefdinir, to amoxicillin and placebo in Malawi (n=2,767). The overall case fatality was 5.4%, and was significantly higher for children receiving placebo (7.4%) than for those receiving either amoxicillin 80-90mg/kg/day (4.8%, p=0.02) or cefdinir 14mg/kg/day (4.1%, p=0.003). This corresponds to a 36% (95% CI 7% to 55%) **reduction in mortality when given amoxicillin**, and a 44% (95% CI 18% to 62%) **reduction in mortality with cefdinir**. Children who received either antibiotic agent also had **greater increases in mid-upper-arm circumference** than did those who received placebo. The authors concluded that these results provided clear evidence to support the recommendation for routine oral antibiotics as part of the outpatient management of SAM. However, in assessing any policy move towards widespread oral cephalosporin usage, there was no significant improvement in clinical efficacy using third-generation cephalosporin and this would need to be weighed against the risk of promoting antimicrobial resistance in this vulnerable group and more generally in the community.<sup>15</sup>

In contrast, Isanaka et. Al.'s 2016 RCT of n=2,399 children (6-59 months) with uncomplicated SAM across four rural treatment centres in Niger (GRADE B level evidence) found **no significant difference in the likelihood of recovery between those children treated with amoxicillin 80mg/kg/day versus**

**placebo** (RR with amoxicillin 1.05, 95% CI 0.99-1.12).<sup>13</sup> Amoxicillin significantly accelerated early gains in weight and MUAC (week 1: RR 3.8, 3.1 to 4.6,  $p < 0.001$ ), but had no significant effect on overall weight or height gain by week 4. Among children who recovered, **time to recovery was significantly shorter with amoxicillin** than with placebo (mean treatment 28 vs 30 days,  $p < 0.001$ ). **Amoxicillin decreased the risk of transfer to inpatient care**, RR 0.86 (95% CI 0.76 to 0.98,  $P = 0.02$ ), for acute gastroenteritis in particular, RR 0.67, (95% CI 0.48 to 0.94,  $p = 0.02$ ). This is a surprising finding in light of the pathogens primarily responsible for gastroenteritis in young children being reported to have limited sensitivity to amoxicillin,<sup>50</sup> while gastrointestinal side effects are also a common side effect of the therapy, perhaps reflecting the antibiotic's effect on reducing small bowel flora and modifying the composition of the gut microbiome.<sup>51</sup> Importantly, **amoxicillin reduced hospital admission** amongst those transferred for inpatient care, RR 0.76 (95% CI 0.62 to 0.92,  $P = 0.005$ )

The trial by Isanaka et. al. challenged the view that antibiotic therapy is always necessary or beneficial, concluding that 'eliminating routine antibiotic use could represent an important simplification of treatment, resulting in substantial cost savings with respect to drugs, staff, and systems for delivery and encouraging expanded service provision and responsible antibiotic stewardship.'<sup>13,25</sup> The international literature responded to these conclusions with mixed views. Some supported the view that broad-spectrum mass antibiotic use has unintended consequences that outweigh the benefits of such administration,<sup>52</sup> highlighting the importance of ensuring essential and effective antimicrobials are available for the treatment of clinical infections.<sup>52</sup> Others noted that a lack of growth improvement in children receiving amoxicillin should not be extrapolated to mean any antibiotics are not beneficial in children with SAM, as it may simply be that amoxicillin is no longer the most appropriate antibiotic.<sup>53</sup>

These two RCTs were then analysed by Milion et. al. in a meta-analysis (GRADE A level evidence),<sup>36</sup> who also pointed out the limitation of Isanaka et. al. not having included children with oedema – a potential selection bias since the WHO definition of uncomplicated SAM includes mild to moderate bilateral oedema. This meta-analysis (total events: 1,610 amoxicillin; 1,535 placebo) revealed **an overall benefit for survival in children with all three clinical forms of SAM** (kwashiorkor, marasmic kwashiorkor and marasmus; summary risk ratio 1.03, 95% CI 1.00-1.06,  $p = 0.03$ ). There was **a beneficial for survival for amoxicillin in children with marasmus** (summary risk ratio 1.05, 95% CI 1.00-1.11,  $p = 0.05$ ). There was minimal observed inconsistency between the two studies in tests for heterogeneity ( $I^2 = 0\%$ ) and the authors concluded that the benefits of antibiotics revealed by their analysis should reaffirm **continuity of the current WHO recommendations**. The authors also postulate that cephalosporins may have a (non-significantly) greater efficacy in light of their current research suggesting a proliferation of gut aerotolerant pathogens in SAM (particularly *Proteobacteria*), which are better inhibited by cephalosporins.<sup>54</sup>

One additional observational study deserves comment despite the limits in its methodology. A retrospective cohort study of 628 children with uncomplicated SAM managed via an outpatient therapeutic programme in rural Ethiopia found children who took amoxicillin (dosage not specified) recovered significantly faster compared to children who did not, with a higher rate of recovery (HR 1.95, 95% CI 1.17-3.23).<sup>47</sup> However, the methodology was unclearly described and children were not observed in the administration of their medication (which included a package of interventions, such as RUTF, vitamin A and de-worming tablets).

In conclusion, amoxicillin is a relatively safe medication with minimal serious adverse side effects (see table 6, below), reaching therapeutic plasma levels via oral administration in malnourished children.<sup>55,56</sup>



Clinical trials in Malawi and Niger have found that amoxicillin improves outcomes. **The currently available evidence supports the continued routine administration of amoxicillin 80mg/kg/day in two divided doses for 7 days for children with uncomplicated SAM treated within the community.** This is the dosage currently recommended in the 2013 WHO Pocketbook for Hospital Care for Children for outpatient treatment of pneumonia for all children. The dosage of amoxicillin for uncomplicated SAM was not specified in the 2013 WHO guideline update on SAM. Previous WHO and national guidelines have specified dosages as low as 15mg/kg three times daily (see below).

### 3.2.4. Evidence for current guidelines in complicated SAM

Lazzerini's 2011 systematic review<sup>32</sup> revealed only one interventional study (completed in 1996) assessing the clinical efficacy of ampicillin and gentamicin versus either co-trimoxazole or penicillin plus gentamicin in 300 children, revealing a case fatality reduction in children receiving antibiotics from 20% to 6% (OR = 4; 95% CI: 1.7 to 9.8).<sup>57</sup> However, this was administered alongside a new protocol for the treatment of hypoglycaemia and other aspects of care for SAM, and therefore cannot be attributed to the antibiotic regimen alone. No other interventional trials assessing empirical parenteral therapy in children with complicated SAM were identified in this updated review. Alcoba's systematic review revealed susceptibilities of >80% to amoxicillin-gentamicin and gentamicin in blood, urine and CSF cultures (Table 4).<sup>33</sup>

Observational evidence includes a prospective cohort study conducted in 2015 in n=407 children admitted to the Dhaka hospital of ICDDR,B between 2011-2012.<sup>48</sup> Inclusion criteria were respiratory compromise and radiological pneumonia. The study evaluated those treated with parenteral ampicillin and gentamicin (for children assessed to have treatment failure, antibiotics were changed to second-line agents - ceftriaxone plus levofloxacin - following the hospital's protocol). Overall, 18 children (4.4%) had bacteraemia, and 111 (27%) of those admitted exhibited WHO defined 'danger signs' of severe pneumonia (hypoxaemia, cyanosis, grunting, convulsions, inability to drink or persistent vomiting).<sup>4</sup> These children were significantly more likely to exhibit treatment failure (RR 3.14, 95% CI 2.30 to 4.29, p<0.001) and death (RR 2.78, 95% CI 2.06 to 3.75, p<0.001). The authors postulated that the bacterial aetiology of pneumonia among SAM children may be caused by Gram-negative bacteria (secondary to higher circulating levels of aflatoxin due to small bowel overgrowth and subsequent higher levels of endotoxin).<sup>58</sup> The study revealed a low yield of positive blood cultures as a cause of pneumonia, which is consistent with the low culture yield previously published children with pneumonia<sup>59</sup> although is a likely underestimate, as 16% of children in the study population had received prior antibiotic therapy. The few cultures which were positive demonstrated greater *in vitro* susceptibility to fluoroquinolones and extended-spectrum cephalosporins over ampicillin and gentamicin, however **the study did not clearly distinguish community from nosocomial infection. Overall, only 6/407 (1.4%) children in the study had a blood culture isolate that was not susceptible to ampicillin and gentamicin.** On the other hand, 3/407 (0.7%) study children also exhibited blood culture isolates that were not susceptible to ceftriaxone, and 1/407 (0.2%) that was not susceptible to ciprofloxacin.<sup>48</sup>

Another observational study<sup>20</sup> completed a clinical and biological characterisation of infections in children admitted with complicated SAM in Niger (n=311 children aged 6-59 months in 2007-2008) who were administered parenteral amoxicillin or ceftriaxone in cases of suspected severe or complicated infections with subsequent treatment targeted towards the infection type suspected. Gentamicin was not listed as an administered medication. The research revealed gastroenteritis was the most frequent

clinical diagnosis on admission, followed by respiratory tract infections and malaria. The majority of the presumed pathogenic organisms identified were Gram-negative bacilli, most frequently *Salmonella* spp (n=14, 4.5%) followed by Gram-positive cocci (*S. aureus*, n=17, 5.5%). Other pathogens (in order of frequency) included *E. coli*, *Klebsiella pneumonia*, *Salmonella typhi*, *Streptococcus pneumonia*, *Enterococcus faecium*, *Enterococcus faecalis* and *Streptococcus pyogenes*. Most Enterobacteriaceae isolated in this study were **resistant to amoxicillin and co-trimoxazole but susceptible to ceftazidime/ceftriaxone, gentamicin and quinolones**. Among the organisms isolated from urine (*E. Coli* and *K. pneumoniae*), almost 20% were resistant to gentamicin. Three specimens were identified with extended-spectrum beta-lactamase (ESBL) production (2 *E coli* and one *K. pneumoniae*). Almost all *S. aureus* (n=16/17, 94%) was resistant to penicillin, but all were sensitive to cloxacillin. These results concur with a recent epidemiological study in Niger,<sup>60</sup> where faecal carriage of extended spectrum beta-lactamase producing enterobacteriaceae (ESBL-E) on (n=55) children aged 6-59 months at a paediatric nutrition centre (part of the patient population documented by Page et. al.'s study), had a carriage rate of 31% (n=17/55) at admission; with an acquisition rate of 94% (n=15/16) among those who were not carriers at admission and were re-sampled on discharge. Of note, the CTX-M-15 gene was found in >90% of carriers. All children had received antibiotic treatment during hospitalisation, with 75% receiving more than one type (including amoxicillin, ceftriaxone and ciprofloxacin).<sup>60</sup>

Intestinal carriage of ESBL-E is a significant concern for the dissemination of multidrug-resistant bacterial infections, which would leave few therapeutic options open for treatment of sepsis; and the CTX-M gene is (in particular) of major concern due to its known spread in both hospital and community settings.<sup>61</sup> Previous research has revealed a link between beta-lactam exposure and intestinal colonisation by enterobacteria resistant to cephalosporins,<sup>62</sup> a consideration of concern when monitoring ongoing resistance patterns in children with SAM. If the spread of ESBL results in clinically effective antimicrobial therapy being narrowed to carbapenems, the consequences of further dissemination would be of extreme concern given their expense and general unavailability in low-income settings. These observational studies highlight the importance of continued monitoring of ESBL producing organisms in children admitted with SAM.

Current recommendations for administration of 2 days of penicillin/ampicillin followed by oral amoxicillin for a further 5 days, with concurrent gentamicin for the 7 days are based on no supporting evidence. Many children with complicated SAM will require more than 2 days of parenteral antibiotics for their primary condition.<sup>22,26,63</sup> Others will rapidly improve and become uncomplicated and ready for discharge home before 7 days. It is recognised that unnecessary inpatient care exposes these vulnerable children to the risks of hospital acquired infection and prolonged admission poses a significant financial burden on families.<sup>3</sup>

The current guidelines supporting a prolonged 7 day course of gentamicin are not based on RCT evidence of efficacy or risks.<sup>15</sup> Ototoxicity and nephrotoxicity effects may be more likely among children with complicated SAM, who often have abnormal renal function or dehydration. Gentamicin, an aminoglycoside antibiotic distributed into the extracellular fluid and eliminated by the kidneys, has its clinically efficacy determined by the relationship between the peak concentration and minimal inhibitory concentration (MIC), with similar pharmacokinetic parameters in malnourished and eutrophic children.<sup>64</sup> Gentamicin has advantages in covering many Gram-negative organisms including many *Pseudomonas* species (not covered by ceftriaxone), and convenient once daily dosing. For children with SAM this has been considered clinically effective and safe,<sup>65</sup> however no research has investigated the possible adverse effects caused by a prolonged course, and its safety is dependent upon children having

normal renal function (which may be impaired in children with complicated SAM presenting with dehydration). Furthermore, the British National Formulary advises serum gentamicin concentrations should be checked after the 3<sup>rd</sup> – 4<sup>th</sup> dose in a multiple dose regimen to avoid nephrotoxicity, an expensive and logistically impossible in low-income settings where SAM is usually treated.<sup>66</sup> **The implications of prolonged administration of gentamicin therefore requires consideration given inability to monitor renal function and serum concentrations in low-income settings.**

### 3.2.5. Evidence for alternative antibiotic therapies

Alcoba’s meta-analysis of 2,767 children with (all grades of) malnutrition pooled from observational data assessed antibiotic resistance data of bacterial cultures (blood, urine, cerebrospinal fluid) among children with SAM. Aside from the improved susceptibility (described above) for amoxicillin over co-trimoxazole, this analysis also documented susceptibilities for chloramphenicol and amoxicillin-clavulanate as 73.7% and 30.7% (respectively). Gentamicin, amoxicillin-gentamicin, ceftriaxone and ciprofloxacin exhibited the highest rates of susceptibility (>80%). These aggregated data (presented in Table 4) reveal the generally high resistances to first-line antibiotics in a population of mixed, moderate and severely malnourished children, in sub-Saharan Africa and Turkey.<sup>33</sup>

Antibiotic	Median	Interquartile Range	Population-weighted mean (meta-analysis)*
Amoxicillin	42	27-55	52.9
Co-trimoxazole	22	17-23	35.4
Gentamicin	80	77-85	72.8
Amoxicillin-Gentamicin combination	91.4	87-96	90.7
Chloramphenicol	57.5	46-69	73.7
Ciprofloxacin	93	82-93	90.0
Ceftriaxone	84	80-94	89.3
Amoxicillin-Clavulanate	51	23-56	30.7

\*Mean susceptibility weighed proportionally (coefficient) to number of patients (n) per study

**Table 4: Bacterial antibiotic susceptibilities (%) for common first- and second-line therapies for treating children with SAM; results of meta-analysis of n=767 children from Uganda, Kenya, Turkey, Nigeria, Kenya and South Africa<sup>33</sup>**

#### 3.2.5.1. Metronidazole

Metronidazole has anti-anaerobic and anti-protozoal activity and is effective against small bowel bacterial overgrowth and *Clostridium difficile* colitis. The 2013 WHO guidelines state “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.”<sup>4</sup> Metronidazole is commonly used and is effective against Giardia; anaerobic infections, small bowel bacterial overgrowth and *Clostridium difficile* colitis. In a recent trial treating enteropathy in SAM in a Nairobi slum,<sup>67</sup> >30% of children had Giardia on microscopy. In Rwanda, amongst malnourished children, Giardia prevalence was 20% by microscopy and

60% by PCR.<sup>68</sup> Its antimicrobial effect is dependent on its peak concentration, and there is a significant 'post-antibiotic' killing effect.

Small cohort studies suggest benefits for nutritional recovery, which is associated with improved survival. In Jamaica, half of the children admitted for nutritional rehabilitation had evidence of small bowel anaerobic bacterial overgrowth on breath hydrogen testing, associated with reduced appetite and increased stool frequency. Breath hydrogen normalised after 5 days of oral metronidazole.<sup>69</sup> However, metronidazole can cause nausea and anorexia, potentially impairing recovery from malnutrition. It may also cause liver and neurological toxicity (Table 7). The one small pharmacokinetic study of metronidazole in children with SAM, conducted in Mexico, reported significantly prolonged clearance in SAM, suggesting a dosing frequency reduction may be warranted.<sup>70</sup> Their findings concord with a small-animal study. However, these studies are insufficient evidence to be conclusive or to alter policy. **Pending the results of a currently ongoing pharmacokinetic study and clinical trial (see below), its routine use should not be recommended in SAM.**<sup>15</sup>

#### 3.2.5.2. Amoxicillin Clavulanate

There have been no trials or pharmacokinetic studies of Amoxicillin Clavulanate in malnourished children. The (anecdotal) use of this drug in SAM has been with the intention of tackling both systemic infection and small intestinal bacterial overgrowth. However, Alcoba's review<sup>33</sup> (see above) suggests that *in vitro* susceptibility may be limited.

#### 3.2.5.3. Ciprofloxacin

As revealed by Alcoba's review (Table 4), susceptibilities are above 80% for most second-line antibiotics, including ciprofloxacin. Ciprofloxacin could be a suitable alternative antibiotic for the management of sepsis in severely malnourished children, and absorption is not affected by the simultaneous administration of milk feeds.<sup>71</sup> As with third generation cephalosporins however, the risk of dissemination of resistance to this important antimicrobial needs to be weighed against its clinical efficacy. To target its use, in light of the high rates of gastrointestinal presentations in children with complicated SAM, **future clinical studies could investigate the option of oral ciprofloxacin as first- or second line therapy for children with complicated SAM presenting with gastrointestinal symptoms**, together with broad-spectrum parenteral therapy.

#### 3.2.5.4. Chloramphenicol

One clinical trial of initial antibiotic management of 144 Gambian children was published in 1995.<sup>27</sup> Study drugs were administered for one week together with oral metronidazole, vitamins and standardised nutritional therapy. Clinical failure was not related to *in vitro* antimicrobial resistance in the 20 cases in which invasive bacterial isolates were obtained. An equal number in each group failed treatment. There are no trials of parenteral chloramphenicol in SAM. Antimicrobial susceptibilities appear to offer few advantages over other treatments and there are potential concerns regarding reduced drug elimination in SAM (see below).

#### 3.2.5.5. Ceftriaxone

No clinical trials or pharmacokinetic studies in complicated SAM have been published. While the potential superiority of oral third generation cephalosporins (cefdinir) in uncomplicated SAM has been highlighted above,<sup>46</sup> in light of the susceptibility data revealed by Alcoba's review, **parenteral ceftriaxone should also be a focus of clinical trials for children with complicated SAM.** Ceftriaxone has a broad-spectrum

of activity, is logistically simple in its daily dose administration (which may be intra-muscular) and has a wide therapeutic index, which increases its safety and efficacy. Short courses are effective.<sup>32</sup>

#### 3.2.5.6. *Azithromycin*

Azithromycin has been considered a promising possible alternative for uncomplicated SAM since mortality benefits were observed following its mass distribution for trachoma control in Ethiopia.<sup>72</sup> However, no trials or pharmacokinetic studies have yet been conducted in children with SAM, and should be of consideration for the future.

#### 3.2.5.7. *Co-trimoxazole as prophylaxis*

Daily co-trimoxazole prophylaxis is recommended for children with HIV infection, where it reduces all-cause mortality.<sup>73</sup> Although replaced by amoxicillin for treatment in SAM in recent guidelines, a recent multi-centre, double-blind RCT<sup>9</sup> conducted across four sites in Kenya assessed the use of co-trimoxazole as prophylaxis in the same way it is used in HIV. Children (n=1778 HIV-negative children aged 2-59 months admitted with complicated SAM) were randomly assigned to receive either daily co-trimoxazole prophylaxis or a matched placebo for 6 months, after clinical nutritional stabilisation. During 1,527 child-years of observation, 122 (14%) of 887 children in the co-trimoxazole group died, compared with 135 (15%) of 891 in the placebo group (HR 0.90, 95% CI 0.71 to 1.16, p=0.429). There was no significant impact on mortality or growth and it is postulated that differing infections in HIV and/or antimicrobial resistance may be responsible for the lack of clinical impact seen (which would have significance for prophylaxis in HIV).<sup>9</sup>

#### 3.2.6. *Pharmacokinetics in SAM*

The pharmacokinetics of the above therapies in children with SAM (including comparison to eutrophic controls), where available, have been detailed in prior reviews.<sup>32,38</sup> In 2010, Oshikoya et al. published a review of the pharmacokinetics of 34 drugs (including non-antimicrobials) among children with SAM.<sup>38</sup> Absorption was significantly decreased for oral chloramphenicol in kwashiorkor. Otherwise, the available data did not permit drawing firm conclusions on the effects of SAM on drug absorption rates. Several drugs had reduced protein binding: chloramphenicol, (flu)cloxacillin, penicillin and sulphamethoxazole. Clearance was decreased for drugs metabolised in the liver: chloramphenicol and metronidazole, which is of concern regarding potential toxicity. Clearance was largely unchanged for drugs metabolised in the kidneys: cefoxitin, penicillins, gentamicin and amikacin. In the review by Lazzerini et al. in 2011, normal doses of penicillins, co-trimoxazole and gentamicin were deemed safe in malnourished children, while the review concluded, as did Oshikoya et al., that the dosing regimen for chloramphenicol requires adjustment if it is to be used.<sup>32</sup> Lazzerini et al. did not review the pharmacokinetics of metronidazole, which also likely requires adjustment and is discussed above.

Since these reviews were written, in 2011, a population pharmacokinetic study of ciprofloxacin in 52 children with SAM in Kenya reported that 10 mg/kg three times daily (30 mg/kg/day) rather than the usual 10 mg/kg twice daily (20 mg/kg/day) may be a suitable alternative antibiotic for the management of sepsis in severely malnourished children.<sup>71</sup> Absorption was unaffected by the simultaneous administration of milk feeds. In 2016, a population pharmacokinetic study of gentamicin in 26 children with SAM in Mexico reported that an intravenous dose of 7.5 to 15 mg/kg once daily in children with SAM and normal renal function has a high probability of efficacy and low risk of nephrotoxicity.<sup>51</sup>

## 4. Synopsis of international guidelines

There are no international guidelines for the management of complicated or uncomplicated malnutrition published by the IDSA, CDC, AAP, or TG (Australia). A summary of available international guidelines is documented in Table 5. All guidelines currently recommend amoxicillin as their first line therapy in uncomplicated SAM, although they vary in the recommended dosage (from 45mg/kg/day to 100mg/kg/day) and duration (5 days to 7 days).

For complicated SAM, there is variation in the first-line therapy recommended, with *Valid International* recommending chloramphenicol therapy in their 2006 guidelines. Other guidelines provide a range of recommendations which include ampicillin/amoxicillin, gentamicin or alternatives including a wide spectrum of antibiotics – including third generation cephalosporins, ciprofloxacin, co-amoxiclav, metronidazole, and even amikacin. Dosages also vary for medications, with gentamicin recommendations varying from 5mg/kg to 7.5mg/kg; although beta-lactam dosages are consistent throughout.

Author & URL	Year	Guideline Title	Uncomplicated SAM	Complicated SAM
BMJ <a href="http://bestpractice.bmj.com/best-practice/monograph/1022/treatment/details.html">http://bestpractice.bmj.com/best-practice/monograph/1022/treatment/details.html</a>	2011	Clinical Evidence: Kwashiorkor	7 day treatment course <b>Amoxicillin</b> 80-90mg/kg/day orally in to divided doses OR <b>Cefdinir</b> 14mg/kg/day orally as a single dose, or as two divided doses (recommendation based on <sup>46</sup> )	<b>Gentamicin</b> 7.5mg/kg IM/IV once daily for 7 days AND <b>Ampicillin</b> 200mg/kg/day IM/IV in 4 divided doses OR <b>Chloramphenicol</b> 50mg/kg/day IM/IV in divided doses every 6-8 hours *choice depends on local microbiological sensitivity patterns  Second line: <b>Ceftriaxone</b> 50-75mg/kg/day IM/IV in divided doses every 12-24 hours (Based on: <sup>74</sup> )
ACF (Action Contre la Faim) *This regimen is used in many national protocols e.g. Ethiopia, Niger. <a href="http://www.actionagainsthunger.org/sites/default/files/publications/Guidelines%20For%20the%20integrated%20management%20of%20severe%20acute%20malnutrition%20in%20and%20out%20patient%20treatment%2012.2011.pdf">http://www.actionagainsthunger.org/sites/default/files/publications/Guidelines For the integrated management of severe acute malnutrition In and out patient treatment 12.2011.pdf</a>	2011	Guidelines for the treatment of SAM	<b>Amoxicillin</b> for 7 days; 50-100mg/kg/day divided in 2 doses	add "low-dose" Gentamycin 5mg/kg daily If no improvement or signs of sepsis, change to <b>Co-amoxiclav</b> plus antifungal ( <b>Fluconazole</b> )

Author & URL	Year	Guideline Title	Uncomplicated SAM	Complicated SAM
Médecins Sans Frontières <a href="http://refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf">http://refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf</a>	2016	Clinical Guidelines	Amoxicillin for 5 Days (70-100 mg/kg/day) divided in 2 doses	“Since the infectious focus may be difficult to determine, a broad-spectrum antibiotic therapy ( <b>cloxacillin</b> + <b>ceftriaxone</b> ) is recommended” (Dosage and time frame not specified)
Valid International <a href="http://www.fantaproject.org/sites/default/files/resources/CTC-Field-Manual-Oct2006-508.pdf">http://www.fantaproject.org/sites/default/files/resources/CTC-Field-Manual-Oct2006-508.pdf</a>	2006	CTC Field Manual	<b>Amoxicillin</b> for 7 Days (<10kg: 3x125mg; 10-30kg: 3x250mg; >30kg: 3x500mg)	<b>Chloramphenicol PO</b> (2-5.9 kg: 3x62.5mg; 6-9.9kg: 3x125mg; 10-30kg: 3x250mg) (7 Days) as <i>outpatient with moderate complications</i> (e.g. fever not responding).
Indian Academy of Paediatrics <a href="http://medind.nic.in/ibv/t07/i6/ibvt0716p443.pdf">http://medind.nic.in/ibv/t07/i6/ibvt0716p443.pdf</a>	2006 2013	IAP Guidelines 2006 on Hospital Based Management of Severely Malnourished Children	Not documented  updated 2013 guidelines did not address antibiotic use	<b>Ampicillin</b> 50 mg/kg/dose 6 hourly I.M. or I.V. for at least 2 days; followed by <b>oral Amoxycillin</b> 15 mg/kg 8 hourly for five days (once the child starts improving) plus <b>Gentamicin</b> 7.5 mg/kg or <b>Amikacin</b> 15-20 mg/kg I.M or I.V once daily for seven days.  If the child fails to improve within 48 hours, change to IV <b>Cefotaxime</b> (100-150 mg/kg/day 6-8 hourly)/ <b>Ceftriaxone</b> (50-75 mg/kg/day 12 hourly).  “However, depending on local resistance patterns, these regimens should be accordingly modified.”  “Some experienced doctors routinely give <b>metronidazole</b> (7.5 mg/kg 8-hourly for 7 days) in addition to broad-spectrum antibiotics. However, the efficacy of this treatment has not been established by clinical trials.”
Government of Bangladesh <a href="http://www.unicef.org/bangladesh/SAM_Guideline.pdf">http://www.unicef.org/bangladesh/SAM_Guideline.pdf</a>	2008	National Guidelines for the Management of Severely Malnourished Children in Bangladesh	Amoxicillin oral 15 mg/kg 8-hourly for 5 days OR Co-trimoxazole oral; Trimethoprim 5mg/kg and Sulphamethoxazole 25mg/kg 12-hourly for 5 days	Ampicillin IM/IV 50 mg/kg 6-hourly for 2 days, then amoxicillin oral 15 mg/kg 8-hourly for 5 days AND Gentamicin IM/IV 7.5 mg/kg once daily for 7 days. If the child is not passing urine, Gentamicin may accumulate in the body and cause deafness. Do not give second dose until the child is passing urine.  If the child fails to improve clinically by 48 hours or deteriorates after 24 hours,

Author & URL	Year	Guideline Title	Uncomplicated SAM	Complicated SAM
				or if the child presents with septic shock or meningitis, antibiotics with a broader spectrum may be needed (e.g. ceftriaxone 50-100 mg/kg/d IV/IM once daily along with or without gentamicin).
UNICEF, MoH Kenya <a href="http://www.cmamforum.org/pool/resources/kenya-moh-imam-guideline-june-2009.pdf">http://www.cmamforum.org/pool/resources/kenya-moh-imam-guideline-june-2009.pdf</a>	2009	National Guideline for Integrated Management of Acute Malnutrition	Oral Amoxicillin, by weight range, equivalent to 25 to 50mg/kg twice daily  Age <6 months, 30mg/kg twice daily	Add chloramphenicol (do not stop amoxicillin) OR Add gentamicin (do not stop amoxicillin) OR Switch to amoxicillin/clavulanic acid.
Kenya MoH and Kenya Paediatric Association <a href="https://www.tropicalmedicine.ox.ac.uk/_asset/file/basic-paediatric-protocols-2016.pdf">https://www.tropicalmedicine.ox.ac.uk/_asset/file/basic-paediatric-protocols-2016.pdf</a>	2016	Basic Paediatric Protocols	Not covered	Penicillin (or Ampicillin) AND Gentamicin. Give 5 days gentamicin, if improved change Pen to Amoxicillin at 48 hrs.
Malawi Government <a href="http://www.unicef.org/malawi/MLW_resources_severemalnutrition.pdf">http://www.unicef.org/malawi/MLW_resources_severemalnutrition.pdf</a>	2006	Guidelines for the Management of Severe Acute Malnutrition.	Oral Amoxicillin 15mg/kg three times daily.	Gentamicin IM/IV 7.5 mg/kg once daily for 7 days AND Chloramphenicol IM/IV 25mg/kg three times daily for a 5 days

**Table 5: Synopsis of international guidelines**

## 5. Review of Harms and Toxicity – Summary of Evidence on Safety

Of the studies included in this review which included data on safety and adverse events, there was not a significant rate of adverse events documented in antibiotic intervention groups.<sup>9,31,32,37</sup>

### 5.1. Side effects and relevant interactions

Side effects and relevant interactions of the currently recommended therapies for treating SAM, and those which may be of consideration for future clinical trials, are documented in Table 6.



Antibiotic	Life threatening	Mild adverse effects, which may result in discontinuation of treatment	Other	Relevant Interactions
Benzylpenicillin	Hypersensitivity reactions; anaphylaxis (<0.05% of patients)	Joint pain; diarrhoea; rashes; urticaria Allergic reactions occur in up to 10% of exposed individuals	Cerebral irritation; coagulation disorders; haemolytic anaemia; leucopenia; thrombo-cytopaenia	Antagonised by tetracyclines
Ampicillin; Amoxicillin	As for benzylpenicillin	Erythematous rashes may occur with CMV or EBV infections	As for benzylpenicillin	As for benzylpenicillin
Gentamicin	Hypersensitivity reactions	Nausea; stomatitis; vomiting	Nephrotoxicity, especially in children with impaired renal function <u>*of note when administering to children presenting with severe dehydration in complicated SAM</u>  Antibiotic associated colitis; electrolyte disturbances; auditory damage; irreversible ototoxicity; vestibular damage	Plasma concentration of gentamicin in neonates possibly increased by indomethacin -All aminoglycosides have increased risk of nephrotoxicity when administered with amphotericin, capreomycin, cephalosporins, polymyxins, tacrolimus, vancomycin, ciclosporin, and loop diuretics  Plasma monitoring is recommended after 3-4 doses
Amoxicillin-Clavulanate	Hypersensitivity reactions	Cholestatic jaundice; hepatitis; nausea; vomiting; dizziness; headache	Vasculitis	As for benzylpenicillin
Metronidazole	Hypersensitivity reactions	Anorexia; gastrointestinal disturbance; nausea; taste disturbance; vomiting	Aseptic meningitis; ataxia; pancytopenia	
Co-trimoxazole	Agranulocytosis; bone marrow suppression	Diarrhoea; headache; hyperkalaemia; nausea; rash; vomiting	Antibiotic-associated colitis; myocarditis; pericarditis; pancreatitis; vasculitis	-Increase toxicity of anti-neoplastic drugs

Antibiotic	Life threatening	Mild adverse effects, which may result in discontinuation of treatment	Other	Relevant Interactions
Chloramphenicol	<p>-<u>Grey syndrome</u> may occur with intravenous use in neonates (abdominal distension, pallid cyanosis, circulatory collapse)</p> <p>-Bone marrow toxicity: reversible and irreversible aplastic anaemia</p>	Diarrhoea; depression; erythema multiforme; headache; nausea; urticaria; vomiting	Nocturnal haemoglobinuria; optic or peripheral neuritis	<p>-Increases plasma concentration of ciclosporin, anti-epileptic therapies</p> <p>-Metabolism of chloramphenicol is accelerated by rifampicin</p> <p>-Chloramphenicol enhances effects of sulfonyleureas</p>
Fluoroquinolones: Ciprofloxacin	Hypersensitivity reactions; Prolonged QT syndrome	Dyspepsia, headache, diarrhoea, vomiting, hypotension	Tendinitis and tendon rupture; peripheral (poly)neuropathy	<p>-All fluoroquinolones should be used with caution in patients receiving drugs known to prolong the QT interval (see below)</p> <p>-The toxicity of fluoroquinolones is increased by the concurrent use of systemic steroidal medications</p> <p>-Fluoroquinolones' effects are reduced by the co-administration of iron- and zinc-containing products, of importance when zinc-containing products are used to treat diarrhoea in children</p> <p>-Fluoroquinolones cause additive toxicity with non-steroidal anti-inflammatory drugs (Ibuprofen, Meloxicam, Naproxen)</p>
Azithromycin	Hypersensitivity Reactions; Prolonged QT Syndrome	Dyspepsia, flatulence, headache,	Malaise, paraesthesia	-All macrolides are advised to be avoided concomitantly with other drugs which

Antibiotic	Life threatening	Mild adverse effects, which may result in discontinuation of treatment	Other	Relevant Interactions
		disturbance in taste, anorexia		prolong the QT interval, (including anti-malarial medications such as artemether-lumefantrine) due to the risk of ventricular arrhythmias (see below) -Plasma concentrations of azithromycin are increased by ritonavir -Azithromycin in combination with rifabutin results in increased side-effects of rifabutin, including neutropenia
Ceftriaxone	Hypersensitivity reactions	Diarrhoea, headache, abdominal discomfort	Transient cholestatic jaundice due to biliary sludge formation	Relevant interactions for all cephalosporins: -Increased risk of nephrotoxicity when co-administered with aminoglycosides -Enhance anticoagulant effect of coumarins
Cefixime (specific Cefnidir side effects and interactions not published)	Hypersensitivity reactions; immune-mediated haemolytic anaemia	Flatulence, headache, abdominal pain, defecation urgency, nausea, constipation, vomiting	Transient cholestatic jaundice due to biliary sludge formation	As per ceftriaxone

**Table 6: Common adverse reactions to antibiotics used in severe acute malnutrition in children.**<sup>75</sup>

### 5.1.1. Peripheral (poly)neuropathy

For consideration of ciprofloxacin as an alternative therapy for treating children with SAM, the possible adverse event of peripheral (poly)neuropathy should be considered. In 2013, the FDA issued a communique to specifically address the risk of peripheral neuropathy (PN) for all oral fluoroquinolones,<sup>76</sup> predominantly in response to case reports of this adverse event,<sup>77,78</sup> in the absence of large epidemiological studies. The neurotoxic mechanism is thought to be through the inhibition of GABA-receptors, which occurs within days of use, and may be permanent. Between 1997 to 2012, the FDA's AERS recorded 539 reports (1% of all submitted events for fluoroquinolones) pertaining to peripheral neuropathy. A review of these reports found the majority of affected patients were females, with a median age of 48 years (range 9-100 years).<sup>78</sup> This evidence was further investigated by a 2014

pharmaco-epidemiological study which quantified this risk, revealing a relative risk of developing peripheral neuropathy with fluoroquinolone use of 2.07 (95% CI 1.56 to 2.74). In regards to ciprofloxacin specifically, the increased risk was quantified as RR=1.93 (95% CI 1.32 to 2.82); a small but appreciable increase. However, this research was based on a cohort of men with a mean age of 68 years, and it is difficult to extrapolate this data to the paediatric population.<sup>79</sup> Due to the risk of permanent disability due to peripheral neuropathy occurring with fluoroquinolone usage, the most recent FDA warning highlights fluoroquinolone administration as only being indicated when no other treatment option is available.<sup>80</sup>

### 5.1.2. Prolongation of the QT interval

Case reports of fluoroquinolones and macrolides have been associated with prolongation of the QT interval.<sup>81,82</sup> Independently, mild delays in ventricular repolarisation are clinically unnoticeable, though these antimicrobials may serve to amplify the risk for torsades de pointes (TdP), a potentially fatal polymorphic ventricular tachyarrhythmia which may present as sudden death (due to ventricular tachycardia), syncope, palpitations, seizures or asymptotically if the duration is short and terminates spontaneously.<sup>83</sup> Of note, the current literature identifies this risk as requiring the presence of other risk factors, including underlying cardiac disease, electrolyte derangement, or genetic risk factors. The predominant risk factor is co-administration of other medications which are substrates and/or inhibitors of cytochrome P450 (CYP) enzymes, and the associated with 'metabolic liability' resultant from co-administration of medications synergistically interacting with this enzyme. This risk is enhanced by individual allelic variations in CYP3A4, the most important enzyme in human drug metabolism. CYP3A4 is responsible for the biotransformation of approximately 60% of all oxidised drugs<sup>84</sup> and allelic variations can result in patients being poor metabolisers of CYP3A4 inducing medications,<sup>83</sup> resulting in reduced clearance of drug substrates and increasing exposure to toxicity effects. In conclusion, the individual risk of cardiac arrhythmias secondary to these antimicrobials is minimal; yet combined with genetic propensity to poor metabolism of CYP3A4 inducing medications and co-administration with other CYP potentiators, the risk is magnified.

## 6. Summary of Comparative Cost and Cost-effectiveness

Antibiotic	Per Unit Cost	Cost per treatment course (for ~20kg child)	Notes
Amoxicillin	\$0.0090/ml \$0.0063/ml	\$4.03 \$1.41 <i>(based on 40mg/kg bd for 7 days)</i>	125mg/5ml suspension 250mg/5ml suspension
Ampicillin	\$0.2720/vial \$0.3313/vial	\$2.18 <i>(based on 50mg/kg qid for 2 days)</i>	1g vial 500mg vial
Gentamicin	\$0.0802/ml	\$2.11 <i>(based on 7.5mg/kg for 7 days)</i>	40mg/ml ampoule
Benzympenicillin	\$0.6800/vial; 5m IU	\$1.36 <i>(based on 50,000IU/kg qid for 2 days)</i>	Powder form, requires reconstitution
Ciprofloxacin	\$14.10 per 100ml bottle=0.14/ml	\$11.85 <i>(based on 30mg/kg/day for 7 days)</i>	250mg/5mL suspension
Azithromycin	\$0.058/ml	\$0.58 <i>(based on 20mg/kg as a single dose)</i>	200mg/5mL suspension

	Per Unit Cost	Cost per treatment course (for ~20kg child)	Notes
Metronidazole	\$0.0069/ml	\$0.54 <i>(based on 7.5mg/kg tds for 7 days)</i>	200mg/5mL; 100ml suspension
Amoxicillin-clavulanate	\$0.0161/mL	\$2.03	250+62.5mg/5mL suspension
Cefixime * cefdinir data N/A	\$1.40 per 30ml bottle = \$0.047/mL	\$2.62 <i>(based on 8mg/kg/day for 7 days)</i>	100mg/5mL suspension
Ceftriaxone	Median price: 1 vial of 1g= \$0.42/vial	\$1.26 <i>(based on 75mg/kg/day for 2 days)</i>	Parenteral administration
Chloramphenicol	\$0.4830/vial	Not currently clinically indicated	1g vial
Co-trimoxazole (Sulfamethoxazole-Trimethoprim)	\$0.0048/ml	Not currently clinically indicated	200+40mg/5mL suspension

**Table 7: Comparative cost effectiveness of medications used to treat severe acute malnutrition (<https://www.erc.msh.org>)**

A cost comparison of the medications listed in international guidelines is documented in Table 7, based on data from the Management Sciences for Health (MSH) International Drug Price Indicator Guide (<https://www.erc.msh.org>). **The current WHO recommended first-line therapies (amoxicillin/ampicillin, benzylpenicillin, gentamicin) remain the most cost effective options.** The increased cost of oral (for uncomplicated SAM) or parenteral (for complicated SAM) third generation cephalosporins should be of consideration for future guidelines, should further evidence to their superior efficacy (and increased non-susceptibility to beta-lactams) emerge. Similarly, should clinical trials investigate ciprofloxacin or amoxicillin-clavulanate, consideration of the increased cost this would inflict on health systems should be contemplated; although there may also be cost savings to consider, should the administration of these more susceptible antibiotics avoid admission to hospital due to improvements in clinically effective treatment.

## 7. Ongoing clinical trials

The following international trial registries were reviewed: <http://www.who.int/ictrp/en/>; <https://clinicaltrials.gov/>; <http://www.isrctn.com/>; <http://www.anzctr.org.au/>; <https://www.clinicaltrialsregister.eu/>.

**Only one current clinical trial investigating the antimicrobial treatment of severe acute malnutrition in children.** This trial is currently recruiting patients in sub-Saharan Africa and aims to investigate the pharmacokinetics of intravenous ceftriaxone and oral metronidazole in children with complicated SAM and effects on faecal carriage of ESBL at admission and discharge to hospital as a preliminary phase to a large multicentre RCT of these agents for outcomes of mortality and nutritional recovery. For further information: <https://clinicaltrials.gov/ct2/show/study/NCT02746276>.

## 8. Discussion and Recommendations for Further Research

Nearly twenty million children suffer from severe acute malnutrition, resulting in 1 million deaths each year by increasing susceptibility to death from severe infection. Children with SAM benefit from antimicrobial therapy due to the effects on overt infections, covert infection and colonising microorganisms, minimising nutrient diversion by diminishing inflammatory responses, and reducing enteropathy via alterations in the intestinal microbiome. This review has revealed moderate-quality evidence indicating broad-spectrum antibiotic therapy is beneficial for survival in children suffering from uncomplicated SAM. **The currently available evidence supports continued recommendation of empiric parenteral benzyl-penicillin or ampicillin plus gentamicin followed by oral amoxicillin once clinically stable for complicated SAM; and oral amoxicillin for seven days in uncomplicated SAM. For complicated SAM following parenteral antibiotics and for uncomplicated SAM, the amoxicillin dosage should be clarified as 40mg/kg twice daily.** Adaption should be based on sound microbiological data. **Future reporting of anti-microbial susceptibilities needs to be done in a standardised way, with clear denominators, separating data from community and nosocomially-acquired infections, and linked to HIV-status, the treatments given and patient outcomes.**

The implications of a prolonged course of gentamicin (in settings in which trough levels and renal function are not routinely able to be checked) requires ongoing consideration and clarifying the length of gentamicin course required should be a priority research area for future clinical studies.

With increasing antimicrobial resistance, clinical trials are paramount to ensure effective treatments remain available. For complicated SAM, a current pharmacokinetic study and clinical trial investigating parenteral ceftriaxone and oral metronidazole will be important in this regard. For uncomplicated SAM, further **RCTs adhering to CONSORT guidelines should investigate alternative options such as azithromycin, ciprofloxacin, and oral third-generation cephalosporins**, which have previously shown benefit. The risk of further resistance and high rates of community- and nosocomial-acquired ESBL in children with malnutrition who have a high burden of exposure to the healthcare environment will need to be balanced against recommendations to include such therapies in empirical clinical guidelines. Meanwhile, the small but plausible risk of adverse effects of these therapies will need to be considered, bearing in mind that the benefits (and lower cost) may well outweigh the risk of these events in lower-income settings.

## 9. Conclusions

- **The current evidence supports the continued use of broad-spectrum oral antibiotics for treating children as outpatients with uncomplicated SAM.** For uncomplicated SAM, this is based on meta-analysis of two clinical trials which indicates an overall benefit for mortality and a reduction in hospitalisation episodes.
- **The dosage regimen of amoxicillin for uncomplicated SAM, and for complicated SAM (after IV/IM antibiotics and the child has stabilised), should be clarified and harmonised to 40mg/kg twice daily** (it is currently 25-40mg/kg three time daily in the 2013 pocketbook).
- The guidelines should be clarified for complicated SAM, to **continue IV/IM antibiotics beyond 2 days if this is indicated by the clinical condition** e.g. severe pneumonia or sepsis.
- There is very limited evidence suggesting oral cephalosporins might be more effective than amoxicillin in preventing mortality in children with uncomplicated SAM. However, cephalosporins carry an increased risk of exacerbating antimicrobial resistance and therefore **recommendations should not be changed without further evidence from clinical trials of risks and benefit.**
- There is very limited evidence suggesting **parenteral** third-generation cephalosporins might be more effective than ampicillin/gentamicin in treating children with complicated SAM. Cephalosporins carry an increased risk of exacerbating antimicrobial resistance and therefore recommendations **should not be changed without further evidence from clinical trials of risks and benefit.**
- The indication for a 7-day course of gentamicin in complicated SAM who commonly have dehydration and compromised renal function needs **ongoing consideration** due to the potential ototoxic and nephrotoxic adverse events in this population. In developed countries, measurement of trough levels is recommended after 3-4 doses, but this is almost never available in the settings where SAM is treated. However, the risks of toxicity have not been well characterised and there are limited affordable alternative choices of antimicrobials in typical settings.
- There is increasing evidence of non-susceptibility to commonly used antimicrobials in children with SAM, including high rates of community- and nosocomial-acquired ESBL. Monitoring for antimicrobial resistance in the population, including distinguishing community from nosocomial infections, should be a routine practice when empiric broad-spectrum antibiotics are used for any community-treatment of children with life-threatening illness, including SAM.
- There are significant variations in published international guidelines for the suggested antimicrobial therapies for empirical treatment of complicated SAM, many of which pre-date recent trials and new recommendation, and require updating.

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	Author	Title	Year	Methods (Study Type, Setting, Participants)	Results	Conclusions	GRADE level of evidence
1	Alcoba et al. <sup>1</sup>	<b>Do children with uncomplicated severe acute malnutrition need antibiotics? A systematic review and meta-analysis.</b>	2013	<ul style="list-style-type: none"> <li>• Systematic review and meta-analysis</li> <li>• Not restricted by region</li> <li>• Children aged 6-59 months; plus 0-15 years for indirect evidence</li> <li>• Children with HIV and TB were included in the analysis</li> <li>• 2,767 strictly SAM children;</li> <li>• Case definitions: Complicated SAM = WfH&lt;-3 Z-score and/or bilateral pitting oedema and/or WfH&lt;70% of median and/or MUAC&lt;110mm. Uncomplicated SAM = SAM children passing appetite test, afebrile, no clinical infections or complications, treated by health centre</li> <li>• Outcomes: Antibiotic efficacy was defined as a measure of effect such as OR, RR, or risk reduction % in endpoints including: case-fatality rates (CFR), recovery rate, nutritional cure (weight-for-height within normal range &gt;80% of median or &gt;2 Z scores), infection incidence, AB susceptibility/resistance</li> <li>• Due to heterogeneity of inclusion criteria, a meta-analysis of intervention studies was not possible though meta-analysis of observational data was conducted.</li> </ul>	<ul style="list-style-type: none"> <li>• 3 RCTs, 5 Cochrane reviews, 37 observational studies identified as meeting inclusion criteria</li> <li>• <b>Prevalence of serious infections</b> in SAM, pooled from 24 studies, ranged from <b>17% to 35.2%</b>.</li> <li>• One cohort-study showed <b>no increase in nutritional-cure and mortality</b> in uncomplicated SAM where no AB were used (p&gt;0.05).</li> <li>• However, an unpublished RCT in this setting <b>did</b> show mortality benefits (Trehan 2013)</li> <li>• Another RCT <b>did not show superiority of ceftriaxone over amoxicillin</b> for these same outcomes, but addressed SAM children with and without complications (p=0.27).</li> <li>• One RCT showed no difference between amoxicillin and cotrimoxazole efficacies for pneumonia in underweight, but not SAM.</li> <li>• Review of <u>international guidelines</u> revealed <b>inconsistencies</b> in the recommended first-line antibiotic (AMX and CTX) with 5 different dosages: CTX 4-5mg/kg/d, AMX 50-100 or 70-100mg/kg/day or 3 weight classes and 2 different durations (5 or 7 days)</li> </ul>	<ul style="list-style-type: none"> <li>• Meta-analysis of 12 pooled susceptibility-studies for all types of bacterial isolates, including 2767 strictly SAM children, <b>favoured amoxicillin over cotrimoxazole for susceptibility</b> medians: 42% (IQR 27–55%) vs 22% (IQR 17–23%) and <b>population-weighted-means</b> 52.9% (range 23–57%) vs 35.4% (range 6.7–42%).</li> <li>• <b>Susceptibilities to second-line AB were better</b>, above 80%.</li> <li>• No study inferred any association of infection prevalence with AB regimens in SAM.</li> <li>• The authors concluded that: “the evidence underlying current antibiotic recommendations for uncomplicated SAM is weak” and called for placebo-controlled RCTs to demonstrate efficacy</li> <li>• Given that antibiotics have side-effects, costs, and risks as well as benefits, the authors conclude that their routine use needs urgent testing.</li> <li>• The 3 studies that directly evaluate antibiotics in SAM revealed three contrasting results: <ol style="list-style-type: none"> <li>1) AB not superior to no-AB</li> <li>2) CEF superior to AMX and AMX superior to placebo</li> <li>3) CEF not superior to AMX None of these studies provided stratified analyses for HIV+ SAM children.</li> </ol> </li> </ul>	B (Meta-analysis based on observational data)
2	Picot et al. <sup>2</sup>	<b>The effectiveness of interventions to treat severe acute malnutrition in young children: a systematic review</b>	2012	<ul style="list-style-type: none"> <li>• Systematic Review</li> <li>• Children &lt;5 years</li> <li>• Search period 2010-2012</li> <li>• Not restricted by region</li> </ul>	<ul style="list-style-type: none"> <li>• 8 databases were searched: Medline, Embase, Medline in-process and other non-indexed citations, CAB abstracts ovid, Bioline, centre for reviews and dissemination, EconLit EBSCO and Cochrane</li> <li>• 74 articles describing 68 studies (RCTs, CCTs, cohort studies and case-control studies) met the</li> </ul>	<ul style="list-style-type: none"> <li>• The authors concluded that there is very limited evidence regarding many aspects of SAM in children &lt;5 years, including management of subgroups (children &lt;6/12 or children with SAM who are HIV+) and the use of antibiotics</li> </ul>	B (systematic review with only 2 studies retrieved with epidemiological limitations)

				<p>inclusion criteria</p> <ul style="list-style-type: none"> <li>No evidence focused on HIV+ children; and no trials were conducted on children &lt;6/12</li> <li>Two studies (one RCT and one retrospective cohort study - Dubray 2008; Trehan 2010) of moderate methodological quality investigated the use of antibiotic therapy in children with SAM</li> <li>Dubray 2008: An un-blinded RCT conducted in Sudan (n=458) which indicated oral amoxicillin (80mg/kg/day in to divided doses) for 5 days was as effective as IM ceftriaxone for days.<sup>3</sup> ITT analysis revealed that 53.5% (123/230) in the amoxicillin group and 55.7% (127/228, difference 2.2%, 95% CI -6.9-11.3) in the ceftriaxone group had a weight gain of &gt;= 10 g/kg/day during a 14-day period. Recovery rate was 70% (161/230) in the amoxicillin group and 74.6% (170/228) in the ceftriaxone group (p=0.27). Case fatality rates were 3.9% (9/230) and 3.1% (7/228), respectively (p=0.67). Most deaths occurred within the 1st 2 weeks of admission.</li> <li>A second large retrospective study in Malawi (Trehan 2010) compared oral amoxicillin (60mg/kg/day; n=498) for 7 days to no antibiotics (n=1,955), revealing a poorer recovery rate for children receiving amoxicillin at 4 weeks (39.8% vs 70.8%; p &lt; 0.001), but a similar rate of recovery at 12 weeks, with similar rates of death and default.<sup>4</sup> However, this research is at risk of bias not just due to its retrospective data collection, but also due to the different district locations of the to cohorts of patients, ho ere also not stratified by risk of HIV-infectivity status (with a high burden among the study population).</li> </ul>			
3	Lazzerini & Tickell <sup>5</sup>	<b>Antibiotics in severely malnourished children: systematic review of efficacy, safety and pharmacokinetics.</b>	2011	<ul style="list-style-type: none"> <li>Systematic review of CENTRAL, MEDLINE, EMBASE, LILACS, POPLINE, and CAB</li> <li>Abstracts and ongoing trials registers were searched, plus thorough grey literature search.</li> <li>For PK review, all study types, except single case reports, were included.</li> <li></li> </ul>	<ul style="list-style-type: none"> <li>Overall, 23 studies were identified for inclusion:</li> <li>2 RCTs, 1 before-and-after study and 2 retrospective reports on clinical efficacy and safety were retrieved, together with 18 pharmacokinetic studies.</li> <li><b>Trial quality was generally poor and results could not be pooled due to heterogeneity.</b></li> </ul> <p>Conclusion of included studies:</p> <ul style="list-style-type: none"> <li>Oral amoxicillin for 5 days was as effective as intramuscular ceftriaxone for 2 days (1 RCT).</li> <li>For uncomplicated SAM, amoxicillin showed no</li> </ul>	<ul style="list-style-type: none"> <li>The authors concluded that ‘the existing evidence is not strong enough to further clarify recommendations for antibiotic treatment in children with SAM.’</li> <li><b>Pharmacokinetic data suggest that normal doses of penicillins, cotrimoxazole and gentamicin are safe in malnourished children, while the dose or frequency of chloramphenicol requires</b></li> </ul>	B (systematic review with poor quality trials retrieved)

				<p>benefit over placebo (1 retrospective study).</p> <ul style="list-style-type: none"> <li>The introduction of a standardised regimen that included the administration of <b>ampicillin and gentamicin</b> significantly <b>reduced mortality in hospitalized children</b> (odds ratio, OR: 4.0; 95% confidence interval, CI: 1.7–9.8; 1 before-and-after study); however this was pooled with intervention to address hypoglycaemia</li> <li>Oral <b>chloramphenicol</b> was as effective as cotrimoxazole in children with pneumonia (1 RCT); this study was poorly generalisable</li> <li><u>PK Studies</u> support the use of oral penicillin in children with SAM at the same doses as eutrophic children <i>unless severe diarrhea or malabsorption are present</i></li> <li><u>PK Studies:</u> Suggest parenteral Pen+Gent can be safely given to malnourished children at the same doses as eutrophic children, <b>unless renal failure or shock are present</b></li> <li>PK studies on oral chloramphenicol suggest it is erratically absorbed (with a risk of accumulation and toxicity) in malnourished children and parenteral administration is preferable</li> <li>No studies have been published on the efficacy, safety or PK of ciprofloxacin or ceftriaxone in children with SAM</li> </ul>	<p><b>adjustment.</b></p> <ul style="list-style-type: none"> <li><u>First line antibiotics for uncomplicated SAM:</u> benefit vs harm question remains undetermined. There is a lack of epidemiological data on the risk of infection in children with uncomplicated SAM and what data is available has not been stratified by HIV prevalence. Cotrimoxazole is losing efficacy due to resistance; amoxicillin remains a valuable alternative due to findings of similar efficacy of ceftriaxone and cheaper price.</li> <li><u>Complicated SAM:</u> Current data continues to support broad-spectrum antibiotic use in children with complicated SAM; however only one <i>retrospective</i> study has reported on the use of Amp+Gent, which resulted in lower case fatality rates when combined with treatment for hypoglycaemia. The comparative efficacy of other parenteral antibiotics have not been studied</li> <li><u>High rates of in vitro resistance</u> have been reported in several African countries</li> <li>Many institutions vary in their degree of following recommendations and instead give more potent broad-spectrum antibiotics as first-line therapy, largely guided by local in vitro susceptibility data</li> </ul>		
4	Milion et al. <sup>6</sup>	<b>Meta-analysis on efficacy of amoxicillin in uncomplicated severe acute malnutrition</b>	2016	<ul style="list-style-type: none"> <li>Meta-analysis conducted combining Isanaka (2016) and Trehan's (2013) RCTs</li> </ul>	<ul style="list-style-type: none"> <li>A <b>significant beneficial effect was found for amoxicillin in children with marasmus</b> (summary risk ratio, 1.05, 95% CI [1.00-1.11], p=0.05).</li> <li>This <b>significant effect was also found when taking into account all three clinical forms of severe acute malnutrition; kwashiorkor,</b></li> </ul>	<ul style="list-style-type: none"> <li>The authors concluded that further studies should clarify if amoxicillin has a different effect according to clinical presentation of severe acute malnutrition. Cephalosporins may also have higher efficacy (RR of</li> </ul>	A (meta-analysis with large sample size)

					<p><b>marasmic kwashiorkor and marasmus</b> (summary risk ratio, 1.03, 95% CI [1.00-1.06], p=0.03).</p> <ul style="list-style-type: none"> <li>Size effect seems to be higher for children with marasmic kwashiorkor but the sample size was very low in this high-risk subgroup</li> </ul>	<p>treatment failure: 1.64 for placebo vs cefdinir; 1.32 for placebo versus amoxicillin)</p> <ul style="list-style-type: none"> <li>The findings were in accordance with 2 recent research projects (conducted by the authors) that suggest a proliferation of gut aerotolerant potential pathogens, particularly Streptococcus, which is systematically susceptible to amoxicillin, and Proteobacteria, which are better inhibited by cephalosporins, in severe acute malnutrition</li> </ul>	
5	Trehan et al. <sup>7</sup>	<b>Antibiotics as Part of the Management of Severe Acute Malnutrition</b>	2013	<ul style="list-style-type: none"> <li>3 arm placebo-controlled, double blinded RCT in Malawi comparing oral amoxicillin (80-90mg/kg/day in 2 divided doses) vs placebo (twice daily) and an oral third-generation cephalosporin (cefdinir; 14mg/kg/day in 2 divided doses) in uncomplicated SAM</li> <li>N=2,767</li> <li>6-59 months</li> <li>2009-2011 study period</li> <li>Computer-generated block randomisation lists were created in permuted blocks of 54.</li> <li>Participating children were allocated to their study arm when their caregivers drew an opaque envelope containing one of 9 coded letters corresponding to one of the 3 medication groups.</li> <li>Caregivers, study nurses, and all study personnel involved in clinical assessments and data analysis were kept blinded to the intervention each child received.</li> <li>The medications and placebo were distributed in opaque plastic bottles with plastic syringes marked to indicate the dose of medication each child was to receive.</li> <li>After randomisation and distribution of the medications and placebo, study nurses educated each child's caregiver on how to</li> </ul>	<ul style="list-style-type: none"> <li>Less than a third of the children had been tested for HIV; of those, more than a fifth were HIV-positive, and less than a third of those were receiving antiretroviral therapy (ART). About three-quarters of the children's mothers had been tested for HIV, with 19% being HIV-positive; less than half of those were receiving ART.</li> <li>Adherence to the intervention was very high in each of the three study groups</li> <li><b>No reports of severe allergy or anaphylaxis were reported from any children in the study.</b></li> <li><u>Primary Outcomes:</u> The proportion of children that recovered was significantly <b>lower among those that received placebo</b> (85.1%) than among those that received either amoxicillin (88.7%, p = 0.02) or cefdinir (90.9%, p = 0.0001).</li> <li><b>Subgroup analysis</b> showed that, when stratified by type of SAM, children with kwashiorkor that received placebo recovered less frequently than those that received cefdinir (92.2% versus 95.2%, p = 0.04).</li> <li>Similarly, children with marasmus that received placebo also recovered less frequently than those that received cefdinir (74.4% versus 79.2%, p = 0.02)</li> <li>The <b>overall mortality rate</b> was 5.4%, but was <b>significantly higher for children that received placebo</b> (7.4%) than for those that received either amoxicillin (4.8%, p = 0.02) or cefdinir (4.1%, p = 0.003).</li> </ul>	<ul style="list-style-type: none"> <li>Among children who recovered, the rate of weight gain was increased among those who received antibiotics.</li> <li>No interaction between type of severe acute malnutrition and intervention group was observed for either the rate of nutritional recovery or the mortality rate.</li> <li><b>Cefdinir was superior to amoxicillin, and amoxicillin was superior to placebo</b> resulting in significantly improved <b>recovery at 12 weeks</b> (90.9%, 87.7%, 85.1% respectively) and <b>mortality</b> (4.1%, 4.8%, 7.4%).</li> <li>Trial included a high rate of HIV positive children (n=188), however distribution was equitable across intervention groups</li> <li>The authors concluded that these results provide <b>clear evidence to support the recommendation for routine oral antibiotics as part of the outpatient management of SAM.</b></li> </ul>	B (RCT with strong methodological quality)



				<p>use the syringe to give the medications and <b>supervised the administration of the first dose in the clinic</b>; and provided them with a pictorial calendar for recording each dose given, with instructions to give the medication 2x/day for 7 days.</p> <ul style="list-style-type: none"> <li>• Children were brought back for up to 6 follow-up visits at 2-week intervals, at which time repeat anthropometric measurements were taken and caregivers were asked about the child's interim clinical and appetite history</li> <li>• At the first follow-up visit, <b>study nurses assessed how much medication was given</b> to the child by examining how much medication remained in the study bottle, examining how many doses were marked off on the dosing calendar, and considering the caregiver's verbal report.</li> <li>• <u>Primary Endpoints</u>: Rates of nutritional recovery and mortality rates in the three study arms.</li> <li>• <u>Secondary outcomes</u> of interest included weight gain, length gain, tolerance of the medications, and time to recovery</li> </ul>	<ul style="list-style-type: none"> <li>• This corresponds to a 36% (95% CI, 7%–55%) reduction in mortality when given amoxicillin and a 44% (95% CI, 18%–62%) reduction in mortality with cefdinir.</li> </ul>		
6	Isanaka et al. <sup>8</sup>	<b>Routine Amoxicillin for Uncomplicated Severe Acute Malnutrition in Children</b>	2016	<ul style="list-style-type: none"> <li>• Double-blind, placebo-controlled RCT at 4 health centres across rural Niger that assessed the effect of routine amoxicillin use on nutritional recovery in children with severe malnutrition</li> <li>• N=2,399 (1,199 in treatment, 1,200 in placebo)</li> <li>• Children randomly assigned (computer-generated) 1:1 ratio in blocks of 6 to receive 80mg/kg amoxicillin divided into two daily doses or placebo for 7 days; adherence monitored through home visits</li> <li>• <u>Inclusion criteria</u>: Children must not have received any antibiotic treatment within</li> </ul>	<ul style="list-style-type: none"> <li>• Overall, 64% of children enrolled in the study recovered</li> <li>• <b>No significant difference in likelihood of recovery between amoxicillin vs placebo</b> (RR with amoxicillin 1.05, 95% CI 0.99-1.12)</li> <li>• Among children who recovered, <b>time to recovery was significantly shorter with amoxicillin</b> than placebo (mean treatment of 28 vs 30 days, p&lt;0.001)</li> <li>• Amoxicillin had no significant affect among children with confirmed bacterial infection at admission</li> <li>• <u>Secondary outcomes</u>: Amoxicillin tended to</li> </ul>	<ul style="list-style-type: none"> <li>• Routine provision of amoxicillin was not superior to placebo for nutritional recovery in children with uncomplicated severe acute malnutrition.</li> <li>• “This finding challenges the view that routine antibiotic therapy is always necessary or beneficial.”</li> <li>• Amoxicillin reduced the risk of a transfer to inpatient care by 14%, as compared with placebo.</li> <li>• Amoxicillin specifically reduced the risk of transfers to inpatient care for clinical complications due to</li> </ul>	B (RCT with strong methodological quality)

			<p>the prior 7 days; 6-59 months, WfH Z score &lt;-3 and/or MUAC 115mm; pass appetite testing; absence of clinical complications (including oedema)</p> <ul style="list-style-type: none"> <li>• <b>Primary aim:</b> examining the effect of routine antibiotic use</li> <li>• <b>Primary outcome:</b> nutritional recovery by 8 weeks (WfH Z score &gt;-2 on 2 consecutive visits or MUAC &gt; 115mm).</li> </ul>	<p><b>reduce the risk of death</b> among children who were &gt;24 months (RR 0.24, 95% CI 0.02-2.12) but not among children &lt;24 months (RR3.04, 95% CI 0.61-15.01)</p> <ul style="list-style-type: none"> <li>• A total of 13 children died during treatment: 7 in the amoxicillin group and 6 in the placebo group; time to death did not differ significantly between the two groups (p=0.4)</li> <li>• <b>Amoxicillin significantly decreased the overall risk of transfer to inpatient care</b> (26.4% vs 30.7%, RR 0.86; 0.78-0.98, p=0.02) <b>and for acute gastroenteritis in particular</b> (RR 0.67, 0.48-0.94, p=0.02).</li> <li>• Amoxicillin significantly <b>accelerated early gains</b> in weight and MUAC (week 1: RR 3.8, 3.1-4.6, p&lt;0.001), with <b>no significant effect on overall</b> weight gain by week 4 or height gain during treatment</li> <li>• <b>No cases of severe allergy or anaphylaxis were identified; the frequency of diarrhoea was lower in the amoxicillin group than placebo group at week 1. None of the clinical complications or deaths were reported to be related to the study drug.</b></li> <li>• <b>RESISTANCE:</b> the likelihood of resistance to amoxicillin was 35% for enterobacteria isolated from stool in children with diarrhoea, and 66% for enterobacteria isolated from blood</li> </ul>	<p>gastroenteritis. This was an unexpected finding, since the viruses and parasites primarily responsible for gastroenteritis in young children are not sensitive to amoxicillin<sup>1</sup> A possible explanation provided by the authors is that poor mucosal integrity in malnourished children allows the translocation of bacteria across compromised intestinal surfaces, resulting in bacteremia; or that oral antibiotics may reduce excessive proliferation of small-bowel flora, modifying the composition and function of the gut microbiome.</p> <ul style="list-style-type: none"> <li>• Limitations: Assumed a likelihood of nutritional recovery of 80%, which was not achieved → cannot rule out the possibility that amoxicillin had a protective effect of 12% or a harmful effect of 1% on nutritional recovery.</li> <li>• Risk of bias: excluded children with mild-mod oedema → ?patient population too well</li> </ul>	
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<sup>1</sup> Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet 2013;382:209-222

7	Berkley et al. <sup>9</sup>	<b>Daily co-trimoxazole prophylaxis to prevent mortality in children with complicated severe acute malnutrition: a multicentre, double-blind, randomised placebo-controlled trial</b>	2016	<ul style="list-style-type: none"> <li>• A multi-centre, double-blind, randomised, placebo-controlled study in 4 hospitals in Kenya (two rural hospitals in Kilifi and Malindi, and 2 urban hospitals in Mombasa and Nairobi)</li> <li>• N=1,778</li> <li>• 2009-2013</li> <li>• Children aged <b>3 months</b>-59 months <b>without HIV</b> admitted to hospital and diagnosed with (complicated) SAM.</li> <li>• After nutritional stabilization, participants were randomly assigned (1:1) to 6 months of either daily oral co-trimoxazole prophylaxis (water-dispersible tablets; 120 mg per day for age &lt;6 months, 240 mg per day for age 6 months to 5 years) or matching placebo.</li> <li>• Assignment was done with computer-generated randomisation in permuted blocks of 20, stratified by centre and age (younger or older than 6 months).</li> <li>• Treatment allocation was concealed in opaque, sealed envelopes and patients, their families, and all trial staff were masked to treatment assignment.</li> <li>• Children were given recommended medical care and feeding, and followed up for 12 months.</li> <li>• The efficacy of co-trimoxazole was chosen for investigation due to its well documented effect on mortality in children with HIV who present with infectious syndromes that are broadly similar to those noted in children with SAM</li> <li>• <u>Primary endpoint</u> was <b>mortality</b>, assessed each month for the first 6 months, then every 2 months for the second 6 months.</li> <li>• <u>Secondary endpoints</u> were nutritional recovery, readmission to hospital, and illness episodes treated as an outpatient.</li> <li>• Analysis was by intention to treat</li> </ul>	<ul style="list-style-type: none"> <li>• Median age was 11 months (IQR 7–16 months); 306 (17%) were younger than 6 months</li> <li>• 300 (17%) had oedematous malnutrition (kwashiorkor)</li> <li>• 1221 (69%) were stunted (length-for-age Z score &lt;-2).</li> <li>• During 1527 child-years of observation, <b>122 (14%) of 887 children in the co-trimoxazole group died, compared with 135 (15%) of 891 in the placebo group</b> (unadjusted hazard ratio [HR] 0.90, 95% CI 0.71–1.16, <b>p=0.429</b>; 16.0 vs 17.7 events per 100 child-years observed (CYO); difference –1.7 events per 100 CYO, 95% CI –5.8 to 2.4]).</li> <li>• In the first 6 months of the study (while participants received study medication), <b>63 suspected grade 3 or 4 associated adverse events were recorded among 57 (3%) children; 31 (2%) in the co-trimoxazole group and 32 (2%) in the placebo group (incidence rate ratio 0.98, 95% CI 0.58–1.65).</b></li> <li>• The most common adverse events of these grades were urticarial rash (grade 3, equally common in both groups), <b>neutropenia (grade 4, more common in the cotrimoxazole group)</b>, and anaemia (both grades equally common in both groups).</li> <li>• One child in the placebo group had fatal toxic epidermal necrolysis with concurrent <i>Pseudomonas aeruginosa</i> bacteraemia.</li> </ul>	<ul style="list-style-type: none"> <li>• The authors conclude that among HIV-negative Kenyan children with complicated SAM, daily co-trimoxazole given for 6 months was well tolerated, but did not reduce mortality or improve growth.</li> <li>• The authors questioned if low bacterial susceptibility to co-trimoxazole may be the reason for an absence of a protective effect on death</li> <li>• Among children with SAM, two main reasons were noted for initial admission: diarrhoea and pneumonia; raising the hypothesis that SAM with diarrhoea might represent a phenotype amenable to antimicrobial prophylaxis targeting pathogens and commensal microbes, intestinal barrier function, and immune homeostasis that could be tested in further trials.</li> </ul>	B (RCT with strong methodological quality)
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	Author	Title	Year	Methods (Study Type, Setting, Participants)	Results	Conclusions	GRADE level of evidence
1	Chisti et al <sup>1</sup>	<b>Treatment Failure and Mortality amongst Children with Severe Acute Malnutrition Presenting with Cough or Respiratory Difficulty and Radiological Pneumonia.</b>	2015	<ul style="list-style-type: none"> <li>• <b>Cohort study:</b> Prospective enrolment of SAM children aged 0-59 months, admitted to the Intensive Care Unit (ICU) or Acute Respiratory Infection (ARI) ward of the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), between April 2011 - June 2012 with cough or respiratory difficulty and radiological pneumonia.</li> <li>• All the enrolled children were treated with <b>ampicillin and gentamicin</b>, and micronutrients as recommended by the WHO.</li> <li>• Comparison was made among pneumonic children with (n =111) and without WHO defined danger signs of severe pneumonia (n= 296).</li> <li>• <u>Primary Outcomes:</u> treatment failure (if a child required changing of antibiotics) and deaths during hospitalisation.</li> <li>• Further comparison was also made among those who developed treatment failure and who did not</li> </ul>	<ul style="list-style-type: none"> <li>• SAM children with danger signs of severe pneumonia <b>more often experienced treatment failure</b> (58% vs. 20%; p&lt;0.001) <b>and fatal outcome</b> (21% vs. 4%; p&lt;0.001) compared to those without danger signs.</li> <li>• Only 6/111 (5.4%) SAM children with danger signs of severe pneumonia and 12/296 (4.0%) without danger signs had <b>bacterial isolates from blood</b>.</li> <li>• In log-linear binomial regression analysis, after adjusting for potential confounders, danger signs of severe pneumonia, dehydration, hypocalcaemia, and bacteraemia were independently associated both with treatment failure and deaths in SAM children presenting with cough or respiratory difficulty and radiological pneumonia (p&lt;0.01)</li> <li>• Only 2 children with danger signs and 4 without danger signs of severe pneumonia had a blood culture isolate that were <u>not</u> susceptible to ampicillin and gentamicin.</li> <li>• 3 study children had a blood culture isolate which was <u>not</u> susceptible to ceftriaxone and only one children to ciprofloxacin.</li> <li>• Overall 18 (4.4%) children had bacteraemia, and the <b>difference of bacteraemia among the groups was not significant</b></li> <li>• A total of 67 (16.5%) children had history of prior use of antibiotics and</li> </ul>	<ul style="list-style-type: none"> <li>• Ampicillin and gentamicin are <b>insufficient in treating children with complicated SAM presenting with pneumonia</b>.</li> <li>• The result underscores the importance for further research especially a randomized, controlled clinical trial to validate standard WHO therapy in SAM children with pneumonia especially with danger signs of severe pneumonia to reduce treatment failures and deaths.</li> <li>• Biased by previous administration of antibiotics</li> </ul>	C

					among them only 2 (3%) children had bacteraemia		
2	Yebo et al. <sup>2</sup>	<b>Outpatient therapeutic feeding program outcomes and determinants in treatment of severe acute malnutrition in Tigray northern Ethiopia: a retrospective cohort study.</b>	2013	<ul style="list-style-type: none"> <li>Retrospective cohort study</li> <li>n=628 children 6-59 months who had been managed for SAM under outpatient treatment from April 2008 –Jan 2012.</li> <li>The children were selected using systematic random sampling from 12 health posts and 4 health centers.</li> <li>Tigray, Northern Ethiopia</li> <li>Details of amoxicillin mg/kg not clarified</li> <li>Children admitted to the outpatient treatment programme receive weekly rations of Plumpy'Nut and supplements including Vitamin A, Folic acid tabs, antibiotics, de-worming tabs and measles vaccine.</li> <li>Children do not have medication administration supervised.</li> </ul>	<ul style="list-style-type: none"> <li>Children who took <b>amoxicillin had significantly faster recovery compared to children who did not take amoxicillin</b> (<math>X^2=136.59</math>, <math>p&lt;0.0001</math>).</li> <li>Children who took amoxicillin had 95% (HR = 1.95, 95% CI = 1.17-3.23) <b>higher probability of recovery</b> compared to those who didn't take amoxicillin.</li> </ul>	<ul style="list-style-type: none"> <li>The authors conclude that amoxicillin is a positive predictor of faster recovery in children with uncomplicated SAM, and postulate this is secondary to treating small bowel bacterial overgrowth which may be the source of systemic infection by translocation across the bowel wall, resulting in malabsorption of nutrients, failure to eliminate substances excreted in the bile, fatty liver, and intestinal damage causing chronic diarrhoea.</li> <li>Biased by retrospective design and poor monitoring of medication administration</li> </ul>	D
3	Page et al. <sup>3</sup>	<b>Infections in Children Admitted with Complicated Severe Acute Malnutrition in Niger.</b>	2013	<ul style="list-style-type: none"> <li>A clinical and biological characterisation of infections in <b>hospitalised</b> children with <b>complicated</b> SAM in Maradi, Niger.</li> <li>N=311 children 6-59 months</li> <li>Study period October 2007-July 2008</li> <li>SAM WfH&lt;-3 z-score of the median WHO growth standards and/or MUAC &lt;110 mm and/or bipedal oedema</li> <li>Complicated SAM defined as SAM accompanied by anorexia and/or kwashiorkor with bilateral pitting edema and/or another severe condition (severe anemia, severe respiratory tract infection, malaria with signs of severity, other severe infections such as meningitis or sepsis, diarrhea with dehydration, lethargy or acute neurological disorders, sickle cell crisis).</li> <li>A clinical examination, blood, urine and stool cultures, and chest radiography were</li> </ul>	<ul style="list-style-type: none"> <li><u>Prevalence data:</u> Among the 311 children included in the study, <b>gastroenteritis</b> was the most frequent clinical diagnosis on admission, followed by <b>respiratory tract infections and malaria</b>.</li> <li>Blood or urine culture was positive in 17% and 16% of cases respectively, and 36% had abnormal chest radiography.</li> <li>Enterobacteria were sensitive to most antibiotics, <b>except amoxicillin and cotrimoxazole</b>.</li> <li>The median length of stay in the inpatient treatment facility was 8 days (IQR: 6–13 days).</li> <li>29 (9%) of children died; almost half of all deaths (48%, n=14/29) occurred within 48 h of admission.</li> <li><b>The main causes of death</b> recorded</li> </ul>	<ul style="list-style-type: none"> <li>The authors concluded that 'the data confirm the high level of infections and poor correlation with clinical signs in children with complicated SAM, and provide antibiotic resistance profiles from an area with limited microbiological data. These results contribute unique data to the ongoing debate on the use and choice of broad-spectrum antibiotics as first-line treatment in children with complicated SAM and reinforce the call for an <b>update of international guidelines on management of complicated SAM based on more recent data.</b>'</li> <li><u>Limitations:</u> did not reach target sample size (n=1000) due to the premature closure of the MSF program; resulted in missing in particular the months of August to</li> </ul>	D

			<p>performed systematically on admission.</p> <ul style="list-style-type: none"> <li>• Amoxicillin was given systematically, or parenteral ceftriaxone in cases of suspected severe or complicated infectious syndrome. No mention of gentamicin in methodology.</li> <li>• Treatment was modified based on indications such as non-improvement of clinical condition and/or results of bacterial culture and antibiotic sensitivity testing. Depending on the type of infection suspected, <b>cloxacillin</b> (skin infection, severe pneumonia, <i>S. aureus</i> bacteremia) or <b>ciprofloxacin</b> (urinary tract infection, severe, explosive or persistent diarrhea &gt;72 hours, bloody diarrhea, bacteremia with suspected gram negative bacteria) <b>was added in</b> case of treatment failure, based on lack of improvement or worsening of symptoms <b>within 72 hours</b> following treatment.</li> <li>• Children with uncomplicated malaria diagnosed either by rapid test and/or smear microscopy were given oral artesunate and amodiaquine for 3 days. Children with severe or complicated malaria received arthemether IM and then artesunate-amodiaquine if their condition improved, for 7 days total.</li> </ul>	<p>were sepsis (15), respiratory tract infection (4), and clinical suspicion of tuberculosis (2).</p> <ul style="list-style-type: none"> <li>• Overall, 20 (69%) children who died had one or several laboratory or X-ray proven infections, including 8 bacteremia (4 <i>S. aureus</i>, 2 <i>H. influenzae</i>, 1 <i>Salmonella</i> spp., 1 <i>E. coli</i>); 7 UTI (6 <i>E. coli</i>, 1 <i>K. pneumoniae</i>); 3 infectious diarrhea (1 <i>S. flexneri</i>, 1 <i>S. sonnei</i>, 1 <i>Salmonella</i> spp.); 2 malaria; and 2 RTI.</li> <li>• The CFR was 16% (n=8/51, p=0.1) among patients with a positive blood culture, 15% (n=7/41, p=0.2) among children with a UTI, 8.3% (n=4/62, p=0.5) among children with infectious diarrhoea, and 4.5% (n=2/44, p=0.5) among those with malaria.</li> <li>• Clinical signs were poor indicators of infection and initial diagnoses correlated poorly with biologically or radiography-confirmed diagnoses.</li> </ul>	<p>October, which correspond to the malnutrition and malaria peaks; secondly, diagnostic capacity is limited compared to developed country settings and it was difficult to ascertain diagnoses in some cases (eg TB diagnosis made clinically). Third, glycemia was not analysed here because it was measured after children were administered the appetite test, limiting its interpretation. Fourth, high prevalence of blood culture contamination may have resulted in underestimation of children who died from sepsis due to inaccurate characterisation of culture results</p>	
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