

Guidelines for the treatment of severe acute malnutrition: a systematic review of the evidence for antimicrobial therapy

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ABSTRACT

Background: Severe acute malnutrition (SAM) affects nearly 20 million children worldwide and is responsible for up to 1 million deaths per year in children under the age of 5 years. Current WHO guidelines recommend oral amoxicillin for children with uncomplicated malnutrition and parenteral benzylpenicillin and gentamicin for those with complicated malnutrition. Because of cost pressures and increasing antimicrobial resistance, the administration of empirical antibiotics for children with SAM has recently been debated.

Methods: A systematic review of the current published literature was undertaken to assess the efficacy, safety, cost-effectiveness and pharmacokinetics of antimicrobial treatment of children with SAM in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Results: The initial search found 712 papers, eight of which met the inclusion criteria. Quality assessment of the studies was performed as per the Grading of Recommendations Assessment, Development and Evaluation guidelines. International guidelines and clinical data registries were also reviewed which identified inconsistencies in current first- and second-line therapies and dosing regimens.

Conclusion: Current evidence supports the continued use of broad-spectrum oral amoxicillin for treating children with uncomplicated SAM as outpatients. There is no strong evidence to justify changing the current parenteral therapy guidelines for children admitted with complicated SAM, although they should be clarified to harmonise the dosage regimen of amoxicillin for the treatment of SAM to 40 mg/kg twice daily, and to continue parenteral antimicrobials beyond 2 days if indicated by the clinical condition.

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Introduction

Severe acute malnutrition (SAM) affects nearly 20 million children under 5 years and causes up to 1 million deaths annually by increasing susceptibility to death from severe infection [1]. The most vulnerable age for malnutrition is 6–18 months when growth velocity and brain development are especially high. However, with the introduction of solid food in many low-income settings to children as young as 2 months, it is increasingly recognised that SAM may occur in infants aged <6 months [2].

SAM is defined by two distinct clinical entities: (i) severe wasting [marasmus, defined as middle upper-arm circumference (MUAC) < 115 mm in children aged 6–59 months or a weight-for-height/length <–3 Z-scores according to the 2006 WHO growth standards in children aged 0–59 months]; and (ii) nutritional oedema (kwashiorkor, defined as bilateral pitting oedema) [3–5]. Children with SAM are further classified according to the presence or absence of medical complications [4]. Uncomplicated

SAM includes children who are clinically well, i.e. without signs of infection and with a retained appetite ('passed the appetite test') which is regarded as indicative of the absence of severe metabolic disturbance. Complicated SAM includes children with clinical features of infection, metabolic disturbance, severe oedema, hypothermia, vomiting, severe dehydration, severe anaemia or a lack of appetite who require inpatient treatment.

Traditionally, all children with malnutrition were managed as inpatients with empirical broad-spectrum parenteral antibiotics, regardless of whether clinical features of infection (or other complications) were present [6]. However in the past decade, the advent of clinically effective ready-to-use therapeutic foods (RUTF) has resulted in the recommendation that children with uncomplicated SAM (>80% of paediatric SAM cases) be treated as outpatients, following the WHO–UNICEF community-based model for the management of malnutrition [3,6]. This has occurred concurrently with changes to the nutritional and clinical profile of children diagnosed

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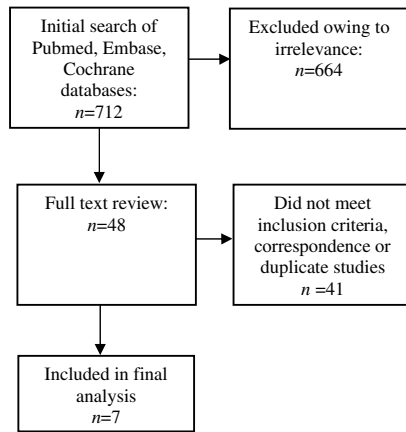


Figure 1. Search strategy.

with (and treated for) SAM following the publication of the 2006 WHO Child Growth Standards which resulted in significant changes to the measurement of nutritional status and a large increase in the number of children classified as having SAM [7,8].

The rationale behind antibiotic treatment for children with SAM lies in the view that malnourished children may not show signs of clinical infection [9]. Older clinical trials suggested evidence for improved growth and decreased mortality in malnourished children treated with antibiotics [10]. The mechanism behind this clinical improvement has been postulated to be secondary to the treatment of underlying covert infection, prevention of colonising micro-organisms, minimisation of nutrient diversion by dampening inflammatory responses and a reduction in enteropathy via alterations in the gut microbiome [10,11]. 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 Gram-positive and Gram-negative organisms, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella* spp, *Salmonella* spp and other enterobacteriaceae [12–17].

With most SAM treatment now being in the outpatient setting, broad-spectrum oral antibiotics for uncomplicated SAM continue to be recommended by WHO and UNICEF. For complicated SAM, intravenous therapy followed by oral therapy (including a prolonged course of an aminoglycoside) is recommended; however, the evidence base for this is weak [4, 18, 19]. Increasing antibiotic resistance is of international concern [20], as are the cost and logistical considerations of empirical antimicrobial treatment and its possible side effects. High rates of non-susceptibility to first- and second-line therapies have been documented in several epidemiological studies in children with SAM [12,13,15,21–25], and 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 [9,26].

This review was therefore undertaken to evaluate the recent international literature for evidence (or otherwise)

pertaining to the clinical efficacy of antibiotic treatment in children with SAM. Current recommendations by WHO (Table 1) are published in the 2013 Pocketbook for Hospital Care for Children [5,27] but, with the global threat of increasing antimicrobial resistance and recently published new data evaluating the efficacy and safety profiles of antimicrobials in children presenting with uncomplicated SAM, a review of the evidence to ensure that current recommendations remain appropriate is warranted.

Methods

A search for systematic reviews, meta-analyses, multi-centre studies and randomised controlled trials (RCTs) was undertaken using the search terms outlined in Table 2. The databases EMBASE, Cochrane Database of Systematic Reviews and Pubmed were searched. Trials were limited to those conducted in humans and published since 2010 in English or French to update the research which informed the 2013 Guidelines [28]. Inclusion and exclusion criteria are outlined in Table 3. 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 Pediatrics, Therapeutic Guidelines (Australia), Action Contre le Faim, Médecins Sans Frontières, Valid International and national guidelines in high-burden countries in Asia and Africa. Clinical trial registries including www.clinicaltrials.gov and <http://www.who.int/ictrp/en/> were searched for ongoing trials relevant to antibiotic treatment of SAM.

Results

The initial search produced 712 papers (Figure 1), 48 of which qualified for full text review. Ultimately, seven studies met the inclusion criteria which were abstracted as detailed in Appendix 1. Quality assessment of the studies was performed as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [29].

Characteristics of the included studies

Since 2010, four systematic reviews and/or meta-analyses (conducted across an international setting) [28,30–32] and three double-blind, placebo-controlled trials conducted in Malawi [33], Niger [26] and Kenya [34] evaluating children with SAM have been published. All papers assessed children aged 6–59 months, apart from one recent RCT which extended the intervention group to severely malnourished children aged ≥ 2 months [34]. The definition of complicated and uncomplicated SAM was the same in all the studies.

The single meta-analysis was classified as GRADE A (high-quality evidence) and the remaining systematic

Table 1. Current WHO inpatient and outpatient management guidelines for severe acute malnutrition.

Condition	Recommendation	Evidence base*	Year updated
Uncomplicated malnutrition [5]	Oral amoxicillin Dosage and time frame not specified — the drug dosage section advises 25 mg/kg twice daily and for pneumonia.	Conditional recommendation, low quality evidence	2013
Complicated malnutrition [4,5]	IV benzylpenicillin 50,000 U/kg IM/IV every 6 h for 2 days OR IV ampicillin 50 mg/kg IM/IV every 6 h for 2 days THEN Oral amoxicillin 25–40 mg/kg/dose every 8 h for 5 days (total 7-day course) AND IV/IM gentamicin 7.5 mg/kg IM/IV once daily for 7 days	Weak recommendation, low quality evidence	2012
Complicated malnutrition [4,5]	Oral 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	None	2013

*At the time of the recommendation.

Table 2. Search terms used in search strategy.

- (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 sulfamethoxazole 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 humans (for clinical safety and efficacy trials) AND published between 2010 and 2016

Table 3. Inclusion and exclusion criteria.

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

reviews and RCTs were classified as GRADE level B (moderate-quality evidence, Appendix 1). Study heterogeneity in interventions and populations prevent further pooling of the results for this review. There was one further review of pharmacokinetics of antimicrobials in children with SAM [35].

Evidence for current guidelines for uncomplicated SAM

A systematic review which informed the current WHO guidelines documented evidence from two studies

assessing the clinical efficacy of amoxicillin in children with uncomplicated SAM [28]. The first, an unblinded RCT in Sudan ($n = 458$), demonstrated that oral amoxicillin (40 mg/kg/day twice daily) for 5 days was as effective as IM ceftriaxone for 2 days [36]. Intention-to-treat analysis in the study showed 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 10 g/kg/day during a 14-day period. The recovery rate was not significantly different [70.0% (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 2 weeks of admission [36].

A retrospective study in Malawi compared oral amoxicillin (60 mg/kg/day, $n = 498$) for 7 days with no antibiotics ($n = 1955$). The recovery rate at 4 weeks was poorer in children receiving amoxicillin (39.8% vs. 70.8%, $p < 0.001$), but was similar at 12 weeks with similar rates of death and default [37]. However, the research was acknowledged to be at risk of bias, not just because of its retrospective data collection but also because of the different district locations of the cohorts of patients who were not stratified by risk of HIV status (with a high prevalence in the study population) [38].

The current search identified two further systematic reviews [30,31] and two RCTs [7,39] assessing the efficacy of amoxicillin in SAM, as well as a meta-analysis combining their results [32]. While excluded from the inclusion criteria, three relevant observational studies were also found in the literature and for the provision of their epidemiological data, these studies are described in Appendix 2 [14,40,41].

A systematic review in 2012 [31] did not find any interventional studies apart from those already documented in the review outlined above. A 2013 systematic review and meta-analysis (of observational data only) [30] favoured amoxicillin over co-trimoxazole for cumulated susceptibilities of all isolated bacteria [median 42% (IQR 27–55%) vs. 22% (IQR 17–23%); population-weighted

means 52.9% (IQR 23–57%) vs. 35.4% (IQR 6.7–42%), yet the authors noted that the evidence from intervention studies (discussed below) revealed conflicting results regarding the efficacy of amoxicillin in children with SAM, which is especially difficult to interpret when patients were not stratified by HIV infectivity status.

A 2013 double-blind, three-armed RCT [42] (GRADE level B) compared the third-generation oral cephalosporin cefdinir with amoxicillin and placebo in Malawi ($n = 2767$). The overall case fatality rate was 5.4% and it was significantly higher in children receiving placebo (7.4%) than in those receiving amoxicillin (4.8%, $p = 0.02$) or cefdinir (4.1%, $p = 0.003$). This corresponds to a 36% (95% CI 7.0–55) reduction in mortality when given amoxicillin and a 44% (95% CI 18.0–62.0) reduction when given cefdinir. Children who received either antibiotic agent also had greater increases in MUAC than those who received placebo. The authors concluded that the results provide clear evidence to support the recommendation of routine oral antibiotics as part of the outpatient management of SAM. However, in considering the potential benefit of any policy move towards the widespread use of oral cephalosporin, this would need to be weighed against the risk of promoting community-based antimicrobial resistance [9].

In contrast, a 2016 RCT of 2399 children aged 6–59 months with uncomplicated SAM in four rural treatment centres in Niger found no significant difference in the likelihood of recovery between those treated with amoxicillin and those who received placebo (RR with amoxicillin 1.05, 95% CI 0.99–1.12) [26]. Amoxicillin significantly accelerated early gains in weight and MUAC (week 1 RR 3.8, 95% CI 3.1–4.6, $p < 0.001$) 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 (by only 2 days, however) than with placebo (mean treatment 28 vs. 30 days, $p < 0.001$); amoxicillin tended to reduce the risk of death in children who were >24 months (RR 0.24, 95% CI 0.02–2.12), but not in younger children (<24 months, RR 3.04, 95% CI 0.61–15.01). Notably, however, amoxicillin decreased the risk of transfer to inpatient care, (RR 0.86, 95% CI 0.76–0.98, $p = 0.02$), for acute gastroenteritis in particular (RR 0.67, 95% CI 0.48–0.94, $p = 0.02$). This is surprising because the causative organisms primarily responsible for gastroenteritis in young children tend to be less sensitive to amoxicillin [43]. Gastrointestinal side effects are common with amoxicillin so this clinical improvement may in fact reflect the antibiotic's effect on reducing small bowel flora, modifying the composition of the gut microbiome [44]. Overall, amoxicillin significantly reduced hospital admission in those transferred for inpatient care (RR 0.76, 95% CI 0.62–0.92, $p = 0.005$).

This trial challenged the view that antibiotic therapy is always necessary or beneficial in the management of SAM and concluded that, by eliminating the routine

prescription of antibiotics in children with uncomplicated SAM, treatment could be simplified (with associated cost savings, and limiting the spread of antibiotic resistance) [26]. The international literature response to these conclusions was mixed. Some supported the view that the use of broad-spectrum mass antibiotics has unintended consequences which outweigh the benefits of routine administration [45], emphasising the importance of ensuring that essential and effective antimicrobials are available to treat *all* clinical infections in children [45]. Others noted that a lack of clinical improvement in children receiving amoxicillin should not be extrapolated to mean that antibiotics are not beneficial in children with SAM as it may simply be that amoxicillin is no longer the most appropriate antibiotic [46].

These two RCTs [26,42] were subsequently analysed in a 2016 meta-analysis (GRADE A high-quality evidence) [32] which highlighted limitations in the RCT undertaken in Niger, notably its failure to include 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 1610 amoxicillin, 1535 placebo) revealed an overall benefit to 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, $p = 0.03$) and survival benefits of amoxicillin in children with marasmus (summary risk ratio 1.05, 95% CI 1.00–1.11, $p = 0.05$). Minimal inconsistency was observed between the two studies in tests for heterogeneity ($I^2 = 0\%$) and the authors concluded that the benefits of antibiotics demonstrated in their analysis should reaffirm continuity of the current WHO recommendations.

Despite the limitations of its methodology, one additional observational study deserves comment. A retrospective cohort study of 628 children with uncomplicated SAM managed by an outpatient therapeutic programme in rural Ethiopia found that children who received amoxicillin recovered significantly more quickly than children who did not and with a higher rate of recovery (HR 1.95, 95% CI 1.17–3.23) [40]. However, the methodology was unclearly described and children were not observed in the administration of their medication (which also included a package of interventions such as RUTF, vitamin A and deworming tablets).

Evidence for current guidelines for complicated SAM

A systematic review in 2011 [28] found only one interventional study (completed in 1996) which assessed the clinical efficacy of ampicillin and gentamicin in 300 children, reporting a case fatality reduction in children receiving antibiotics from 20 to 6% (OR 4.0, 95% CI 1.7–9.8) [47]. However, these antibiotics were administered alongside a new protocol for the treatment of hypoglycaemia, and benefits 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, although a 2013 systematic review found susceptibilities of >80% to combined amoxicillin–gentamicin and gentamicin in blood, urine and CSF cultures (Table 4) [30].

Recent observational evidence includes a prospective cohort study published in 2015 of 407 children with respiratory compromise and radiological pneumonia admitted to the Dhaka Hospital of ICDDR,B between 2011 and 2012 [41]. It evaluated patients treated with parenteral ampicillin and gentamicin, and, in children assessed as having treatment failure, antibiotics were changed to second-line agents, ceftriaxone plus levofloxacin, in accordance with hospital protocol. Eighteen 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) [5]. These children were significantly more likely to exhibit treatment failure (RR 3.14, 95% CI 2.30–4.29, $p < 0.001$) and death (RR 2.78, 95% CI 2.06–3.75, $p < 0.001$). The authors postulated that the bacterial aetiology of pneumonia in these children with SAM might be more likely to be owing to Gram-negative bacteria, and the unique combination of severe infection, bacterial endotoxin and small bowel overgrowth often observed in children with SAM (resulting in oxidative stress and endogenous nitric oxide production) might contribute to the high levels of treatment failure and mortality [48]. Consistent with previous publications [49], there was a low yield of positive blood cultures in children with pneumonia and SAM, although 16% of the study population had received prior antibiotic therapy. The few cultures which were positive demonstrated better *in vitro* susceptibility to fluoroquinolones and extended-spectrum cephalosporins than ampicillin and gentamicin. Only six children had a blood culture isolate that was not susceptible to ampicillin and gentamicin, and three of 407 children had blood

culture isolates that were not susceptible to ceftriaxone and only one was not susceptible to ciprofloxacin [41].

Another observational study in Niger [14] undertook clinical and biological characterisation of infections in 311 children aged 6–59 months admitted during 2007/2008 with complicated SAM who received parenteral amoxicillin or ceftriaxone for suspected severe or complicated infections, with subsequent treatment targeted towards the suspected type of infection. Gentamicin was not listed as an administered medication. Gastroenteritis was the most frequent clinical diagnosis on admission, followed by respiratory tract infections and malaria. Blood cultures were positive in 17% of cases, more than half of which were considered to be contaminants. The majority of isolates were Gram-negative bacilli (most frequently *Salmonella* spp.), followed by (in order of frequency) *S. aureus*, *E. coli*, *K. pneumonia*, *S. typhi*, *S. pneumonia*, *E. faecium*, *E. faecalis* and *S. pyogenes*. Most enterobacteriaceae isolated were resistant to amoxicillin and co-trimoxazole but susceptible to ceftazidime/ceftriaxone, gentamicin and quinolones. These results concur with a recent epidemiological study in Niger [50] in which faecal carriage of extended-spectrum β -lactamase-producing enterobacteriaceae (ESBL-E) in 55 children aged 6–59 months in a paediatric nutrition centre was 31% ($n = 17/55$) on admission, with an acquisition rate of 94% ($n = 15/16$) among those who were not carriers on admission and were resampled on discharge. Of note, the CTX-M-15 gene was found in >90% of carriers. All children had received antibiotic treatment while in hospital, with the majority (75%) receiving multiple antimicrobial therapies including amoxicillin, ceftriaxone and ciprofloxacin [50].

Intestinal carriage of ESBL-E is a significant concern for the dissemination of multidrug-resistant bacterial infections as it might leave few therapeutic options for the treatment of sepsis. Furthermore, the CTX-M gene is of particular concern because of its known spread in hospital and community settings [51]. Previous research has detected a link between β -lactam exposure and intestinal colonisation by enterobacteriaceae resistant to cephalosporins [52], which is of concern when monitoring ongoing resistance patterns in children with SAM. If the spread of ESBL results in the narrowing of clinically effective antimicrobial therapy to carbapenems, the consequences of further dissemination would be of extreme concern given their expense and general lack of availability in low-income settings. These observational studies highlight the importance of continued monitoring of ESBL-producing organisms in children admitted with SAM.

Current guidelines support a prolonged (7-day) course of gentamicin despite no previous supporting RCT evidence of efficacy [9]. The ototoxicity and nephrotoxicity effects should be considered in children with SAM who may have reduced renal function or dehydration. The clinical efficacy of gentamicin, an aminoglycoside antibiotic distributed in the extracellular

Table 4. Bacterial antibiotic susceptibilities (%) for common first- and second-line therapies for treating children with SAM: results of a meta-analysis of 767 children from Uganda, Kenya, Turkey, Nigeria, Kenya and South Africa [30].

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 per study.

Table 5. Synopsis of international guidelines on antimicrobial therapy for children with severe acute malnutrition.

Author	Year	Guideline title	Uncomplicated SAM	Complicated SAM
BMJ	2011	Clinical evidence: kwashiorkor	7-day course Amoxicillin 80–90 mg/kg/day orally in two divided doses OR Cefdinir 14 mg/kg/day orally as a single dose, or as two divided doses (recommendation based on ref. 40)	Gentamicin 7.5 mg/kg IM/IV once daily for 7 days AND Ampicillin 200 mg/kg/day IM/IV in four divided doses OR Chloramphenicol 50 mg/kg/day IM/IV in divided doses every 6–8 hours ^a Second line: Ceftriaxone 50–75 mg/kg/day IM/IV in divided doses every 1–4 hrs (based on ref. 63)
ACF (Action Contre la Faim) ^b	2011	Guidelines for the treatment of SAM	Amoxicillin for 7 days: 50–100 mg/kg/day in two divided doses	Add 'low-dose' gentamicin 5 mg/kg daily if no improvement or signs of sepsis; change to co-amoxiclav plus antifungal (fluconazole)
Médecins Sans Frontières	2016	Clinical guidelines	Amoxicillin for 5 days (70–100 mg/kg/day) in two divided doses	"Since the infectious focus may be difficult to determine, a broad-spectrum antibiotic therapy (cloxacillin + ceftriaxone) is recommended" (dosage and time-frame not specified)
Valid International	2006	CTC Field Manual	Amoxicillin for 7 days (<10 kg 3 × 125 mg; 10–30 kg 3 × 250 mg; >30 kg 3 × 500 mg)	Chloramphenicol PO (2–5.9 kg: 3 × 62.5 mg; 6–9.9 kg: 3 × 125 mg; 10–30 kg: 3 × 250 mg) (7 days) as outpatient with moderate complications (e.g. fever not responding)
Indian Academy of Pediatrics	2006 2013	IAP Guidelines 2006 on Hospital Based Management of Severely Malnourished Children	Not documented Updated 2013 guidelines did not address antibiotic use	Ampicillin 50 mg/kg/dose 6-hourly IM or IV for at least 2 days; followed by oral Amoxicillin 15 mg/kg 8-hourly for 5 days (once the child starts improving) plus Gentamicin 7.5 mg/kg or Amikacin 15–20 mg/kg IM or IV once daily for 7 days. If the child fails to improve within 48 hours, change to IV Cefotaxime (100–150 mg/kg/day 6–8-hourly)/Ceftriaxone (50–75 mg/kg/day 12-hourly). "However, depending on local resistance patterns, these regimens should be accordingly modified". "Some experienced doctors routinely give metronidazole (7.5 mg/kg 8-hourly for 7 days) in addition to broadspectrum antibiotics. However, the efficacy of this treatment has not been established by clinical trials".
Government of Bangladesh	2008	"National Guidelines for the Management of Severely Malnourished Children in Bangladesh"	Amoxicillin oral 15 mg/kg 8-hourly for 5 days OR cotrimoxazole oral; trimethoprim 5 mg/kg and sulphamethoxazole 25 mg/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 hrs or deteriorates after 24 hrs, or 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 with or without gentamicin).
UNICEF, MoH Kenya	2009	National Guideline for Integrated Management of Acute Malnutrition	Oral amoxicillin, by weight range, equivalent to 25–50 mg/kg twice daily	Add chloramphenicol (do not stop amoxicillin) OR add gentamicin (do not stop amoxicillin) OR Switch to a moxycillin/davulinic acid.
Kenya MoH and Kenya Paediatric Association	2016	Basic Paediatric Protocols	Age <6 months, 30 mg/kg twice daily Not covered	Penicillin (or ampicillin) AND gentamicin. Give 5 days gentamicin, if improved change Pen to amoxicillin at 48 hrs.
Malawi Government	2006	Guidelines for the Management of Severe Acute Malnutrition.	Oral amoxicillin 15 mg/kg three times daily.	Gentamicin IM/IV 7.5 mg/kg once daily for 7 days AND chloramphenicol IM/IV 25 mg/kg three times daily for 5 days

^aChoice depends on local microbiological sensitivity patterns.

^bThis regimen is used in many national protocols e.g. Ethiopia, Niger.

fluid and eliminated by the kidneys, is determined by the relationship between peak concentration and minimal inhibitory concentration (MIC), with similar pharmacokinetic parameters in malnourished and eutrophic children [53]. Gentamicin has advantages in covering many Gram-negative organisms including *Pseudomonas* spp. (not covered by ceftriaxone), and convenient once-daily dosing. However, no research has investigated the possible adverse effects caused by a prolonged course, and its safety depends on children having normal renal function. Most international guidelines require the serum gentamicin concentration to be monitored after the third or fourth dose to avoid nephrotoxicity, which is expensive and logistically difficult in the low-income settings in which SAM is usually treated [54]. Therefore, in these settings, the implications of prolonged gentamicin require consideration.

Evidence for alternative antibiotic therapies

A meta-analysis in 2013 of 2767 children with all grades of SAM pooled from observational data assessed the antibiotic resistance of blood, urine and CSF cultures [30]. Apart from the improved susceptibility of amoxicillin over co-trimoxazole (as described above), the analysis also documented that the susceptibilities of chloramphenicol and amoxicillin–clavulanate were 73.7% and 30.7%, respectively. Gentamicin, amoxicillin–gentamicin, ceftriaxone and ciprofloxacin had the highest rates of susceptibility (>80%). These aggregated data document the generally high resistance to first-line antibiotics in a population of mixed, moderate and severely malnourished children in sub-Saharan Africa and Turkey (Table 4).

Metronidazole. Metronidazole has anti-anaerobic and anti-protozoal activity and is effective against small bowel bacterial overgrowth and *Clostridium difficile* colitis. Its antimicrobial effect depends on peak concentration and there is a significant 'post-antibiotic' killing effect. 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" [5]. Small cohort studies suggest that metronidazole has benefits for nutritional recovery in SAM, and improved nutrition is associated with improved survival. Metronidazole is highly effective against protozoa such as *Giardia*, which has been shown (by microscopy) to be prevalent in more than 30% of children with SAM in a Nairobi slum [55], and up to 60% of malnourished children in Rwanda (by PCR) [56]. In Jamaica, half of a population of 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, with breath hydrogen normalising after a 5-day course of oral metronidazole [57].

However, metronidazole can cause nausea and anorexia, potentially impairing recovery from malnutrition and, rarely, liver and neurological toxicity (Table 6). In Mexico, a small pharmacokinetic study of metronidazole in children with SAM reported significantly prolonged clearance, suggesting that it may be warranted to reduce dosing frequency [58]. Therefore, current evidence is insufficient to be conclusive or to alter policy, and, pending the results of a current pharmacokinetic study and clinical trial (<https://clinicaltrials.gov/ct2/show/NCT02746276>), the routine use of metronidazole should be avoided [9].

Amoxicillin–clavulanate. There have been no trials or pharmacokinetic studies of amoxicillin–clavulanate in children with SAM, although its routine use is often prescribed with the anecdotal intention of tackling systemic infection and small intestinal bacterial overgrowth [9].

Ciprofloxacin. Ciprofloxacin could be a suitable alternative for the management of sepsis in severely malnourished children, and absorption is not affected by the simultaneous administration of feeds [59]. As with third-generation cephalosporins, however, the risk of causing resistance to this important antimicrobial needs to be weighed against its clinical efficacy. To target its use, considering 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. A 2013 systematic review documented ciprofloxacin susceptibilities of IQR 82–93% (median 93%) [30].

Ceftriaxone. The potential value of oral third-generation cephalosporins (cefdinir) in uncomplicated SAM has been documented above [39]. In view of the favourable susceptibility data (median 84, IQR 80–94%) identified by the above 2013 systematic review (Table 4), parenteral ceftriaxone should in future be a focus of clinical trials for children with complicated SAM. Ceftriaxone has a broad spectrum of activity, is effective in short courses, is logistically simple in its daily dose administration (which may be intramuscular) and has a wide therapeutic index which increases its safety and efficacy [28].

Azithromycin. Since mortality benefits were observed after its mass distribution for trachoma control in Ethiopia, azithromycin has been considered

Table 6. Common adverse reactions to antibiotics used in severe acute malnutrition in children [55].

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; thrombocytopenia As for benzylpenicillin	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, of note when administering to children presenting with severe dehydration in complicated SAM Antibiotic associated colitis; electrolyte disturbances; auditory damage; irreversible ototoxicity; vestibular damage Vasculitis	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, cyclosporin, 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 Grey syndrome may occur with intravenous use in neonates (abdominal distension, pallid cyanosis, circulatory collapse)	Diarrhoea; headache; hyperkalaemia; nausea; rash; vomiting	Antibiotic-associated colitis; myocarditis; pericarditis; pancreatitis; vasculitis	Increase toxicity of anti-neoplastic drugs
Chloramphenicol	Grey syndrome may occur with intravenous use in neonates (abdominal distension, pallid cyanosis, circulatory collapse)	Diarrhoea; depression; erythema multiforme; headache; nausea; urticaria; vomiting	Nocturnal haemoglobinuria; optic or peripheral neuritis	Increases plasma concentration of cyclosporin, anti-epileptic therapies Metabolism of chloramphenicol is accelerated by rifampicin Chloramphenicol enhances effects of sulfonylureas
Fluoroquinolones: ciprofloxacin	Bone marrow toxicity: reversible and irreversible aplastic anaemia Hypersensitivity reactions; Prolonged QT syndrome	Dyspepsia, headache, diarrhoea, vomiting, hypotension	Tendinitis and tendon rupture; peripheral neuropathy	All fluoroquinolones should be used with caution in patients receiving drugs known to prolong the QT interval (see below) The toxicity of fluoroquinolones is increased by the concurrent use of systemic steroidal medications 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 Fluoroquinolones cause additive toxicity with non-steroidal anti-inflammatory drugs (ibuprofen, meloxicam, naproxen) All macrolides are advised to be avoided concomitantly with other drugs which prolong the QT interval, (including anti-malarial medications such as artemether-lumefantrine) owing to the risk of ventricular arrhythmias (see below)
Azithromycin	Hypersensitivity reactions; Prolonged QT syndrome	Dyspepsia, flatulence, headache, disturbance in taste, anorexia	Malaise, paraesthesia	Plasma concentrations of azithromycin are increased by ritonavir Azithromycin in combination with rifabutin results in increased side effects of rifabutin, including neutropenia Relevant interactions for all cephalosporins: increased risk of nephrotoxicity when co-administered with aminoglycosides. Enhance anticoagulant effect of coumarins As per ceftriaxone
Ceftriaxone	Hypersensitivity reactions	Diarrhoea, headache, abdominal discomfort	Transient cholestatic jaundice owing to biliary sludge formation	
Cefixime (specific cefdinir side effects and interactions not published)	Hypersensitivity reactions; immune-mediated haemolytic anaemia	Flatulence, headache, abdominal pain, defaecation urgency, nausea, constipation, vomiting	Transient cholestatic jaundice owing to biliary sludge formation	

a promising possible alternative for uncomplicated SAM [60]. However, no pharmacokinetic studies have been undertaken in children with SAM, although they should be considered in the future.

Co-trimoxazole as prophylaxis. Although replaced by amoxicillin in the current SAM treatment guidelines, a recent multi-centre, double-blind RCT [34] in four sites in Kenya assessed co-trimoxazole as prophylaxis in the same way it is used for children with HIV infection for which it has reduced all-cause mortality [61]. A total of 1778 HIV-negative children aged 2–59 months with complicated SAM were randomly assigned to receive daily co-trimoxazole prophylaxis or a matched placebo for 6 months after clinical nutritional stabilisation. There was no significant impact ($p = 0.429$) on growth or mortality in those receiving cotrimoxazole [34].

Pharmacokinetics in SAM

When available, the pharmacokinetics of the above therapies in children with SAM (including comparison with well nourished controls) has been detailed in previous reviews [28,35]. In 2010, a pharmacokinetic review of 34 drugs including non-antibiotics in children with SAM concluded that the available data did not allow firm conclusions to be drawn on the effects of SAM on drug absorption rates [35]. Several drugs have reduced protein-binding — chloramphenicol, (flu)cloxacillin, penicillin and sulphamethoxazole — and clearance is decreased for drugs metabolised in the liver (chloramphenicol and metronidazole), which is of concern because of potential toxicity. However, clearance appears largely unchanged for drugs renally metabolised (cefoxitin, penicillins, gentamicin and amikacin) [35]. Two papers have identified the need for adjustment of chloramphenicol dosage in children with SAM [28,35].

A 2011 population pharmacokinetic study in Kenya of ciprofloxacin in 52 children with SAM reported that 10 mg/kg thrice daily (30 mg/kg/day) rather than 10 mg/kg twice daily (20 mg/kg/day) might be a suitable alternative antibiotic for sepsis in severely malnourished children, and absorption was unaffected by the simultaneous administration of feeds [59]. In 2016, a population pharmacokinetic study of gentamicin in 26 children with SAM in Mexico reported that an intravenous dose of 7.5–15 mg/kg once daily in children with SAM and normal renal function has a high probability of efficacy and low risk of nephrotoxicity [44].

Synopsis of international guidelines

A summary of the available international guidelines for the use of antibiotics in SAM is documented in Table 5. Currently, all guidelines recommend amoxicillin as the first-line therapy in uncomplicated SAM, although

there is variation in recommended dosages (from 50 to 100 mg/kg/day) and the duration of therapy (5–7 days).

For complicated SAM, there is inconsistency in the first-line therapy recommended, including ampicillin/amoxicillin, gentamicin and alternatives that comprise a wide spectrum of antibiotics including third-generation cephalosporins, ciprofloxacin, co-amoxiclav, metronidazole and even amikacin. Dosages of medications also differ with gentamicin recommendations ranging from 5 to 7.5 mg/kg, although β -lactam dosage guidelines are consistent throughout.

Review of harms and toxicity: summary of evidence on safety

Of the studies which included data on safety and adverse events, no significant rate of adverse events was documented for any antibiotic intervention group [26,28,33,34]. Side effects and relevant interactions between the currently recommended therapies for SAM, and those which may be considered in future clinical trials are documented in Table 6.

Discussion

On the basis of a meta-analysis of two clinical trials which indicate an overall survival benefit and reduction in admission rates, the current evidence supports the continued use of broad-spectrum oral antibiotics for treating children with uncomplicated SAM (26, 32, 42). Ideally, the choice of antibiotic should be dictated by local resistance patterns and common pathogens [5]. However, where malnutrition is common, microbiological data are rarely available and may be misleading if laboratories are not externally quality-controlled. The choices of antibiotic are therefore influenced by cost, availability, ease of administration and local susceptibility profiles [10].

Amoxicillin is relatively safe with minimal serious adverse side effects and reaches therapeutic plasma levels after oral administration in malnourished children; it has been proven to improve outcomes in children with SAM [62,63]. Currently available evidence supports the continued routine administration of amoxicillin for children with uncomplicated SAM treated in the community at a clarified and harmonised dose of 80 mg/kg/day in two divided doses for 7 days. This should also be the regimen for children with complicated SAM after they have stabilised.

For complicated SAM, there is limited evidence suggesting that third-generation cephalosporins might be more effective than ampicillin/gentamicin as parenteral therapy during stabilisation. However, cephalosporins carry an increased risk of exacerbating antimicrobial resistance and therefore recommendations should not be changed until further clinical trials have been conducted. Parenteral treatment should be continued beyond 2 days

if indicated by the clinical condition, such as in severe pneumonia or sepsis. The rationale for a 7-day course of gentamicin in children with complicated SAM, who commonly have dehydration and compromised renal function, needs ongoing consideration because of the potential ototoxic and nephrotoxic adverse events in this population. However, the risks of toxicity have not been well characterised and there are limited affordable alternative choices with a similar spectrum of cover.

There is increasing evidence of non-susceptibility to commonly used antimicrobials in children with SAM, including high rates of nosocomially and community-acquired ESBL. Monitoring antimicrobial resistance including distinguishing community from nosocomial infections should be routinely undertaken when empirical broad-spectrum antibiotics are used for any community treatment of children with a life-threatening illness, including SAM. Future clinical trials adhering to CONSORT (Consolidated Standards of Reporting Trials) guidelines should investigate alternative options such as azithromycin, ciprofloxacin and oral third-generation cephalosporins which have been shown to exhibit benefit, while improving the available pharmacokinetic data for children with SAM and assessing the impact on local resistance rates where these antimicrobials are used.

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Appendix 1

Author	Title	Year	Methods (study type, setting, participants)	Results	Conclusions	GRADE level of evidence
Alcoba et al. [43]	Do children with uncomplicated severe acute malnutrition need antibiotics? A systematic review and meta-analysis	2013	<ul style="list-style-type: none"> Systematic review and meta-analysis Not restricted by region Children aged 6–59 months; plus 0–15 years for indirect evidence Children with HIV and TB were included in the analysis 2767 strictly SAM children; Case definitions: Complicated SAM = WFH < -3 Z-score and/or bilateral pitting oedema and/or WFH < 70% of median and/or MUAC < 110 mm. Uncomplicated SAM = SAM children passing appetite test, afebrile, no clinical infections or complications, treated by health centre 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 >80% of median or >2 Z scores), infection incidence, AB susceptibility/resistance Owing to heterogeneity of inclusion criteria, a meta-analysis of intervention studies was not possible though meta-analysis of observational data were conducted 	<ul style="list-style-type: none"> 3 RCTs, 5 Cochrane reviews, 37 observational studies identified as meeting inclusion criteria Prevalence of serious infections in SAM, pooled from 24 cohorts, ranged from 17% to 35.2% One cohort-study showed no increase in nutritional-cure and mortality in uncomplicated SAM where no AB were used ($p > 0.05$) However, an unpublished RCT in this setting did show mortality benefits (Trehan 2013) Another RCT did not show superiority of ceftriaxone over amoxicillin for these same outcomes, but addressed SAM children with and without complications ($p = 0.27$) One RCT showed no difference between amoxicillin and cotrimoxazole efficacies for pneumonia in underweight, but not SAM Review of international guidelines revealed inconsistencies in the recommended first-line antibiotic (AMX and CTX) with 5 different dosages: CTX 4–5 mg/kg/d, AMX 50–100 or 70–100 mg/kg/day or 3 weight classes and 2 different durations (5 or 7 days) 	<ul style="list-style-type: none"> Meta-analysis of 12 pooled susceptibility studies for all types of bacterial isolates, including 2767 strictly SAM children, favoured amoxicillin over cotrimoxazole for susceptibility medians: 42% (IOR 27–55%) vs. 22% (IOR 17–23%) and population-weighted-means 52.9% (range 23–57%) vs. 35.4% (range 6.7–42%) Susceptibilities to 2nd-line AB were better, above 80% No study inferred any association of infection prevalence with AB regimens in SAM The authors concluded that: “the evidence underlying current antibiotic recommendations for uncomplicated SAM is weak” and called for placebo-controlled RCTs to demonstrate efficacy Given that antibiotics have side effects, costs and risks as well as benefits, the authors conclude that their routine use needs urgent testing The 3 studies that directly evaluate antibiotics in SAM revealed three contrasting results: <ul style="list-style-type: none"> AB not superior to no AB CEF superior to AMX and AMX superior to placebo CEF not superior to AMX. None of these studies provided stratified analyses for HIV+ SAM children The authors concluded that there is very limited evidence regarding many aspects of SAM in children <5 years, including management of subgroups (children <6/12 or children with SAM who are HIV+) and the use of antibiotics 	B (meta-analysis based on observational data)
Picot et al. [31]	The effectiveness of interventions to treat severe acute malnutrition in young children: a systematic review	2012	<ul style="list-style-type: none"> Systematic review Children <5 years Search period 2010–2012 Not restricted by region 	<ul style="list-style-type: none"> 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 74 articles describing 68 studies (RCTs, CCTs, cohort studies and case-control studies) met the inclusion criteria No evidence focused on HIV+ children; and no trials were conducted on children <6/12 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 Dubray 2008: An unblinded RCT conducted in Sudan ($n = 458$) which indicated oral amoxicillin (80 mg/kg/day in two divided doses) for 5 days was as effective as IM ceftriaxone for 2 days [36]. 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 ≥ 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 A second large retrospective study in Malawi (Trehan 2010) compared oral amoxicillin (60 mg/kg/day, $n = 498$) for 7 days with no antibiotics ($n = 195$), revealing a poorer recovery rate in children receiving amoxicillin at 4 weeks (39.8% vs. 70.8%; $p < 0.001$), but a similar rate of recovery at 12 weeks, with similar rates of death and default [37]. However, this research is at risk of bias not just owing to its retrospective data collection, but also because of the different district locations of the two cohorts of patients, who were also not stratified by risk of HIV-infectivity status (with a high burden in the study population) 	<ul style="list-style-type: none"> The authors concluded that there is very limited evidence regarding many aspects of SAM in children <5 years, including management of subgroups (children <6/12 or children with SAM who are HIV+) and the use of antibiotics 	B (systematic review with only 2 studies retrieved with epidemiological limitations)

(Continued)



Appendix 1. (Continued).

Author	Title	Year	Methods (study type, setting, participants)	Results	Conclusions	GRADE level of evidence
Lazzerini and Tickell [38]	Antibiotics in severely malnourished children: systematic review of efficacy, safety and pharmacokinetics	2011	<ul style="list-style-type: none"> Systematic review of CENTRAL, MEDLINE, EMBASE, LILACS, POPLINE, and CAB Abstracts and ongoing trials registers were searched, plus thorough grey literature search For PK review, all study types, except single case reports, were included 	<ul style="list-style-type: none"> Overall, 23 studies were identified for inclusion: 2 RCTs, 1 before-and-after study and 2 retrospective reports on clinical efficacy and safety were retrieved, together with 18 pharmacokinetic studies Trial quality was generally poor and results could not be pooled owing to heterogeneity 	<p>The authors concluded that 'the existing evidence is not strong enough to further clarify recommendations for antibiotic treatment in children with SAM.'</p> <ul style="list-style-type: none"> Pharmacokinetic data suggest that normal doses of penicillins, cotrimoxazole and gentamicin are safe in malnourished children, while the dose or frequency of chloramphenicol requires adjustment First-line antibiotics for uncomplicated SAM: Benefit vs. harm remains undetermined. There is a lack of epidemiological data on the risk of infection in children with uncomplicated SAM and what data there are have not been stratified by HIV prevalence. Cotrimoxazole is losing efficacy owing to resistance; amoxicillin remains a valuable alternative owing to findings of similar efficacy of ceftriaxone and cheaper price Complicated SAM: Current data continue to support broad-spectrum antibiotics for children with complicated SAM; however, only one retrospective 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 has not been studied High rates of <i>in vitro</i> resistance have been reported in several African countries Many institutions vary in their extent of following recommendations and instead give more potent broad-spectrum antibiotics as 1st-line therapy, largely guided by local <i>in vitro</i> susceptibility data 	B (systematic review with poor quality trials retrieved)
Milion et al.[32]	Meta-analysis on efficacy of amoxicillin in uncomplicated severe acute malnutrition	2016	<ul style="list-style-type: none"> Meta-analysis combining Isanaka's (2016) and Trehan's (2013) RCTs 	<p>Conclusion of included studies:</p> <ul style="list-style-type: none"> Oral amoxicillin for 5 days was as effective as intramuscular ceftriaxone for 2 days (1 RCT) For uncomplicated SAM, amoxicillin showed no benefit over placebo (1 retrospective study) The introduction of a standardised regimen that included the administration of ampicillin and gentamicin significantly reduced mortality in hospitalised children (OR 4.0; 95% CI 1.7–9.8; 1 before-and-after study); however, this was pooled with intervention to address hypoglycaemia Oral chloramphenicol was as effective as cotrimoxazole in children with pneumonia (1 RCT); this study was poorly generalisable PK studies 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> PK studies: Suggest parenteral Pen+Gent can be safely given to malnourished children at the same doses as eutrophic children, unless renal failure or shock are present 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 No studies have been published on the efficacy, safety or PK of ciprofloxacin or ceftriaxone in children with SAM 	<ul style="list-style-type: none"> The authors concluded that further studies should clarify whether amoxicillin has a different effect according to clinical presentation of SAM. Cephalosporins may also have greater efficacy (RR of treatment failure: 1.64 for placebo vs. cefdinir; 1.32 for placebo vs. amoxicillin) 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 systemically susceptible to amoxicillin, and proteobacteria, which are better inhibited by cephalosporins in SAM 	A (meta-analysis with large sample size)



Trehan et al. [33]	2013	Antibiotics as part of the management of severe acute malnutrition	2013	3-arm placebo-controlled, double-blinded RCT in Malawi comparing oral amoxicillin (80–90 mg/kg/day in 2 divided doses) vs. placebo (twice daily) and an oral 3rd-generation cephalosporin (ceftriaxone, 14 mg/kg/day in 2 divided doses) in uncomplicated SAM	6–59 months 2009–2011 study period Computer-generated block randomisation lists were created in permuted blocks of 54 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 Caregivers, study nurses, and all study personnel involved in clinical assessments and data analysis were blinded to the intervention each child received 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 After randomisation and distribution of the medications and placebo, study nurses educated each child's caregiver on how to use the syringe to give the medications, supervised administration of the first dose in the clinic, and provided them with a pictorial calendar for recording each dose given, with instructions to give the medication twice daily for 7 days 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 At the first follow-up visit, study nurses assessed how much medication was given 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 Primary endpoints: Rates of nutritional recovery and mortality rates in the 3 study arms Secondary outcomes of interest included weight gain, length gain, tolerance of the medications and time to recovery	B (RCT with strong methodological quality)
In children who recovered, the rate of weight gain was increased in those who received antibiotics	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	Adherence to the intervention was very high in each of the 3 study groups	No reports of severe allergy or anaphylaxis were reported in any children in the study	Primary outcomes: The proportion of children who recovered was significantly lower in those who received placebo (85.1%) than in those who received either amoxicillin (88.7%, $p = 0.02$) or ceftriaxone (90.9%, $p = 0.0001$)	Subgroup analysis showed that, when stratified by type of SAM, children with kwashiorkor who received placebo recovered less frequently than those who received ceftriaxone vs. 95.2% vs. 92.2% ($p = 0.04$)	Similarly, children with marasmus who received placebo also recovered less frequently than those who received ceftriaxone (74.4% vs. 79.2%, $p = 0.02$)
No interaction between type of SAM and intervention group was observed for the rate of nutritional recovery or mortality	Cefdinir was superior to amoxicillin, and amoxicillin was superior to placebo, resulting in significantly improved recovery at 12 weeks (90.9%, 87.7%, 85.1%, respectively) and mortality (4.1%, 4.8%, 7.4%)	Trial included a high rate of HIV+ children ($n = 188$); however, distribution was equitable across intervention groups	The authors concluded that these results provide clear evidence to support the recommendation for routine oral antibiotics as part of the outpatient management of SAM	The overall mortality rate was 5.4%, but significantly higher in children who received placebo (7.4%) than in those who received either amoxicillin (4.8%, $p = 0.02$) or ceftriaxone (4.1%, $p = 0.003$)	This corresponds to a 36% (95% CI, 7%–55%) reduction in mortality when given amoxicillin and a 44% (95% CI 1.8%–62%) reduction in mortality with cefdinir	Routine provision of amoxicillin was not superior to placebo for nutritional recovery in children with uncomplicated SAM.
Routine provision of amoxicillin was not superior to placebo for nutritional recovery in children with uncomplicated SAM.	“This finding challenges the view that routine antibiotic therapy is always necessary or beneficial”	Amoxicillin reduced the risk of a transfer to inpatient care by 14% compared with placebo	Amoxicillin specifically reduced the risk of transfer to inpatient care for clinical complications owing to gastroenteritis. This was unexpected as the viruses and parasites primarily responsible for gastroenteritis in young children are not sensitive to amoxicillin [30]. 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 bacteraemia, or that oral antibiotics may reduce excessive proliferation of small-bowel flora, modifying the composition and function of the gut microbiome	Limitations: Assumed a likelihood of nutritional recovery of 80%, which was not achieved so cannot rule out the possibility that amoxicillin had a protective effect of 12% or a harmful effect of 1% on nutritional recovery	Risk of bias: excluded children with mild-moderate oedema – ?patient population too well	B (RCT with strong methodological quality)
Overall, 64% of children enrolled in the study recovered	No significant difference in likelihood of recovery between amoxicillin vs. placebo (RR with amoxicillin 1.05, 95% CI 0.99–1.12)	Among children who recovered, time to recovery was significantly shorter with amoxicillin than placebo (mean treatment of 28 vs. 30 days, $p < 0.001$)	Amoxicillin had no significant effect in children with confirmed bacterial infection on admission	Secondary outcomes: Amoxicillin tended to reduce the risk of death in children who were >24 months (RR 0.24, 95% CI 0.02–2.12) but not in those <24 months (RR 3.04, 95% CI 0.61–15.01)	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 ($p = 0.4$)	Amoxicillin significantly decreased the overall risk of transfer to inpatient care (26.4% vs. 30.7%, RR 0.86, 95% CI 0.78–0.98, $p = 0.02$) and for acute gastroenteritis in particular (RR 0.67, 95% CI 0.48–0.94, $p = 0.02$)
Amoxicillin significantly accelerated early gains in weight and MUAC (week 1: RR 3.8, 95% CI 3.1–4.6, $p < 0.001$), with no significant effect on overall weight gain by week 4 or height gain during treatment	No cases of severe allergy or anaphylaxis were identified; diarrhoea was less frequent in the amoxicillin group than in the placebo group at week 1. None of the clinical complications or deaths were reported to be related to the study drug	RESISTANCE: the likelihood of resistance to amoxicillin was 35% for enterobacteria isolated from stool in children with diarrhoea, and 66% for enterobacteria isolated in blood				
Double-blind, placebo-controlled RCT at 4 health centres in rural Niger to assess the effect of routine amoxicillin on nutritional recovery in children with severe malnutrition	2016	Routine amoxicillin for uncomplicated/severe acute malnutrition in children	2016	Children randomly assigned (computer-generated) 1:1 ratio in blocks of 6 to receive 80 mg/kg amoxicillin in 2 daily doses or placebo for 7 days; adherence monitored by home visits	Inclusion criteria: Children must not have received any antibiotic treatment within the prior 7 days; 6–59 months, WH Z-score < -3 and/or MUAC 115 mm; passed appetite testing; absence of clinical complications (including oedema)	Primary aim: examining the effect of routine antibiotic use Primary outcome: nutritional recovery by 8 weeks (WH Z-score > -2 on 2 consecutive visits or MUAC > 115 mm)

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Appendix 1. (Continued).

Author	Title	Year	Methods (study type, setting, participants)	Results	Conclusions	GRADE level of evidence
Berkley et al. [34]	Daily co-trimoxazole prophylaxis to prevent mortality in children with complicated severe acute malnutrition: a multicentre, double-blind, randomised placebo-controlled trial	2016	<ul style="list-style-type: none"> 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) n = 1778 2009–2013 Children aged 3 months–59 months without HIV admitted to hospital and diagnosed with (complicated) SAM After nutritional stabilisation, 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 <6 months, 240 mg per day for age 6 months to 5 years) or matching placebo Assignment was done with computer-generated randomisation in permuted blocks of 20, stratified by centre and age (younger or older than 6 months) Treatment allocation was concealed in opaque, sealed envelopes and patients, their families, and all trial staff were masked to treatment assignment Children were given recommended medical care and feeding, and followed up for 12 months 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 Primary endpoint was mortality, assessed each month for the first 6 months, then every 2 months for the second 6 months Secondary endpoints were nutritional recovery, readmission to hospital, and illness episodes treated as an outpatient Analysis was by intention to treat 	<ul style="list-style-type: none"> Median age was 11 months (IQR 7–16 months); 306 (17%) were younger than 6 months 300 (17%) had oedematous malnutrition (kwashiorkor) 1221 (69%) were stunted (length-for-age Z score < -2) During 1527 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 (unadjusted hazard ratio [HR] 0.90; 95% CI 0.71–1.16, p = 0.429; 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) In the first 6 months of the study (while participants received study medication), 63 suspected grade 3 or 4 associated adverse events were recorded in 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) The most common adverse events of these grades were urticarial rash (grade 3, equally common in both groups), neutropenia (grade 4, more common in the co-trimoxazole group) and anaemia (both grades equally common in both groups) One child in the placebo group had fatal toxic epidermal necrolysis with concurrent <i>Pseudomonas aeruginosa</i> bacteraemia 	<ul style="list-style-type: none"> The authors conclude that in HIV-negative Kenyan children with complicated SAM, daily co-trimoxazole for 6 months was well tolerated but did not reduce mortality or improve growth. The authors questioned if low bacterial susceptibility to co-trimoxazole may be the reason for an absence of a protective effect on mortality In children with SAM, two main reasons were noted for initial admission, diarrhoea and pneumonia, which raised 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. 	B (RCT with strong methodological quality)



Appendix 2

Authors	Title	Year	Methods (study type, setting, participants)	Results	Conclusions	GRADE level of evidence
Chisti et al. [41]	Treatment failure and mortality amongst children with severe acute malnutrition presenting with cough or respiratory difficulty and radiological pneumonia	2015	<ul style="list-style-type: none"> Cohort study: Prospective enrolment of SAM children aged 0–59 months admitted to the Intensive Care Unit or Acute Respiratory Infection ward of the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh in April 2011 to June 2012 with cough or respiratory difficulty and radiological pneumonia All the enrolled children were treated with ampicillin and gentamicin and micronutrients as recommended by the WHO Comparison was made between pneumonic children with ($n = 111$) and without ($n = 296$) WHO-defined danger signs of severe pneumonia Primary outcomes: Treatment failure (if a child required change of antibiotics) and deaths during hospitalisation Further comparison was made of those who developed treatment failure and those who did not 	<ul style="list-style-type: none"> SAM children with danger signs of severe pneumonia more often experienced treatment failure (58% vs. 20%, $p < 0.001$) and fatal outcome (21% vs. 4%, $p < 0.001$) than those without danger signs Only 6/111 (5.4%) SAM children with danger signs of severe pneumonia and 12/296 (4.0%) without danger signs had bacterial isolates in blood In log-linear binomial regression analysis, after adjusting for potential confounders, danger signs of severe pneumonia, dehydration, hypocalcaemia and bacteraemia were independently associated with treatment failure and deaths in SAM children presenting with cough or respiratory difficulty and radiological pneumonia ($p < 0.01$) Only 2 children with danger signs and 4 without danger signs of severe pneumonia had a blood culture isolate that was not susceptible to ampicillin and gentamicin 3 study children had a blood culture isolate which was not susceptible to ceftriaxone and only one child to ciprofloxacin Overall, 18 (4.4%) children had bacteraemia, and the difference in bacteraemia between the groups was not significant 67 (16.5%) children had a history of prior use of antibiotics and only 2 (3%) of them had bacteraemia 	<ul style="list-style-type: none"> Ampicillin and gentamicin are insufficient for children with complicated SAM presenting with pneumonia The result underscores the importance of further research, especially a randomised, controlled clinical trial to validate standard WHO therapy in SAM children with pneumonia, especially with danger signs of severe pneumonia, to reduce treatment failure and deaths Biased by previous administration of antibiotics 	C
Yebo et al. [40]	Outpatient therapeutic feeding program outcomes and determinants in treatment of severe acute malnutrition in Tigray northern Ethiopia: a retrospective cohort study	2013	<ul style="list-style-type: none"> Retrospective cohort study 628 children 6–59 months who had been managed for SAM as outpatients from April 2008 to Jan 2012 The children were selected using systematic random sampling from 12 health posts and 4 health centres Tigray, Northern Ethiopia Details of amoxicillin mg/kg not clarified Children admitted to the outpatient treatment programme receive weekly rations of Plumpy Nut and supplements including vitamin A, folic acid tabs, antibiotics, deworming tabs and measles vaccine Children did not have medication administration supervised 	<ul style="list-style-type: none"> Children who took amoxicillin had significantly faster recovery compared to children who did not take amoxicillin ($\chi^2 = 136.59$, $p < 0.0001$) Children who took amoxicillin had 95% (HR 1.95, 95% CI 1.17–3.23) a higher probability of recovery compared to those who didn't take amoxicillin 	<ul style="list-style-type: none"> 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 Biased by retrospective design and poor monitoring of medication administration 	D

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Appendix 2. (Continued).

Authors	Title	Year	Methods (study type, setting, participants)	Results	Conclusions	GRADE level of evidence
Page et al. [14]	Infections in Children Admitted with Complicated Severe Acute Malnutrition in Niger	2013	<ul style="list-style-type: none"> A clinical and biological characterisation of infections in hospitalised children with complicated SAM in Maradi, Niger 311 children 6–59 months Study period October 2007 to July 2008 SAM WHZ < -3 Z-score of the median WHO growth standards and/or MUAC < 110 mm and/or bipedal oedema Complicated SAM defined as SAM accompanied by anorexia and/or kwashiorkor with bilateral pitting oedema and/or another severe condition (severe anaemia, severe respiratory tract infection, malaria with signs of severity, other severe infections such as meningitis or sepsis, diarrhoea with dehydration, lethargy or acute neurological disorders, Clinical examination, blood, urine and stool cultures and chest radiography were performed systematically on admission Amoxicillin was given systematically or parenteral ceftriaxone in cases of suspected severe or complicated infectious syndrome. No mention of gentamicin in methodology 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, cloxacillin (skin infection, severe pneumonia, <i>S. aureus</i> bacteraemia) or ciprofloxacin (urinary tract infection, severe, explosive or persistent diarrhoea > 72 hours, bloody diarrhoea, bacteraemia with suspected Gram-negative bacteria) was added in case of treatment failure, based on lack of improvement or worsening of symptoms within 72 hours of treatment 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 in all 	<ul style="list-style-type: none"> Prevalence data: In the 311 children in the study, gastroenteritis was the most frequent clinical diagnosis on admission, followed by respiratory tract infections and malaria. Blood or urine culture was positive in 17% and 16% of cases, respectively, and 36% had abnormal chest radiography. Enterobacteria were sensitive to most antibiotics except amoxicillin and cotrimoxazole. The median length of stay in the inpatient treatment facility was 8 days (IQR 6–13 days). 29 (9%) of children died; almost half of all deaths (48%, $n = 14/29$) occurred within 48 h of admission. The main causes of death recorded were sepsis (15), respiratory tract infection (4) and clinical suspicion of tuberculosis (2). Overall, 20 (69%) children who died had one or several laboratory or X-ray-proven infections, including 8 bacteraemia (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 diarrhoea (1 <i>S. flexneri</i>, 1 <i>S. sonnei</i>, 1 <i>Salmonella</i> spp.); 2 malaria and 2 RTI. The CFR was 16% ($n = 8/51$, $p = 0.1$) in patients with a positive blood culture, 15% ($n = 7/41$, $p = 0.2$) in children with a UTI, 8.3% ($n = 4/62$, $p = 0.5$) in children with infectious diarrhoea and 4.5% ($n = 2/44$, $p = 0.5$) in those with malaria. Clinical signs were poor indicators of infection and initial diagnoses correlated poorly with biologically or radiography-confirmed diagnoses 	<ul style="list-style-type: none"> 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 update of international guidelines on management of complicated SAM based on more recent data. Limitations: Did not reach target sample size ($n = 1000$) owing to the premature closure of the MSF programme; resulted in missing data in particular the months of August to October, which correspond to the malnutrition and malaria peaks; secondly, diagnostic capacity is limited compared with developed country settings and it was difficult to ascertain diagnoses in some cases (e.g. TB diagnosed clinically). Third, glycaemia 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 owing to inaccurate characterisation of culture results 	D