Antibiotic Use for Sepsis in Neonates and Children: 2016 Evidence Update

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TABLE OF CONTENTS

1. INTRODUCTION

1.1. Aims

Sepsis remains a leading cause of mortality and morbidity, especially during the first five days of life and in low and middle-income countries (LMIC) [1]. Hospital infection also remains a major cause of mortality in children despite progress encountered in the last decades.

WHO recommends ampicillin (or penicillin; cloxacillin if staphylococcal infection is suspected) plus gentamicin for empiric treatment of neonates with suspected clinical sepsis; when referral is not possible, once daily gentamicin plus oral amoxicillin may be used. It is known, however, that in many countries, agents with a broader spectrum, such as third-generation cephalosporins, are commonly used to treat neonatal and infant sepsis [2] Against this background, concerns are increasing regarding bacterial pathogens with reduced susceptibility to empiric medication with variations both between and within LMIC [3].

The WHO seeks to provide a paediatric perspective on antibiotics to be included on the list of essential medicines, which is currently in the process of being updated. The potential need to revise the existing WHO guidelines based on new antimicrobial resistance (AMR) data or evidence relating to drug safety in neonates and children must be evaluated. For this purpose, a number of reviews have been commissioned to address these aspects.

This review collates evidence to support current empiric antibiotic recommendations for suspected or confirmed sepsis in neonates and children according to the most recent (≥ year 2012) relevant studies.

1.2. Background

1.2.1. Definition and diagnosis

Neonatal Sepsis

An accepted definition of sepsis in neonates is lacking. According to the report on the expert meeting on neonatal and paediatric sepsis of EMA (2010) [4], neonatal sepsis can be defined by the presence of at least two clinical symptoms and at least two laboratory signs in the presence of or as a result of suspected or proven infection (positive culture, microscopy or polymerase chain reaction) (**Table 1**):

Clinical signs	Laboratory signs
• Modified body temperature: core temperature greater than 38,5 °C or less than 36 °C AND/OR temperature instability • Cardiovascular instability: bradycardia (mean HR less than the 10th percentile for age in the absence of external vagal stimulus, beta-blockers or congenital heart disease OR otherwise unexplained persistent depression over a 0.5 h time period) OR tachycardia (mean HR greater than 2 SD above normal for age in the absence of external stimulus, chronic drugs and painful stimuli OR otherwise unexplained persistent elevation over a 0,5 h to 4 h time period) AND/OR rhythm instability reduced urinary output (less than 1 mL/kg/h), hypotension (mean arterial pressure less than the 5th percentile for age), mottled skin, impaired peripheral perfusion • Skin and subcutaneous lesions: petechial rash, sclerema	• White blood cells (WBC) count: <4,000 x10^9 cells/L OR >20,000 x10^9 cells/L • Immature to total neutrophil ratio (I/T) greater than 0.2 • Platelet count <100,000 x10^9 cells/L • C reactive protein > 15 mg/L OR procalcitonin ≥ 2 ng/ml (The cut-off for procalcitonin in neonatal sepsis has not been clearly defined, as the currently available published data are still controversial). • Glucose intolerance confirmed at least 2 times: hyperglycaemia (blood glucose >180 mg/dL or 10 mMol/L) OR hypoglycaemia (glycaemia < 45 mg/dL or 2.5 mMol/L) when receiving age specific normal range glucose amounts • Metabolic acidosis: Base excess (BE) <-10 mEq/L OR Serum lactate > 2 mMol/L

Clinical signs	Laboratory signs
• Respiratory instability: apnoea episodes OR tachypnea episodes (mean respiratory rate (RR) over 2 SD above normal for age) OR increased oxygen requirements OR requirement for ventilation support • Gastrointestinal: feeding intolerance, poor sucking, abdominal distention • Non-specific: irritability, lethargy and hypotonia	

Table 1. Clinical signs and laboratory signs (presence of at least two clinical symptoms and at least two laboratory signs) associated with neonatal sepsis according to the report on the expert meeting on neonatal and paediatric sepsis of EMA (2010)

In resource-limited settings with limited and/or intermittent access to laboratory evaluations this definition is not workable. Consequently, a highly specific definition of neonatal sepsis is not available for LMIC settings. Instead it is recommended that initiation of antibiotics should be prompted by clinical signs of Possible Serious Bacterial Infection (PSBI), a highly sensitive definition aiming to reduce the number of false negatives (i.e. missed cases of sepsis). Clinical signs of PSBI, according to the Young Infants Clinical Signs Clinical Study criteria of WHO's Integrated Management of Childhood Illness (IMCI) guidelines, are defined as the presence of any one of a history of difficulty feeding, history of convulsions, movement only when stimulated, respiratory rate of 60 or more breaths per min, severe chest retractions, or a temperature of 37.5 °C or higher or 35.5 °C or lower [5].

Paediatric Sepsis

The expert meeting on neonatal and paediatric sepsis of EMA (2010) [4] endorsed the International Paediatric Sepsis Consensus Conference of sepsis definition for paediatric patients, that is:

- *Infection*: A suspected or proven (by positive culture, tissue stain or PCR test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging or laboratory tests (e.g. WBC in a normally sterile blood fluid, perforated viscus, chest Rx consistent with pneumonia, petechial or purpuric rash or purpura fulminans).
- *Systemic inflammatory response syndrome (SIRS)*:
  The presence of at least two of the following four criteria, one of which MUST BE abnormal temperature or leukocyte count:
  - Core temperature greater than 38,5 °C or less than 36 °C
  - Tachycardia (mean HR greater than 2 SD above normal for age in the absence of external stimulus, chronic drugs and painful stimuli OR otherwise unexplained persistent elevation over a 0,5 h to 4 h time period) OR bradycardia-for children less than 1 year old (defined as mean HR less than the 10th percentile for age in the absence of external vagal stimulus, beta-blockers or congenital heart disease OR otherwise unexplained persistent depression over a 0.5 h time period)
  - Mean respiratory rate (RR) over 2 SD above normal for age OR mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anaesthesia.
  - Leukocyte count elevated OR depressed for age (not secondary to chemotherapy-induced leucopenia) OR more than 10% immature neutrophils
- ***Sepsis***: SIRS in the presence or as a result of suspected or proven infection

We were unable to identify a specific WHO definition for paediatric sepsis, which might be due to the lower incidence of sepsis after the neonatal period in LMIC compared to other diseases. A sepsis diagnosis applying the International Paediatric Sepsis Consensus Conference criteria requires laboratory tests. In addition, it may only be feasible to assess complex organ dysfunction criteria at

highly resourced institutions. In many LMIC, even simple laboratory tests, such as leukocyte counts, are often not or only intermittently available [6].

Community versus hospital acquired sepsis

In high-income countries (HIC), early onset neonatal sepsis (EONS) is defined as appearing in the first 72 hours after birth, as opposed to late onset neonatal sepsis (LONS, onset more than or equal to 72 hours after birth). In LMIC settings, many neonates are born outside of healthcare facilities, and might get infected with community acquired pathogens even after 72 h of life. As a result, neonatal sepsis in LMIC is often classified as community- and hospital-acquired instead of early- and late-onset [7].

1.2.2. Microbiology

Pathogens involved in neonatal sepsis are different between HIC and LMIC.

In HIC, the most common causes of EONS are group B streptococcus (GBS) and *Escherichia coli (E.Coli)*. The remaining cases of EONS are caused by *Staphylococcus aureus (S. aureus)*, coagulase-negative staphylococci (CoNS), *Listeria monocytogenes* and other Gram-negative bacteria [7]. In LONS (mainly in very-low-birth-weight infants), the main pathogens are CoNS, responsible for half of the episodes. Other important etiologic agents are *E. coli*, *Klebsiella* spp. and *Candida* spp. Less common causes of LONS include *S. aureus*, *Enterococcus* spp. and *Pseudomonas aeruginosa* [7, 8].

Etiological data from LMIC, particularly from rural, community-based studies, are very limited. Considering existing systematic reviews on this topic, the commonest causes of neonatal bacteremia in LMIC are: *S. aureus*, *E. coli* and *Klebsiella* spp., and in older infants, *S. aureus*, *Streptococcus pneumoniae (S. pneumoniae)*, *Klebsiella* spp. and *E. coli*, and non-typhoidal *Salmonella* [9, 10]. Although some similarities exist between community- and hospital- acquired sepsis, available data is of insufficient quality to be able to draw firm conclusions [7]. *Acinetobacter* spp., for example, appear to be predominant in some regions [11, 12], while the incidence is very low in other regions. GBS is responsible for only 2–8% of cases in LMIC. It is possible that infants with GBS infection are underreported, since this pathogen usually presents very early in life and infected newborns might die or be adequately treated before blood cultures or other relevant microbiological samples are obtained. CoNS is responsible for a lower proportion of hospital-acquired infections compared to HIC [7], and this may be related to the use of invasive medical devices, e.g. central venous catheters.

Considering local variations, figures 1 (neonates) and 2 (children) show the pathogen distribution for studies conducted in specific LMIC countries and reported after 2005. These data demonstrate the heterogeneity likely to be encountered in settings, for which the WHO essential medicines list might be relevant. In particular, it is not presently possible to definitively delineate the specific role played by difficult to treat bacteria, such as *Klebsiella* spp. and *Acinetobacter* spp. Clearly, even when antimicrobial resistance patterns are not considered, the relative incidence of these pathogens may have a considerable impact on the likely cover provided by different empiric regimens.

1.2.3. Burden of sepsis

In 2012, an estimated 6.9 million (uncertainty range 5.5 – 8.3 million) possible serious bacterial infections occurred in neonates in South Asia, sub-Saharan Africa, and Latin America [1]. In 2015, among the 5.941 million of all deaths in children under the age of 5 years, 45% died in the neonatal period. This portion exceeds 50 percent in several regions [13]. Neonatal sepsis is the third most common cause of death in this age group with an estimated 0.401 million of deaths (uncertainty range [0.280–0.522], 6.8% [4.7–8.6]) in 2015, the vast majority of which are in developing countries [14]. Outside the neonatal period, the period up to 12 months of age carries the highest risk of death from sepsis.

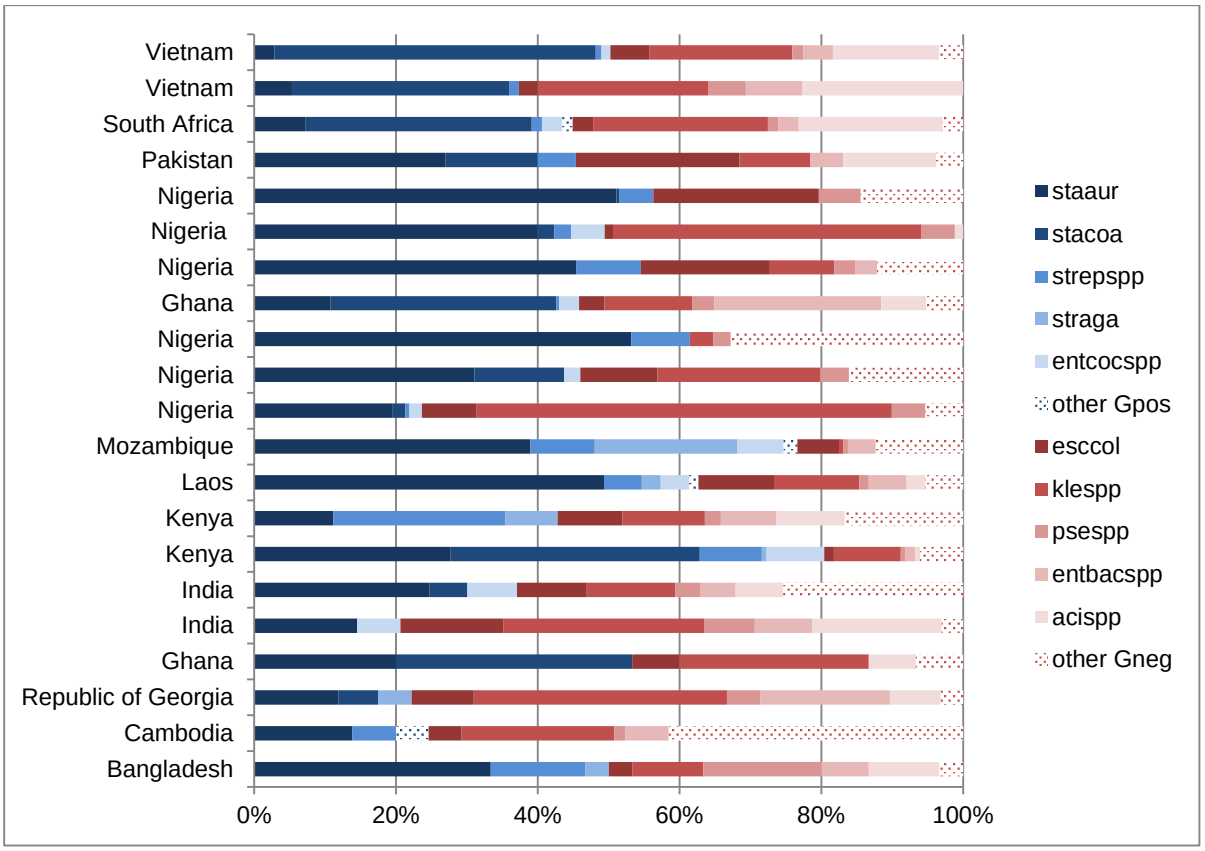

Figure 2. Pathogen distribution for studies conducted in a specific setting and reported after 2005 in neonates. staaur: *S. aureus*, stacoa: coagulase-negative staphylococci, strepspp: streptococci, straga: *S. agalactiae*, entcocspp: enterococci, other Gpos: other Gram positive pathogens, esccol: *E. coli*, klespp: *Klebsiella* spp., psespp: *Pseudomonas* spp., entbacspp: *Enterobacter* spp., acispp: *Acinetobacter* spp., other Gneg: other Gram negative pathogens.

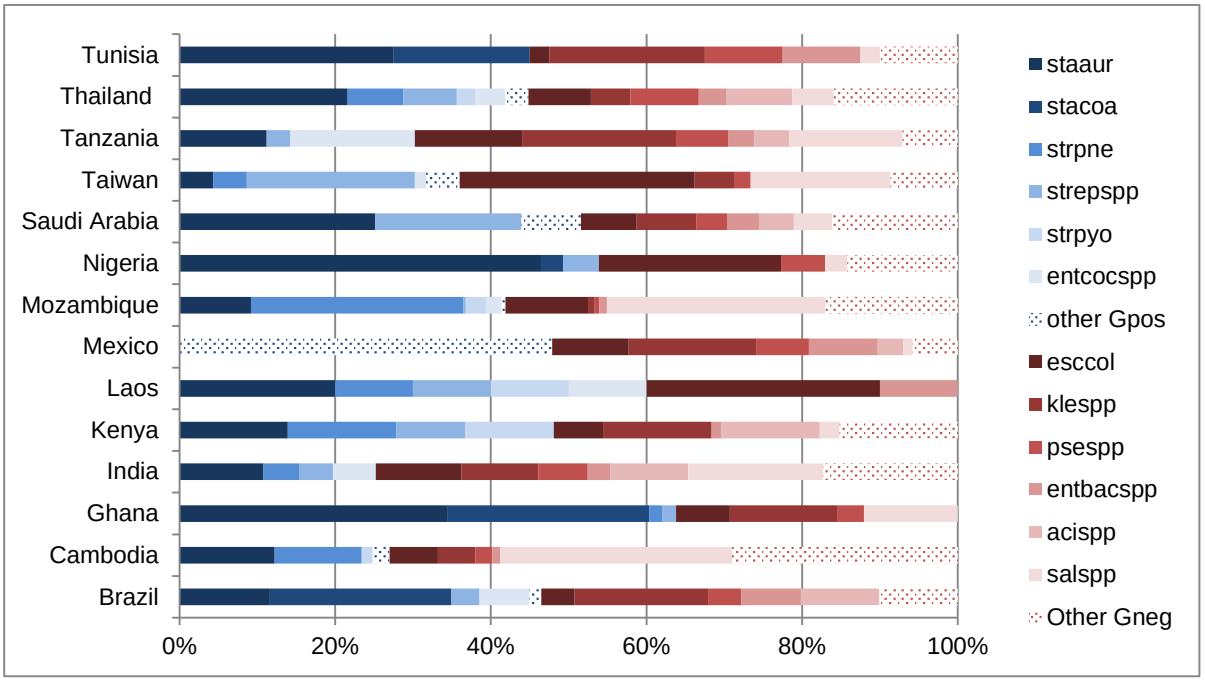

Figure 3. Pathogen distribution for studies conducted in a specific setting and reported after 2005 in children. staaur: *S. aureus*, stacoa: coagulase-negative staphylococci, strpne: *S. pneumoniae*, strepspp: streptococci, strpyo: *S. pyogenes*, entcocspp: enterococci, other Gpos: other Gram positive pathogens, esccol: *E. coli*, klespp: *Klebsiella* spp., psespp: *Pseudomonas* spp., entbacspp: *Enterobacter* spp., acispp: *Acinetobacter* spp., salspp: *Salmonella* spp., other Gneg: other Gram negative pathogens.

1.2.4. Current WHO guidelines

WHO provide guidelines for the management of common childhood illnesses, through the *Pocket book of hospital care for children* released for the first time in 2005 [15]. The second edition has been available since 2013 [16]. It is one of a series of documents and tools that support *the Integrated Management of Childhood Illness* (IMCI). These guidelines focus on the management of the major causes of childhood mortality in countries with limited healthcare (and other) resources. Recommendations for prevention of neonatal infection and for the management of possible serious bacterial infection have not changed between the 2 editions. IMCI recommends providing prophylactic intramuscular (IM) or intravenous (IV) **ampicillin** and **gentamicin** in neonates with documented risk factors for infection for at least 2 days and to reassess. Treatment should be continued only if there are signs of sepsis (or positive blood culture).
IMCI recommends **hospitalization** and IM or IV antibiotic therapy with a combination of **gentamicin** and **benzylpenicillin or ampicillin** for at least 7–10 days in infants aged <2 months for infants fulfilling the case definition of serious bacterial infection. If infants are deemed at risk of staphylococcal infection, IV **cloxacillin** and **gentamicin** are recommended.

In many LMIC, this kind of parenteral treatment might only be available at sites able to provide inpatient neonatal and paediatric care, and access to this kind of treatment is limited by transportation, financial, and/or cultural factors. Even when these constraints were addressed in previous studies, a substantial proportion of families still refused referral to hospital for young infants with PSBI. A body of research has been conducted in the past decade leading to the development and release in 2015 of the first guideline for *Managing possible serious bacterial infection in young infants when referral is not possible* [17] in infants aged < 59 days. The guideline recommends:

- *Option1:* IM **gentamicin** 5–7.5 mg/kg (for low-birth-weight infants gentamicin 3–4 mg/kg) once daily for 7 days and twice daily oral **amoxicillin**, 50 mg/kg per dose for 7 days.
- *Option2:* IM **gentamicin** 5–7.5 mg/kg (for low-birth-weight infants gentamicin 3–4 mg/kg) once daily for 2 days and twice daily oral **amoxicillin**, 50 mg/kg per dose for 7 days.

The current guidance including recommended dose and duration is summarized in Table 2.

Reference	Conditions	Antibiotics	Dosing regimen
Pocket book of hospital care for children, 2013	Prophylaxis in neonates with documented risk factors	IM or IV ampicillin and gentamicin for at least 2 days	**Gentamicin** (IM/IV)**:** First week of life : Low-birth-weight infants: 3 mg/kg once a day; Normal birth weight: 5 mg/kg per dose once a day Weeks 2–4 of life: 7.5 mg/kg once a day **Ampicillin** (IM/IV)**:** First week of life: 50 mg/kg every 12 h Weeks 2–4 of life: 50 mg/kg every 8 h **Benzylpenicillin (penicillin G)** (IM)**:** First week of life: 50 000 U/kg every 12 h; Weeks 2–4 and older: 50 000 U/kg every 6 h **Procaine Benzylpenicillin** (IM)**:** 50 000 U/kg once a day **Cloxacillin** (IV)**:** First week of life: 25–50 mg/kg every 12 h; Weeks 2–4 of life: 25–50 mg/kg every 8 h
	Case definition PSBI	IM or IV gentamicin and benzylpenicillin or ampicillin for at least 7–10 days	
	Greater risk of staphylococcus infection	IV cloxacillin and gentamicin for at least 7–10 days	
Managing possible serious bacterial infection in young infants when referral is not possible, 2015	Referral to hospital for young infants with PSBI is not possible	*Option1:* IM gentamicin once daily for 7 days and oral amoxicillin twice daily for 7 days.	**Gentamicin**: IM 5–7.5 mg/kg (for low-birth-weight infants gentamicin 3–4 mg/kg) once daily **Amoxicillin**: Oral 50 mg/kg twice daily oral
		Option2: IM gentamicin once daily for 2 days and oral amoxicillin twice daily for 7 days.	

Table 2: Current WHO recommendation for antibiotic therapy in infants 0 – 59 days with signs of PSBI or for prophylaxis

1.2.5. Trial design

The lack of harmonisation on study design, inclusion/exclusion criteria and endpoints is a major barrier to comparative analysis and translation into clinical practice. In a systematic review of antibiotic clinical trials in complicated clinical infection syndromes in children and neonates, Folgori et al. assessed whether standardised European Medicines Agency (EMA) and US Food and Drug Administration (FDA) guidance for adults was used in paediatrics, and whether paediatric clinical trials applied consistent definitions for eligibility and outcomes [18]. Evaluation of 82 studies – including 18 sepsis studies – showed that study design, inclusion and exclusion criteria, and endpoints varied very substantially across the included studies. Diagnosis of a severe infection was mainly based on individual study definitions of combinations of clinical signs and laboratory tests. Furthermore, the timing of assessment of clinical endpoints in sepsis paediatric trials was heterogeneous and did not comply with adult European Medicines Agency guidelines.

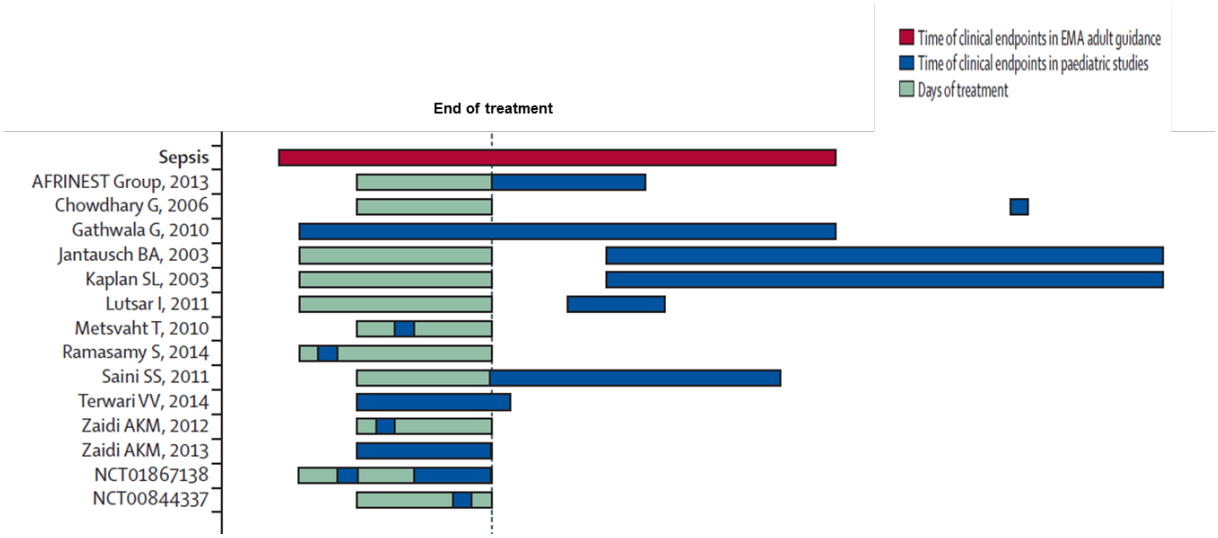

Figure 1. Timing of assessment of clinical endpoints in paediatric trials for sepsis compared with adult European Medicines Agency (EMA) guidelines

2. METHODS

An iterative systematic literature search was undertaken to identify published clinical evidence relevant to the review question. Searches were conducted in MEDLINE and Embase. Databases were searched using relevant medical subject headings, free-text terms and study-type filters, where appropriate. Search terms included variations of 'anti-bacterial agents', 'antibiotic', 'sepsis', 'bacteraemia'. Limits were set for the appropriate population i.e. 'all child (0 to 18 years) '. Studies published in languages other than English were not reviewed. The search was undertaken for manuscripts published from 2012 to cover the most recent WHO guidelines (*WHO pocket book hospital care for children, 2013*) and the final search was conducted on 19 October 2016. No papers added to the databases after the date of the final search were considered.

Potentially relevant studies were identified from the search results by reviewing titles and abstracts. Full papers were then obtained and reviewed against pre-specified inclusion (antimicrobial choice, comparisons between different antibiotics and/or antibiotic classes and/or comparisons to placebo, drug therapeutic use, drug efficacy, drug safety and harm, drug resistance) and exclusion criteria (only bacterial sepsis was considered, case reports were not considered) to identify studies that addressed the review question. Fungal and viral sepsis were not taken into account in this review, although invasive candidiasis is an important emerging cause of LONS.

The Cochrane Database for Systematic Reviews was also searched using the terms 'sepsis' AND 'antibiotic'. Ongoing clinical trials registered with ClinTrialsGov that investigates antibiotic regimen for sepsis in children were searched with terms 'sepsis' AND 'antibiotic' for 'Child (birth-17)'.

3. RESULTS

3.1. Synopsis of review results

An ideal choice of empiric antimicrobial agents for sepsis is to cover the most common pathogens without providing unwarranted selection pressure for antibiotic resistance [19]. It also requires taking into account the constraints of low-resource settings.

3.1.1. Evidence for currently recommended penicillin, gentamicin and ceftriaxone

Penicillin and gentamicin

A randomized controlled trial (RCT) conducted in 3 low-income communities from Pakistan evaluated the failure rates of 3 clinic-based antibiotic regimens in young infants with clinical signs of PSBI (≤ 59 days; n = 434) whose family refused hospital referral [20]. Infants were randomly allocated to receive: (1) procaine penicillin and gentamicin, reference arm, (2) ceftriaxone, or (3) oral trimethoprim-sulfamethoxazole and gentamicin for 7 days. Results showed that the efficacy of a procaine benzylpenicillin–gentamicin combination was much higher than that of trimethoprim/sulfamethoxazole - gentamicin (treatment failure was significantly higher with trimethoprim/sulfamethoxazole - gentamicin compared with penicillin-gentamicin [relative risk 2.03, 95% confidence interval: 1.09 - 3.79]). Differences were not significant in the ceftriaxone versus penicillin-gentamicin comparison [relative risk 1.69, 95% confidence interval 0.89–3.23).

The SATT trial from Banglasdesh, was a large RCT conducted in 5 centres (4 urban hospitals and one urban field) in Bangladesh that included young infants (≤ 59 days, n = 2490) when referral to a hospital was not possible. It compared the standard treatment of injectable procaine benzylpenicillin–gentamicin for 7 days (group A) to 2 alternative regimen: (i) injectable gentamicin and oral amoxicillin for 7 days (group B), (ii) intramuscular procaine benzylpenicillin and gentamicin for 2 days, then oral amoxicillin for 5 days (group C) [21]. The results suggested that the 2 alternative regimens were as efficacious as the standard regimen when hospital admission was refused. In group A, 78 (10%) infants had treatment failure, compared with 65 (8%) infants in group B and 64 (8%) infants in group C. Risk difference between groups C and A was -1.5% (95% CI -4.3 to 1.3) and risk difference between groups B and A was -1.7% (-4.5 to 1.1). Non-fatal severe adverse events were rare. Three infants in group A, two infants in group B, and three infants in group C had severe diarrhoea.

One of two large RCT from the AFRINEST Group compared oral amoxicillin to injectable procaine benzylpenicillin plus gentamicin, in 5 African centres in young infants (≤ 59 days, n = 2333) with fast breathing as a single sign of illness of PSBI when referral was not possible. In the procaine benzylpenicillin–gentamicin group, 234 infants (22%) failed treatment, compared with 221 (19%) infants in the oral amoxicillin group (risk difference –2·6%, 95% CI –6·0 to 0·8). The results were interpreted to indicate that young infants with fast breathing alone can be effectively treated with oral amoxicillin on an outpatient basis when referral to a hospital is not possible [22].

The second large RCT from the AFRINEST Group, performed in the same countries, compared the current reference treatment for PSBI consisting of injectable procaine benzylpenicillin–gentamicin for 7 days (group A) to a simplified regimen in young infants (≤ 59 days, n = 3564) when referral was not possible. Simplified regimens investigated were as follows: (i) injectable gentamicin and oral amoxicillin for 7 days (group B), (ii) injectable procaine benzylpenicillin–gentamicin for 2 days, then oral amoxicillin for 5 days (group C), (iii) or injectable gentamicin for 2 days and oral amoxicillin for 7 days (group D) [23]. Sixty seven (8%) infants failed treatment in group A compared with 51 (6%) infants in group B (risk difference –1.9%, 95% CI –4.4 to 0.1), 65 (8%) in group C (–0.6%, –3.1 to 2.0), and 46 (5%) in group D (–2.7%, –5.1 to 0.3). The results suggest that the three simplified regimens were as effective as injectable procaine benzylpenicillin–gentamicin for 7 days on an outpatient basis in young

infants with clinical signs of severe infection, without signs of critical illness, and whose caregivers did not or could not accept referral for hospital admission.

In these 4 studies, the equivalence margin was predefined to 5%. With a benzylpenicillin and gentamicin regimen a significant proportion of bacteraemia is not covered in LMIC based on in vitro data (43% in neonates and 37% in older infants 1-12 months) [9]. Overall, mortality was low in the Bangladesh SATT and AFRINEST studies: 2% within each group comparing the reference treatment of injectable procaine benzylpenicillin–gentamicin for 7 days to 2 alternative regimen [21], < 1% within each group comparing amoxicillin to benzylpenicillin–gentamicin [22] and ≤ 2% within each group comparing the reference treatment of injectable procaine benzylpenicillin–gentamicin for 7 days to the 3 simplified dosing regimens [23].

One retrospective study in hospitalized neonates and children (≤ 59 months, n = 183) from Bangladesh investigated injected ampicillin and gentamicin as a first line combination for the management of sepsis [24]. Most patients (n = 181) received ampicillin and gentamicin as a first line combination while 2 patients received ceftriaxone and gentamicin as a first line combination; 7 patients died who received ampicillin and gentamicin and none died among the 2 patients who received ceftriaxone and gentamicin. A p-value = 1 based on 2 patients is provided to compare those 2 groups. Moreover, the statistical methods used for analyses were insufficiently specified. In addition, no clear outcome was specified. Nonetheless, the authors concluded that the combination of ampicillin and gentamicin was effective as the first-line antibiotics for the management of sepsis in children even beyond the neonatal age was effective.

Another single-centre prospective study including Indian hospitalized neonates (≤ 59 months, n = 90) compared two empiric regimens: a cloxacillin and amikacin combination (n=40) versus a cefotaxime and gentamicin combination (n=50) for at least 10 days in cases of late-onset sepsis [25]. The report of the results is not clear and does not address the stated primary outcome. Instead of the comparison of the two regimens, the authors focused on a mortality comparison between low-birth weight babies with babies with a weight > 2.5 kg. A comment is provided on the observed increased mortality in the group receiving cefotaxime and gentamicin (10 deaths) compared to the group receiving cloxacillin and amikacin (3 deaths) but it did not reach statistical significance (no p-value provided). The authors concluded that there was no significant difference between the two antibiotic regimens with regard to outcome of LOS (mortality before discharge from hospital and complications including shock, disseminated intravascular coagulation, acidosis, renal failure and re-hospitalization within 2 weeks of discharge), however, results are not provided for the different conditions.

All other studies retrieved from the last 5 years comparing the impact of different antibiotic regimens and or routes of administration on outcome were performed in hospitalized patient in HIC, mainly in North America. Because of the considerable differences in pathogen spectrum, resistance patterns, but also levels and types of underlying diseases, it is unlikely that the results of these studies are directly generalizable to the LMIC setting.

A retrospective study (neonates at birth with body weight ≤ 1500g, n = 714) compared a combination of ampicillin and gentamicin (historical cohort) to piperacillin/tazobactam before and after practice change for suspected early-onset sepsis in neonates [26]. They found a significant reduction in the incidence of NEC with piperacillin/tazobactam treatment compared with a combination of ampicillin and gentamicin in both the unmatched and matched analyses. There were more late-onset infections during the ampicillin and gentamicin epoch than the piperacillin/tazobactam epoch, but this difference did not reach statistical significance after the Bonferroni correction (due to multiple testing for various variables not mentioned here).

A prospective observational study that included neonates and young infants (n = 265; ≤ 59 days) compared empiric antibiotic therapy with ampicillin and gentamicin with monotherapy third-generation cephalosporins and a third-generation cephalosporin and ampicillin combination in case of

serious bacterial infection confirmed by positive blood culture (meningitis, bacteraemia, urinary tract infection) [27]. When meningitis was not suspected, ampicillin/gentamicin and third-generation cephalosporin-based regimens provided effective empiric coverage for 96% and 97% of infants, respectively (P = 0.78).

Third generation cephalosporin monotherapy versus in combination with another antibiotic

In vitro susceptibility data suggest that third-generation cephalosporins are no more effective in treating sepsis than the currently recommended antibiotics, benzylpenicillin and gentamicin [9].
Broad-spectrum antibiotics are associated with an increased risk of invasive candidiasis and death, and prolonged duration of antibiotic therapy is associated with increased risks of necrotizing enterocolitis (NEC), death, and late-onset sepsis [28, 29]. Virulent late-onset pathogens, such as Enterobacteriaceae other than *E. coli*, are often not susceptible to cefotaxime, and cefotaxime is not effective against other common pathogens including *Pseudomonas* spp, *Enterococcus* spp, *Acinetobacter* spp, and *Listeria monocytogenes* [28].
Concerns have been raised about ceftriaxone in neonates due to potential toxicity, although ceftriaxone is used (and licensed for use) in this population in some settings [30]. In theory, high protein binding may displace bilirubin progressing to hyperbilirubinemia. Concurrent administration with calcium-containing solutions may produce insoluble precipitates (ceftriaxone-calcium salts) leading to cardiorespiratory complications. Thus concomitant administration of intravenous ceftriaxone and calcium-containing solutions is not recommended, further studies are required to provide more solid evidence [29, 31].
Combination therapy has been used historically to both increase coverage, but also for its potential additive clinical effect. While studies tend to show that there is no difference in clinical outcomes or mortality between mono- and combined therapy there are documented increased toxicities with combination therapy.

We found four studies in the last 5 years, comparing beta-lactam monotherapy versus beta-lactam in combination with aminoglycoside, in paediatric patients [27, 32-34]. All studies were performed in hospitalized patients in the USA.

In the retrospective studies of Berkowitz et al. [32] (n = 203) and Tama [34] (n = 879), there was no difference in 30-days mortality between the beta-lactam monotherapy and the combination therapy of aminoglycoside and beta-lactams for Gram negative bacteria in children. Combination therapy consisting of a beta-lactam agent and an aminoglycoside agent was not superior to monotherapy with a beta-lactam agent alone for managing *Enterobacteriaceae* bacteraemia in children. But, patients receiving combination therapy had approximately twice the odds of nephrotoxicity compared with those receiving monotherapy (odds ratio, 2.15; 95%CI, 2.09-2.21) [34].

In a study that included neonates and young infants (n = 265; ≤ 59 days), third-generation cephalosporins combined with ampicillin would have been effective for 98.5% of infants and unnecessarily broad for 83.8% [27]. Third-generation cephalosporin monotherapy was less effective than either combination (P < 0.001) and this difference was because of the 20 *Enterococcus faecalis* isolates (7.5% of identified pathogens), which are intrinsically resistant to cephalosporins.

In a retrospective study in which children receiving empirical combination therapy were matched 1:1 to children receiving empirical monotherapy [33], the ten-day mortality was similar between children (n = 452; > 2 months – 14 years) receiving empirical combination therapy versus empirical monotherapy (odds ratio, 0.84; 95% CI, 0.28 to 1.71). A survival benefit was observed when empirical combination therapy was prescribed for children growing multidrug-resistant Gram-negative organisms (n=46) from the bloodstream (odds ratio, 0.70; 95% CI, 0.51 to 0.84).

A systematic review in 2013 assessed beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy in patients with sepsis. It included 69 randomized and quasi-randomized trials but only four included children. In trials comparing the same beta lactam, there was no difference between study groups with regard to all-cause mortality (RR 0.97, 95% CI 0.73 to 1.30) and clinical failure (RR 1.11, 95% CI 0.95 to 1.29). In studies comparing different beta lactams a trend for benefit with monotherapy for all-cause mortality (RR 0.85, 95% CI 0.71 to 1.01) and a significant advantage for clinical failure (RR 0.75, 95% CI 0.67 to 0.84) was observed, but included studies were generally classified as being of low quality. No significant disparities emerged from analyses assessing participants with Gram-negative infection. Nephrotoxicity was significantly less frequent with monotherapy (RR 0.30, 95% CI 0.23 to 0.39) [35].

3.1.2. Data on antimicrobial resistance

Only very limited reliable data on antimicrobial susceptibility are available from Asia, Latin America and Africa. From existing summaries of the data, it is evident that considerable antibiotic resistance is observed to many commonly used antibiotics with variations both between and within regions in LMIC [10, 36]

According to the systematic review and meta-analysis of Downie et al., among community-acquired neonatal bacteraemia, resistance or reduced susceptibility to the combination of penicillin and gentamicin and to third-generation cephalosporins occurs in more than 40% of cases. Among community acquired bacteraemia in infants 1–12 months, resistance or reduced susceptibility to the combination of penicillin and gentamicin and to third-generation cephalosporins occurs in more than 35% of cases. Among neonates, the gaps in antibiotic coverage with either benzylpenicillin/ampicillin and gentamicin or third-generation cephalosporins regimens were mostly in infections due to enteric Gram-negative bacilli, particularly *Klebsiella* spp [9].

Similar findings were reported in 2015 in a systematic review of studies that estimated AMR rates in Gram-negative bloodstream infections among children from LMIC settings [11]. Gram-negative bacteria accounted for 67% of all episodes among the studies that were included in this review. The predominance of Klebsiella spp. with high resistance prevalence to gentamicin in Asia (69%, IQR 19-95%) and Africa (54%, IQR 0-68%) and the overall level of resistance in Gram negative bacteria to third generation cephalosporins (Asia: 84%, IQR 45-95%; Africa: 50%: IQR 0-87%) were very concerning findings.

All reviews published so far note the very low number of studies with adequate data. In particular, many of the included studies had a high risk of bias with substantial uncertainty about how representative presented data are for the populations served in each setting. There are concerns that the published data is predominantly from larger tertiary neonatal units, many of whom may have higher rates of resistance due to a nosocomial outbreak. In addition, virtually no clinical outcome data are reported (a finding confirmed by this review), particularly relating the underlying disease, pathogen phenotype, empiric antibiotic treatment, and clinical outcome. This imposes major limitations on the selection of empiric regimens on the basis of their clinical impact.

3.1.3. Evidence for alternative regimen

One RCT conducted in India compared amikacin monotherapy versus piperacillin/tazobactam monotherapy as empirical treatment for suspected early-onset neonatal sepsis (n = 187) [37]. In this centre, amikacin was the standard regimen since reported resistance rates previously ranged between 86 – 89% for ampicillin, gentamicin and cefotaxime in their unit. Treatment failure with use of amikacin or piperacillin-tazobactam was very low (n = 3 and n= 2, respectively; p = 0.44). No increased risk or significant difference in the incidence of secondary infection within 7 days of stopping the study antibiotic, no difference in the incidence of fungal sepsis and no difference in the all-cause mortality

at day 7 and day 28 between the two study groups (p > 0.4) was observed. Only five blood cultures were positive.

In one retrospective single centre study in neonates (5 – 37 days, n = 10), with persistent CoNS bacteraemia (LOS), addition of rifampicin to vancomycin for infection resolution was investigated [38]. Bacteraemia persisted for a median of 9 (range 6–19) days until rifampicin initiation. Bacteraemia was resolved in all cases on vancomycin–rifampicin with no serious side effects. In all patients, the blood cultures became negative on vancomycin–rifampicin, taken between 24 to 72 h after the initiation of rifampicin. No serious side effects were observed.

3.1.4. Alternative and new drugs not included in clinical trials

Alternative therapeutic options (such as fluoroquinolones and carbapenems) are limited, expensive and may be inappropriate for the community setting [3, 9]. Additionally, most of the possible alternative antimicrobial options have not been studied in neonates and children, and even in adults data are rather weak to allow any recommendation at present. Below, we list the different antimicrobials currently available on the market for potential discussion as alternative therapeutics for further research [19, 39-44].

Fluoroquinolones could be an option for sepsis or severe infection due to MDR bacteria as second line. Paediatric safety data are encouraging, although debate is on-going regarding potential toxicity affecting developing joint cartilage. Of the β-lactams, the **carbapenems** (**meropenem, imipenem/cilastatin**) possess the broadest range of in-vitro activity against Gram-positive and Gram-negative bacteria, including extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae. They are considered antibiotics of last resort. **Piperacillin/tazobactan** is a broad-spectrum beta-lactam/beta-lactamase inhibitor combination, active against most Gram-positive and Gram-negative aerobic and anaerobic bacteria, including many producing beta-lactamases. As it has been suggested that extensive use might play a role in the emergence of multi-resistant Enterobacteriaceae, widespread use as first-line antibiotic therapy may not be desirable.
Rifampicin is not typically use for sepsis and is at risk for a number of clinically significant drug–drug interactions (strong inducer of CYP3A4, CYP 2C9, CYP 2C8, CYP 2C19)
Among the most recent antibiotics still under patent, **ceftaroline fosamil** is a new broad-spectrum parenteral cephalosporin antibiotic (fifth generation) with activity against many bacteria, including *Streptococcus pneumoniae* (both penicillin-nonsusceptible and multidrug-resistant strains), and *Staphylococcus aureus,* including MRSA. Neonatal and paediatric pharmacokinetic and safety data are not available yet. **Tigecycline** is a new antimicrobial from the glycycline class that is active against many Gram-positive bacteria including MRSA, VRE, but also difficult-to-treat Gram-negative bacteria. It is a good candidate for the treatment of infections caused by highly resistant microorganisms. No studies have reported the use of tigecycline in children below 8 years of age. A higher overall mortality rate in tigecycline treated patients versus comparator drugs that achieve higher concentrations in the lung and bloodstream was observed. It is suggested to restrict its use to situations where no alternatives are available.
The rise of multidrug resistant Gram-negative bacteria (especially carbapenem-resistant) has led to the reintroduction of old antibiotics, the use of which was limited up until the past decade, such as **Colistin** and **polymixin B**. The use of these drugs is limited by significant toxicity (nephrotoxicity, neurotoxicity, elevated Na, K, Mg) and the rapid evolution of antimicrobial resistance.
Fosfomycin is also an old agent active against multidrug-resistant bacteria. It has excellent in vitro bactericidal activity against MRSA, MRSE, penicillin-resistant *S. pneumoniae*, VRE, ESBL-producing Gram-negative pathogens and the majority of *P. aeruginosa* strains.

3.2. Synopsis of international guidelines

Five international guidelines were reviewed: the Surviving Sepsis Campaign endorsed by the Infectious Diseases Society of America (IDSA) [45], the National Institute for Health and Care Excellence (NICE) [46, 47], the American Academy of Pediatrics (AAP) [48-50], the British Medical Journal (BMJ) clinical evidence [51], and the British National Formulary for Children (BNFc) [52]. A summary of their recommendations is listed in Table 3.

Most guidelines suggest relying on data about antibiotic resistance patterns in locally prevalent pathogens at the institutional level when selecting empirical treatment regimens. They recommend individualizing empirical antibiotic recommendations according to local antibiotic protocols and local pathogen susceptibility. There is little if any detail on how such data are to be used for selecting treatment regimens.

For EONS, most guidelines are in line with WHO recommendations: NICE, AAP, BMJ and BNFc recommend the use of benzylpenicillin or ampicillin combined with gentamicin as empiric treatment and list third generation cephalosporins as an alternative. Of note, guidelines often state that the aim is to target the most common pathogens encountered in EONS, that GBS and *E. coli* in HIC. More variability is seen in the suggested empirical treatment for LONS.

Guideline	Last Update	Recommendations
Surviving Sepsis Campaign (endorsed by IDSA)	2012	• Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy. • **Initial empiric anti-infective therapy** of **one or more drugs** that have **activity against all likely pathogens** (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B). • **Combination empirical therapy** for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an **extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone** is for *P. aeruginosa* bacteraemia (grade 2B). A combination of **beta-lactam and macrolide** for patients with septic shock from bacteraemic *Streptococcus pneumoniae* infections (grade 2B). • Empiric combination therapy should not be administered for more than 3–5 days (grade 2B). • Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus;* some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C). <u>Special pediatric consideration:</u> • The empiric drug choice should be changed as epidemic and endemic ecologies dictate (grade 1D). • **Clindamycin** and anti-toxin therapies for toxic shock syndromes with refractory hypotension (grade 2D). • Clostridium difficile colitis should be treated with enteral antibiotics if tolerated. **Oral vancomycin** is preferred for severe disease (grade 1A)

Guideline	Last Update	Recommendations
NICE	2016	• Neonates presenting in hospital with suspected sepsis in their first 72 hours: iv **benzylpenicillin** 25 mg/kg twice daily (increase to 3 times daily if clinically concerned) and **gentamicin** (starting dose 5 mg/kg every 36 hours). Minimum 7 day course of iv antibiotics for strong suspicion of sepsis or a positive blood culture • Neonates, community acquired sepsis: o > 40 weeks corrected gestational: **ceftriaxone** 50 mg/kg unless already receiving an intravenous calcium infusion at the time. o ≤ 40 weeks corrected gestational age or receiving an intravenous calcium infusion: **cefotaxime** 50 mg/kg every 6 to 12 hours, depending on the age of the neonate. • Up to 17 years, community acquired sepsis: **ceftriaxone** 80 mg/kg once a day with a maximum dose of 4 g daily at any age. • Up to 17 years, hospital acquired sepsis or patients who are known to have previously been infected with or colonized with ceftriaxone-resistant bacteria: **consult local guidelines** for choice of antibiotic. • For children younger than 3 months, give an additional antibiotic active against listeria (for example, **ampicillin or amoxicillin**).
AAP	2012, 2015	• Early-onset sepsis: o Broad-spectrum antimicrobial agents (**ampicillin** 150 mg/kg per dose intravenously (IV) every 12 hours and an aminoglycoside (usually **gentamicin** 4 mg/kg per dose IV every 24 hours)). Once a pathogen is identified, antimicrobial therapy should be narrowed (unless synergism is needed). o Third-generation cephalosporins (eg, **cefotaxime**) represent a reasonable alternative to an aminoglycoside. For 10 days Notes: - Antimicrobial therapy should be discontinued at 48 hours in clinical situations in which the probability of sepsis is low (controversial). - Risk of resistance with cefotaxime. Due to excellent CSF penetration, suggest to restrict to infants with meningitis attributable to Gram-negative organisms - To cover GBS and Escherichia Coli • Late-onset sepsis admitted from the community: **ampicillin** 75 mg/kg per dose iv every 6 hours and **gentamicin** 4 mg/kg per dose iv every 24 hours • Late-onset sepsis hospitalized since birth: **vancomycin**: 10 to 20 mg/kg every 12 to 48 hours according serum creatinine and **gentamicin** 4 mg/kg per dose iv every 24 hours
BMJ Clinical Evidence	2016	Treatment should be initiated with broad-spectrum antibiotic cover appropriate for the prevalent organisms for each age group and geographical area. This should be changed to an appropriate narrow-spectrum antibiotic regimen once a causative pathogen is identified • Early-onset sepsis: *cited as example*: **benzylpenicillin** plus **gentamicin** (from NICE guidelines) OR **ampicillin** plus **gentamicin** or **cefotaxime** Note: to cover group B streptococci (GBS) and gram-negative bacilli • Late-onset sepsis: (selective therapy for empirical antibiotics regimen): o *cited as example:* **ampicillin** plus **gentamicin** OR **cefotaxime**, OR **vancomycin** plus **gentamicin** OR **cefotaxime**. o **Ceftazidime** or **piperacillin/tazobactam** may be added to the empirical regimen if Pseudomonas is suspected.

Guideline	Last Update	Recommendations
		○ **Metronidazole** or **clindamycin** may be added to the empirical regimen to cover for anaerobes/necrotising enterocolitis. • Infants and young infants, community-acquired infection: **Third-generation cephalosporin** (e.g., cefotaxime, ceftriaxone) • Infants and young infants, hospital-acquired infection: **Extended-spectrum penicillin** (e.g., piperacillin/tazobactam) OR **carbapenem** (e.g., meropenem). Additional broadening of this cover (e.g., with gentamicin, ciprofloxacin, or vancomycin) may be considered depending on case-specific factors. **Clindamycin** should be used for toxin-induced toxic shock syndromes with refractory hypotension.
BNFc	2015	• Septicemia in neonates ≤ 72 hours old: ○ **Benzylpenicillin sodium**, 50 mg/kg in neonate under 7 days every 12 hours, in neonate 7–28 days every 8 hours AND **Gentamicin** 5 mg/kg in Neonate up to 6 days every 36 hours, in neonate 7-28 days: every 24 hours ○ If Gram-negative septicemia suspected: ADD **cefotaxime** im or iv 25 mg/kg in neonate under 7 days every 12 hours, in Neonate 7–21 days every 8 hours, neonate 21–28 days every 6–8 hours; dose doubled in severe infection and meningitis AND stop benzylpenicillin sodium if Gram-negative infection confirmed • Septicemia in neonates > 72 hours old: ○ **Flucloxacillin**, oral 25 mg/kg in Neonate under 6 days twice daily, neonate 7–20 days 3 times daily, neonate 21–28 days 4 times daily; iv 25 mg/kg in neonate under 6 days every 12 hours, in neonate 7–20 days every 8 hours, in neonate 21–28 days every 6 hours; may be doubled in severe infection AND **Gentamicin** (see dose above) ○ OR **Amoxicillin** iv 50 mg/kg in neonate under 7 days every 12 hours, in neonate 7–28 days: every 8 hours, OR **Ampicillin** iv 50 mg/kg in neonate up to 6 days: every 12 hours, in neonate 7 - 20 days: every 8 hours, in neonate 21 - 28 days: every 6 hours AND **Cefotaxime** (see dose above) For 7 days • Child 1 month – 18 years , community-acquired sepsis: ○ Aminoglycoside e.g. **gentamicin** initially 7 mg/kg, then adjusted according to serum-gentamicin concentration *or* multiple daily dose regimen with child 1 month–12 years: 2.5 mg/kg every 8 hours and child 12–18 years: 2 mg/kg every 8 hours AND **Amoxicillin** 50 mg/kg every 4–6 hours (max. 2 g every 4 hours) OR **Ampicillin** 50 mg/kg every 4-6 hours (max. per dose 2g every 4 hours) ○ OR **Cefotaxime alone** 50 mg/kg every 8–12 hours; increase to every 6 hours in very severe infections and meningitis (max. 12 g daily) OR Ceftriaxone alone im or iv 1g daily, increased to 2 – 4 g daily, increased dose to be used in severe infections

Guideline	Last Update	Recommendations
		o If pseudomonas or resistant-microorganism suspected: broad-spectrum antipseudomonal beta-lactam (**Piperacillin-tazobactam:** 90 mg/kg (max. 4.5 g) every 6 hours) o If anaerobic infection suspected, add **Metronidazole**, oral in child 1–2 months 7.5 mg/kg every 12 hours, in child 2 months–12 years 7.5 mg/kg (max. 400 mg) every 8 hours in child 12–18 years 400 mg every 8 hours; rectal in child 1 month–1 year 125 mg 3 times daily for 3 days, then twice daily thereafter in child 1–5 years 250 mg 3 times daily for 3 days, then twice daily thereafter, in child 5–10 years 500 mg 3 times daily, for 3 days, then twice daily thereafter, in child 10–18 years 1 g 3 times daily for 3 days, then twice daily thereafter; iv in child 1–2 months 15 mg/kg as a single loading dose followed after 8 hours by 7.5 mg/kg every 8 hours, in child 2 months–18 years 7.5 mg/kg (max. 500 mg) every 8 hours o If Gram positive infection suspected, add **Flucloxacillin** oral in child 1 month–1 years 62.5–125 mg 4 times daily, in child 2–9 years 125–250 mg 4 times daily, in child 10–17 years 250–500 mg 4 times daily; im in child 1 month–18 years 12.5–25 mg/kg every 6 hours (max. 500 mg every 6 hours); iv in child 1 month–18 years 12.5–25 mg/kg every 6 hours (max. 1 g every 6 hours); may be doubled in severe infection OR **Vancomycin** 15 mg every 8 hours (max. 2g per day) OR **Teicoplanin** Initially 10 mg/kg every 12 hours (max. per dose 400 mg) for 3 doses, then (by iv injection or by iv infusion or by im injection) 6 mg/kg once daily (max- per dose 400 mg), (After initial 3 doses subsequent doses can be given by im route, if necessary, although, iv route is preferable). For severe infection: Initially 10 mg/kg every 12 hours for 3 doses, 10 mg/kg once daily. For 5 days • Child 1 month – 18 years , hospital-acquired sepsis: o Broad-spectrum antipseudomonal beta-lactam: **Piperacillin-tazobactam** 90 mg/kg (max. 4.5 g) every 6 hours OR **Ticarcillin/clavulanic acid**, child under 40kg: 80mg/kg every 8 hours (increased if necessary to 80 mg/kg every 6 hours, increased frequency used for more severe infections) Child ≥ 40kg: 3.2 g every 6-8 hours (increased if necessary to 3.2 g mg/kg every 4 hours, increased frequency used for more severe infections) OR **Imipenem/cilastatin**, in child 1-2 months, iv 20 mg/kg every 6 hours, in child 3 months – 17 years, iv 15 mg/kg every 6 hours (max. per dose 500 mg) (life-threatening infection: 25 mg/kg every 6 hours, max. per dose 1g) OR **meropenem**, in child 1 months – 11 years (body weight ≥ 50 kg): 2g every 8 hours, in child 12-17 years 2g every 8 hours o If pseudomonas or resistant-microorganism suspected: ADD **aminoglycoside** (see dose above) o If MRSA suspected: ADD **vancomycin** OR **teicoplanin** (see dose above) o If anaerobic infection suspected, ADD **metronidazole** (see dose above) to a broad spectrum **cephalosporin** (see dose above for cefotaxime and ceftriaxone) For 5 days

Table 3. Current international guidelines for the empirical treatment of suspected sepsis or blood infection

4. SAFETY DATA

Antibiotic	Adverse events Contraindications	Relevant Interactions
Aminoglycoside: **Gentamicin**	• Hypersensitivity reactions • Nephrotoxicity: usually transient. Associated with high trough levels. • Ototoxicity: may be irreversible. Proportional to the amount of exposure. A proportion of aminoglycoside-related ototoxicitiy is explained by the human DNA mitochondrial 155A>G mutation. The attributable risk associated with this mutation have not been yet clarified, and importantly other mitochondrial DNA mutations can contribute to deafness following aminoglycoside therapy • Increased risk of toxicity in preterm, low birth weight and jaundiced • Aminoglycosides can enhance the effects of muscle relaxants and anticholinesterases, and can potentially cause a reversible, dose-related myasthenia-like syndrome Other potential adverse reactions include drug-induced hypersensitivity, hypomagnesaemia and encephalopathy (very rare) • Rare contraindication: myasthenia gravis (aminoglycosides can impair neuromuscular transmission to clinically significant degree)	Concomitant use of: - loop diuretics (e.g. furosemide) - nephrotoxic agents (e.g. indomethacin, non-steroidal anti-inflammatory drugs, vancomycin, colistin, cyclosporin, other aminoglycosides) - ototoxic drugs (e.g. cisplatin, furosemide) should be avoided where clinically feasible.
Natural Penicillin: **Benzylpenicillin sodium** Aminopenicillin: **Ampicillin** **Amoxicillin** Antistaphylococcal penicillin: **Cloxacillin**	Serious toxicity is rare in association with penicillin therapy. • Diarrhoea is the most common. Incidence is increased following use of amoxicillin/clavulanate (broad spectrum therapy) compared to the use of amoxicillin There is some evidence that different ratios of the amoxicillin to clavulanic acid components may affect the proportion of children who experience diarrhoea. The incidence of diarrhea following amoxicillin use was significantly lower for b.i.d. than with t.i.d. regimen (6.7 – 9.6 versus 10.3 – 26.7%, respectively) in one study. • Drug-induced rash, hypersensitivity, anaphylaxis. Penicillins allergy have been estimated to affect 1 – 10 % of people given penicillins. True incidence of penicillin allergy in	Concomitant use with bacteriostatic antibacterial agents (ie, tetracyclines, sulfonamides, erythromycins, chloramphenicol) should be avoided Caution should also be exerted with the use of certain other β-lactam antibiotics, namely cephalosporins (especially first-generation and second generation, eg, cefalexin, cefaclor) and carbapenems (eg, meropenem), as cross-reactivity in the allergies between these classes can occur (but its importance has frequently been overstated)

Antibiotic	Adverse events Contraindications	Relevant Interactions
	patients who report that they are allergic is actually less than 10%. • Very rarely, seizures. Important consideration if higher than usual doses or dose frequencies, or following rapid administration of high intravenous doses (therefore should be infused over at least 30 min) • Electrolyte imbalances (e.g. sodium salts) • Hepatotoxicity, mild/moderate GI	
3rd generation cephalosporin: **Cefotaxime**	• Mainly hypersensitivity and gastrointestinal effects (mostly diarrhoea) • Rarely causes nephrotoxicity or seizures in neonates	Concurrent use of cephalosporin with: - nephrotoxic drugs (aminoglycosides) increased risk of nephrotoxicity - warfarin may result in an increased risk of bleeding.
3rd generation cephalosporin: **Ceftriaxone**	• Mainly hypersensitivity and gastrointestinal effects (mostly diarrhoea) • Hyperbilirubinemia (ability of ceftriaxone to displace bilirubin from serum albumin binding sites) • Cholestasis and pseudolithiasis due to biliary sludging (with high concentration of ceftriaxone in the system) • Concomitant administration of intravenous ceftriaxone and calcium-containing solutions is not recommended since concurrent administration with calcium-containing solutions may produce insoluble precipitates (ceftriaxone-calcium salts) leading to cardiorespiratory complications	Concurrent use of cephalosporin with: - nephrotoxic drugs (aminoglycosides) increased risk of nephrotoxicity - warfarin may result in an increased risk of bleeding.

Table 4. Safety data summary for empirical antibiotic treatment used in PSBI [31, 53-60]

5. DOSING CONSIDERATIONS

Comparison of international guidelines reveals differing dosing regimens for gentamicin, from 4 mg/kg to 5 mg/kg every 24 hours to 36 hours. The current WHO guidelines recommend a once daily dosing regimen, from 3 mg/kg to 7.5 mg/kg per day according to age and birth-weight.
Although gentamicin is an old agent, debate around the best dosing regimen in neonates remains highly active. Aminoglycosides, like gentamicin, have a narrow therapeutic index due to their pharmacokinetic / pharmacodynamics characteristics: efficacy of aminoglycosides has been associated with high peak concentrations relative to minimum inhibitory concentration (MIC) of the infecting microorganism with a ratio peak concentration / MIC > 8 – 10, whereas low trough concentrations appear to be associated with reduced risk of nephro- and oto- toxicity (at least < 2 mg/L, but < 1 mg/L is also often advocated) [61].

Although the incidence of detected ototoxicity following aminoglycoside exposure remains low (1-3%) and less than the rates reported in adults, gentamicin appears to be the least cochleotoxic. The specific association between hearing loss and aminoglycoside exposure is complicated mainly due to

the presence of many other confounding factors in this population (low gestational age, birth weight, intrauterine and postnatal infection neonatal asphyxia, prolonged oxygen therapy and respiratory support, hyperbilirubinemia requiring exchange transfusion, hyponatremia, surgery, congenital malformation, family history of hearing impairment, and exposure to ototoxic drugs such as diuretics or antibiotics). An association with high peak concentration has been suggested in the past but recent studies are not so categorical [62, 63].
Nephrotoxicity rates have been difficult to define in the neonatal population and studies are inconsistent in their findings. It has historically been associated with high trough levels [63].
A recent systematic review considered the risk of gentamicin toxicity in neonates treated for PBSI in LMIC with the WHO recommended first-line antibiotics (gentamicin with penicillin) [57]

- Six trials reported formal assessments of ototoxicity outcomes in neonates treated with gentamicin, and the pooled estimate for hearing loss was 3% (95% CI 0–7%).
- Nephrotoxicity was assessed in 10 studies, but could not be evaluated due to variation in case definitions used.
- Estimates of the number of neonates potentially affected by gentamicin toxicity were not undertaken due to insufficient data.

The authors concluded that data were insufficient to assess the potential for harm in terms of toxicity associated with gentamicin treatment

A better understanding of the aminoglycoside pharmacokinetics in neonates in the past decades has led to a switch from multiple daily dosing to once daily dosing during the last couple of years [64-68]. The volume of distribution of gentamicin is larger in preterm neonates as a consequence of a higher percentage of body water compared to term neonates. Kidney function in preterm neonates is reduced due to incomplete nephrogenesis. As a consequence, recent trends are in favor of higher doses (> 4 mg/kg, up to 5 mg/kg) with extended dose intervals in preterm neonates(> 24 hours, up to 48 hours for the most preterm infants or more according to some authors), to achieve higher peak concentrations for improved efficacy while maintaining low trough concentrations for safety. Term infants should receive about 4 to 4.5 mg/kg every 24 hours according to the currently available knowledge [69-71].

However, rates of multidrug resistance Gram negative (MRD GN) infection are increasing worldwide and particularly in LMICs. It means that with many Enterobacteraciae, gentamicin MICs being 4 or higher nowdays (as compared to 0.5 or 1 mg/L in the past, when dosing recommendations were developed), determining appropriate dosing recommendation has become very challenging. It might be possible that even higher doses (> 8mg/kg?) are required to reach effective exposure (10x MIC) with longer extended dosing interval periods (to prevent toxicity). Such questioning emphases the urgent need of further prospective studies in populations with MRD GN specifically collecting PBSI isolates (few isolates to date) with MICs to gentamicin, actual dosing and peak concentration/trough estimation, and both clinical outcomes (infection resolution, toxicity).

Trough concentration monitoring is recommended for treatment > 48 – 72 hours to diminish the risk of toxicity associated with aminoglycosides, but may not be feasible in all healthcare facilities or in the outpatient setting. Using a 24 hours dosing interval in all neonates as suggested by WHO recommendations may expose a large proportion of patients at risk of toxicity, especially in case of prolonged treatment (> 48 hours) due to possible drug accumulation. However, providing various dosing intervals that stratify neonates may complicate feasibility and acceptability.

Pharmacokinetics data are rather scarce in neonates and make us unable to discuss the current dosing regimens of beta-lactams presented here. Antibacterial activity of β-lactams is best characterized by time-dependent killing. The pharmacokinetic-pharmacodynamic parameter that correlates with the clinical and bacteriological efficacy of beta-lactam antibiotics is the percentage of time that the serum free drug concentration exceeds the MIC for the pathogen (time above the MIC). Overall, beta-lactams

present a favorable safety profile and most dosing recommendation suggested by WHO are in line with the current knowledge [71].

Of note, a pharmacokinetic study of cefotaxime in neonates has been published recently, the largest one to our knowledge. According to simulations performed for MIC = 2 mg/L (when postnatal age (PNA) < 7 days, for EOS) and MIC = 4 mg/L (when PNA < 7 days, for LOS), authors suggest the following dosing regimen: 50 mg/kg every 12 hours for newborns with a PNA of <7 days, 50 mg/kg every 8 hours for newborns with a PNA of ≥7 days and a gestational age (GA) of <32 weeks, and 50 mg/kg every 6 hours for newborns with a PNA of ≥7 days and GA of ≥32 weeks. These results are quite similar to the dosing regimens suggested by the NICE guideline and WHO [72].

Further characterization of relationships between pharmacokinetics and pharmacodynamics (taking into account pathogens and resistance in LMIC) in neonates are essential to optimize drug dosing strategies in this vulnerable group. A number of pharmacokinetic studies is on-going and will hopefully complement the current state of knowledge within the next years.

6. COST PER TREATMENT COURSE

Costs per treatment course of antibiotic therapy were calculated using the *International Drug Price Indicator Guide* (https://www.msh.org/resources/international-drug-price-indicator-guide) from the Management Sciences for Health (MSH). Costs were calculated using the median price buyer prices for 2014 (latest available) for a representative 5 kg neonate.

Drug and Dosage	Strength and Dosage Form	Median Price	Cost per treatment course for 5kg neonate
Amoxicillin PO 50mg/kg q12h	125 mg/5 ml suspension	0.0090 /ml	US$ 1.260 (7 days)
	250 mg/5 ml suspension	0.0063 /ml	US$ 0.441 (7 days)
Gentamicin INJ 7.5 mg/kg q24h	10 mg/ml ampoule	0.0942 /ml	US$ 0.471 (2 days) US$ 1.648 (7 days)
	40 mg/ml ampoule	0.0802 /ml	US$ 0.100 (2 days) US$ 0.351 (7 days)
Ampicillin INJ 50 mg/kg q12h	1 g vial	0.2720 /vial	US$ 0.272 (2 days) US$ 0.952 (7 days)
	500 mg vial	0.3313 /vial	US$ 0.663 (2 days) US$ 2.319 (7 days)
	250 mg vial	0.5294 /vial	US$ 2.118 (2 days) US$ 7.412 (7 days)
Ampicillin INJ 50 mg/kg q6h	1 g vial	0.2720 /vial	US$ 0.544 (2 days) US$ 1.904 (7 days)
	500 mg vial	0.3313 /vial	US$ 1.325 (2 days) US$ 4.638 (7 days)
	250 mg vial	0.5294 /vial	US$ 4.235 (2 days) US$ 14.823 (7 days)
Benzyl penicillin INJ 50 000 IU/kg q12h	1m IU powder	0.3238 /vial	US$ 0.324 (2 days) US$ 1.130 (7 days)
	3m IU powder	0.2164 /vial	US$ 0.043 (2 days) US$ 0.151 (7 days)
Benzyl penicillin INJ 50 000 IU/kg q6h	1m IU powder	0.3238 /vial	US$ 0.648 (2 days) US$ 2.266 (7 days)
	3m IU powder	0.2164 /vial	US$ 0.086 (2 days) US$ 0.303 (7 days)
Cloxacillin INJ 25 mg/kg q12h	500 mg vial	0.8300 /vial	US$ 3.102 (7 days)
	250 mg vial	0.8864 /vial	US$ 5.810 (7 days)
Cloxacillin INJ 25 mg/kg q6h	500 mg vial	0.8300 /vial	US$ 6.205 (7 days)
	250 mg vial	0.8864 /vial	US$ 11.620 (7 days)
Cloxacillin INJ 50 mg/kg q12h	500 mg vial	0.8300 /vial	US$ 6.205 (7 days)
	250 mg vial	0.8864 /vial	US$ 11.620 (7 days)
Cloxacillin INJ 50 mg/kg q6h	500 mg vial	0.8300 /vial	US$ 12.410 (7 days)
	250 mg vial	0.8864 /vial	US$ 23.240 (7 days)
Cefotaxime INJ 50 mg q6h	1 g vial	0.8323 /vial	US$ 2.913 (7 days)
	500 mg vial	0.6004 /vial	US$ 4.203 (7 days)
Cefotaxime INJ 50 mg q12h	1 g vial	0.8323 /vial	US$ 5.826 (7 days)
	500 mg vial	0.6004 /vial	US$ 8.406 (7 days)
Ceftriaxone INJ 80 mg/kg q24h	1 g vial	0.4192 /vial	US$ 1.174 (7 days)
	500 mg vial	0.4610 /vial	US$ 2.582 (7 days)
	250 mg vial	0.5726 /vial	US$ 6.413 (7 days)
Ceftriaxone INJ 50 mg/kg q12h	1 g vial	0.4192 /vial	US$ 1.467 (7 days)
	500 mg vial	0.4610 /vial	US$ 3.227 (7 days)
	250 mg vial	0.5726 /vial	US$ 8.016 (7 days)

7. OTHER INTERVENTIONS

Various interventions may affect the incidence of observed sepsis or PSBI and the type of responsible micro-organisms [73, 74], including:

- Intrapartum antibiotics to reduce the risk of vertical transmission, e.g. of GBS, from colonized mothers during or just before birth: Identification of women at risk and administration of intrapartum antibiotics are very difficult in many LMIC settings, may not always be affordable, and impossible for home deliveries. Clean delivery condition and maternal education on hygienic delivery
- Decontamination: Chlorhexidine wipes of the birth canal during labor and of the newborn at birth were evaluated in a large clinical trial South Africa with no evidence of efficacy in terms of the incidence of culture-confirmed or clinical neonatal sepsis.
- Development of maternal vaccines against prevalent pathogens: Immunization of pregnant women with a GBS vaccine represents an alternate pathway to protecting newborns from GBS disease, through the transplacental antibody transfer to the foetus in utero. This approach to prevent GBS disease in young infants is currently under development, and is approaching late stage clinical evaluation.
- Maternal micronutrient supplementation might contribute to preventing early onset neonatal bacterial sepsis.
- A role for breastfeeding and kangaroo care has been suggested.
- Postpartum care, during the first hours after birth and throughout the first month of life. For the neonate, such care should emphasize the prevention, timely recognition, and treatment of infection.

Overall, the effectiveness of the approaches on a larger scale and their impact on the choice of antimicrobial strategy is difficult to interpret.

8. ONGOING CLINICAL TRIALS

The results from a second SATT trial, taking place in Pakistan, are awaited (NCT01027429). This large RCT is similar to the SATT trial based in Bangladesh. It will investigate if in young infants (≤ 59 days) with PSBI whose families refuse facilitated hospital referral therapy with intramuscular procaine penicillin and gentamicin (reference therapy) for 7 days is equivalent to (i) injectable gentamicin once daily and oral amoxicillin twice daily for seven days; (ii) injectable penicillin and gentamicin once daily for two days followed by oral amoxicillin twice daily for five days. This study started in 2009 and was to be completed in 2013 with an estimated enrollment of 2543 patients. To our knowledge, results have not as yet been reported and the study is registered as currently open.

Ceftaroline fosamil is a broad-spectrum cephalosporin antibiotic with activity against many bacteria, including Streptococcus pneumoniae (both penicillin-nonsusceptible and multidrug-resistant strains) and Staphylococcus aureus (including methicillin-resistant S. aureus). A multicentre study based in the United States, Hungary, Italia and Spain, evaluates the safety and tolerability of cetaroline-fosamil for the treatment of LOS in neonates and young infants (7 to < 60 days) (NCT02424734). Primary outcomes include adverse events, serious adverse events, deaths, and discontinuations due to adverse events. The study started in August 2015 with an estimated study completion date in October 2017 for an estimated enrollment of 24 patients.

An Italian trial (NCT02899143) is being conducted to compare, in children and adults in intensive care, with infection or sepsis, the effect of a short course targeted antimicrobial therapy (5-days) versus a targeted 10-days therapy on sepsis-related organ dysfunction. The study has started in September 2016 with an estimated enrollment of 320 patients and an estimated completion date of September 2018.

The 3 following studies were indicated as being completed but published results were not available to our knowledge:

A study was conducted in Malawi, in hospitalized infants < 2 months, with severe sepsis or meningitis to compare the standard treatment consisting in penicillin and gentamicin versus ceftriaxone 80 mg/kg for at least 14 days for infant meningitis (NCT01247909). The primary outcome consisted in recovery versus death or severe residual neurological sequelae at hospital discharge, 1 month and 6 months post discharge. The study started in April 2010 and was completed in April 2015 and planned to enroll 351 patients.

A study based in Buenos Aires evaluated the effectiveness of empiric treatment with cefazolin versus to vancomycin in newborn infants with presumptive clinical signs of hospital acquired bacterial sepsis probably caused by coagulase-negative staphylococci (NCT01867138). It was hypothesized that cefazolin as empiric treatment was not inferior to vancomycin for clinical outcomes. The study has started in March 2007 with an estimated enrollment of 109 patients and was completed in September 2011.

A study conducted by a pharmaceutical company evaluated the safety and efficacy of daptomycin versus standard of care in pediatric participants aged 1-17 years with bacteremia caused by *S. aureus* (NCT01728376). Primary outcomes were (i) number of participants with adverse events and serious adverse events, (ii) levels of serum creatine phosphokinase, (iii) change from baseline in number of participants with abnormal focused (peripheral) neurological assessments. The study started in November 2012 and was completed in January 2016 and planned to enroll 82 patients

9. DISCUSSION & RESEARCH OUTLOOK

In the last 5 years, 4 adequately designed and powered studies that compared antibiotic treatments in a low-risk community setting in neonates and young infants (0 – 59 days) in LMIC were found. These studies addressed potential simplifications of the current WHO treatment of reference, in particular for infants for whom admission to inpatient care was not acceptable or possible. In this group of infants, evidence suggests that treatment regimens could potentially be simplified, for example by using injectable gentamicin for 2 days and oral amoxicillin for 7 days for young infants. We hypothesize that the regimen consisting of injectable gentamicin for 2 days and oral amoxicillin for 7 days would offer advantages over others investigated, by requiring fewer invasive procedures with only 2 injections, promoting treatment adherence, and by allowing administration of high doses of aminoglycoside to target high MIC, while preventing drug accumulation over days and thus potential toxicity (mostly nephrotoxicity) based on a once daily dosing regimen. However, these studies did not evaluate regimens and/or agents outside of those currently on the essential medicines list. Also, they were limited to a specific subpopulation of infants and children (≤ 59 days; weight ≥ 1500 g) with suspected sepsis: enrollment according to the presence of PSBI was based on the presence of any sign of clinical severe infection except signs of critical illness (unconsciousness and convulsions). As this was a community based low risk study, a considerable proportion of treated babies may not have had a bacterial infection. It is also unclear what the rates of antimicrobial resistance were in these settings, but sensitivities to the aminoglycoside based regimens are likely to be higher than in facility based settings. Studies assessing the efficacy of specific antibiotic regimens in infants and children with blood-culture proven sepsis and/or the effectiveness of different regimens in infants and children with nosocomial sepsis are virtually lacking. Given the challenges with increasing levels of antibiotic resistance in LMIC settings (based on the evaluation of blood cultures usually collected from inpatients or at least at presentation to hospital) and considerably different patterns of bacteria causing

bacteraemia, for example with the predominance of *Klebsiella* spp and *Acinetobacter* spp, it may be expected that additional antibiotic options could be required. Closing the existing evidence gap must be a priority to base any additions/changes to the recommended regimens on robust data. All additional trials addressing antibiotic regimens in neonatal and paediatric sepsis that we could identify were disappointing in terms of design (often retrospective), power (low sample size) and outcomes (not performed in LMIC, method not always well reported, drug dose often not reported). In addition, more data on causative pathogens and their susceptibilities are essential to understand which treatment regimens could be effective and should be prioritised for further investigation. There are virtually no relevant studies with rigorous methods to direct therapeutic options in children. Fundamental concepts of effective antimicrobial therapy in critically ill children (proper culture techniques, timely initiation of therapy, selection of agents with a high likelihood of susceptibility and sufficient penetration to the site of infection, adequate doses and intervals to enhance bactericidal activity) are often impractical in LMIC due to resource limitations and infrastructure constraints. Overall, a recommendation to amend the current WHO antibiotic regimens for PSBI cannot be made.

The utility of third generation cephalosporins as second-line treatment is under debate based on the sparse microbiological surveillance data available. Additionally, major concerns exist about the widespread use of third generation cephalosporins and selection for multidrug gram negative infections in neonatal units. Further efforts are urgently needed to investigate alternative older off patent therapeutic antimicrobials, their efficacy and safety in the paediatric population, and to assess which of the alternative antimicrobial regimens can be deployed in LMIC settings, focusing on cost and availability.

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Table 1.a. Study description

Author and year of publication	Title	Period of data collection	Study type	Comparison	Condition, Diagnosis	Country, continent	N	Population	Community versus Hospital
AFRINEST group, 2015 [1]	Simplified antibiotic regimens compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with clinical signs of possible serious bacterial infection when referral is not possible: a randomised, open-label, equivalence trial	2011 - 2013	Prospective, randomised, open-label, equivalence trial 5 centers	3 simplified antibiotic regimens compared with injectable procaine benzylpenicillin plus gentamicin for 7 days	Clinical signs of possible serious bacterial infection PSBI when referral is not possible	DR Congo, Kenya, and Nigeria; Africa	3564 group A (n=894), group B (n=884), group C (n=896), group D (n=890)	Neonates and young infants (range 0 – 59 days) Stratified by age (0–6 days and 7–59 days)	Community
AFRINEST group, 2015 [2]	Oral amoxicillin compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with fast breathing when referral is not possible: a randomised, open-label, equivalence trial	2011 - 2013	Prospective, randomised, open-label, equivalence trial 5 centers	Oral amoxicillin compared with injectable procaine benzylpenicillin plus gentamicin	Fast Breathing as a single sign of illness of PSBI when referral is not possible	DR Congo, Kenya, and Nigeria; Africa	2333 Injectable procaine benzylpenicillin-gentamicin: n = 1170; oral amoxicillin: n = 1163	Neonates and young infants (range 0 – 59 days)	Community
Baqui, 2015 [3]	Safety and efficacy of alternative antibiotic regimens compared with 7 day injectable procaine benzylpenicillin and gentamicin for	2009 - 2013	Prospective, randomised, open-label, equivalence trial	2 simplified antibiotic regimens compared with injectable procaine benzylpenicillin	Clinical signs of possible serious bacterial infection PSBI when referral is not possible	Bangladesh; Asia	2490 group A (n=830), group B (n=831), group C (n=829)	Neonates and young infants (range 0 – 59 days) Stratified by age (0–6 days	Community

Author and year of publication	Title	Period of data collection	Study type	Comparison	Condition, Diagnosis	Country, continent	N	Population	Community versus Hospital
	outpatient treatment of neonates and young infants with clinical signs of severe infection when referral is not possible: a randomised, open-label, equivalence trial		4 urban hospitals and 1 rural field	plus gentamicin for 7 days				and 7–59 days)	
Zaidi, 2012 [4]	Community-based treatment of serious bacterial infections in newborns and young infants: a randomized controlled trial assessing three antibiotic regimens	2003 - 2005	Prospective RCT In 3 low-income communities	Failure rates of 3 clinic-based antibiotic regimens	Clinical signs of possible serious bacterial infection PSBI	Pakistan; Asia	434 Penicillin and Gentamicin, n = 145 Ceftriaxone, n = 145 Cotrimoxazole and Gentamicin, n = 144	Neonates and young infants (range 0 – 59 days)	Community
Berkowitz, 2015 [5]	Empiric Monotherapy Versus Combination Therapy for Enterobacteriaceae Bacteremia in Children	2008 - 2011	Retrospective cohort Single center Confirmed bacteriema	β-lactam monotherapy *vs* β-lactam and aminoglycoside combination	Empiric treatment; laboratory-confirmed bacteremia caused by Klebsiella spp, E Coli, Enterobacter spp. Most infections were primary bacteremia.	USA; North America	203 β-lactam monotherapy: n = 102 (50%); combination: n= 101 (50%)	Children and Young adults (< or = 21 yo) Median age: 18 months (IQR 5 months to 10 years)	Hospital
Cantey, 2015 [6]	Empiric Antibiotics for Serious Bacterial Infection in Young Infants: Opportunities for Stewardship	2011 – 2013	Prospective, observational	Optimal approach to empiric antibiotic therapy:	SBI (positive blood culture)	USA; North America	265 Includes patients with	Neonates and young infants (range 0 – 59 days)	Hospital

Author and year of publication	Title	Period of data collection	Study type	Comparison	Condition, Diagnosis	Country, continent	N	Population	Community versus Hospital
				Gentamicin and ampicillin conbination *versus* monotherapy third-generation cephalosporins *versus* third-generation cephalosporins and ampicillin combination			meningitis (11%), Bacteremia (25%, n=27 with concomitant UTI), UTI alone (64%)	Mean age (sd) = 32 days (16.6) Mean gestational age (sd) = 38.8 (1.9)	
Sick, 2014 [7]	Empiric combination therapy for gram-negative bacteremia	2004 - 2012	Retrospective match-paired cohort Single center	beta-lactam monotherapy *vs* beta-lactam and aminoglycoside combination as empirical therapy	Gram Negative bacteremia	USA; North America	452 Monotherapy: n = 226	Children (range: > 2 months – 14 years)	Hospital
Tamma, 2013 [8]	Less is more: combination antibiotic therapy for the treatment of gram-negative bacteremia in pediatric patients	2002 – 2011	Retrospective Cohort	β-lactam monotherapy *vs* β-lactam and aminoglycoside combination	Definitive treatment; Gram Negative bacteria i.e. Enterobacteriaceae, Pseudomonas species, or Acinetobacter species	USA; North America	879 β-lactam monotherapy: n = 342 (38.9%); combination: n= 537 (61.1%)	Children *Mean (SD)* Combination therapy: 5.7 (6.4) Monotherapy: 6.4 (7.0)	Hospital
Tewari, 2014 [9]	Monotherapy with amikacin or piperacillin-tazobactum empirically in neonates at risk for early-onset sepsis: a	2009 – 2011	Prospective RCT Single center	Comparison of monotherapy with amikacin versus piperacillin / tazobactam	Empiric treatment for early-onset sepsis	India, Asia	187 Asymptomatic cases, amikacin: n = 64; Asymptomatic cases, pip / taz:	Neonates (≥ 28 weeks gestational; ≥ 1000 g)	Hospital

Author and year of publication	Title	Period of data collection	Study type	Comparison	Condition, Diagnosis	Country, continent	N	Population	Community versus Hospital
	randomized controlled trial						n = 64; Symptomatic cases, amikacin: n = 29; Symptomatic cases, pip / taz: n = 30		
Ramasamy, 2014 [10]	Comparison of two empiric antibiotic regimen in late onset neonatal sepsis--a randomized controlled trial	NS	Prospective RCT Single Center	Comparison of two empiric regimens: Cloxacillin and Amikacin combination vs Cefotaxime and Gentamicin	Late-onset sepsis	India, Asia	90 Cloxacillin and Amikacin combination: n = 40 Cefotaxime and Gentamicin: n = 50	Neonates Range: 3 – 28 days	Hospital
Bibi, 2012 [11]	Ampicillin and gentamicin are a useful first-line combination for the management of sepsis in under-five children at an urban hospital in Bangladesh	2009 - 2010	Retrospective Single Center	Ampicillin and Gentamicin as a first line combination for the management of sepsis	Clinical signs of sepsis	Bangladesh; Asia	183 14 Neonates (8%) 121 infants (66%; 1 mo to < 12 mo) 48 chlidren (26%; 12 mo to 59 mo)	Neonates Children (< 5 yo)	Hospital
Chong, 2013 [12]	Results of a two-center, before and after study of piperacillin-tazobactam versus ampicillin and gentamicin as empiric therapy for suspected	2007 - 2011	Retrospective before and after practice change cohort study. 2 centers	Piperacillin / tazobactam vs Ampicillin and Gentamicin	Suspected early-onset sepsis	USA; North America	714 Unmatched cohort: Ampicillin and Gentamicin: n = 199;	Neonates (Birth, body weight ≤ 1500g)	Hospital

Author and year of publication	Title	Period of data collection	Study type	Comparison	Condition, Diagnosis	Country, continent	N	Population	Community versus Hospital
	sepsis at birth in neonates		Both match and unmatch Cohort study (Ampicillin and Gentamicin = historical cohort)				Piperacillin / tazobactam: n = 215 Matched cohort: Ampicillin and Gentamicin: n = 301; Piperacillin / Tazobactam: n = 183		
Rodriguez-Guerinea, 2013 [13]	Combination of vancomycin and rifampicin for the treatment of persistent coagulase-negative staphylococcal bacteremia in preterm neonates	2006 - 2011	Restrospective Single Center	Combination of vancomycin and rifampicin	Late-onset sepsis: Persistent CoNS bacteriemia	Spain; Europe	10	Neonates Median age at the onset of infection: 9 days (range 5–37) Median GA: 26 weeks [range 24 3/7 - 31 4/7]	Hospital

NS: Not specified

Table 1.b. Intervention and outcomes

Author and year of publication	Intervention	Outcome 1	Outcome 2	Conclusion	Limitations / Confounding
AFRINEST group, 2015[1]	Infants were randomly allocated to receive: – injectable procaine benzylpenicillin–gentamicin for 7 days (group A, reference group) – injectable gentamicin and oral amoxicillin for 7 days (group B) – injectable procaine benzylpenicillin–gentamicin for 2 days, then oral amoxicillin for 5 days (group C) – or injectable gentamicin for 2 days and oral amoxicillin for 7 days (group D) Rescue therapy: ceftriaxone for 7 days	*Treatment failure by day 8 after enrolment, defined as clinical deterioration, development of a serious adverse event (including death), no improvement by day 4, or not cured by day 8:* PP: 67 (8%) infants failed treatment in group A compared with 51 (6%) infants in group B (risk diff erence –1.9%, 95% CI –4.4 to 0.1), 65 (8%) in group C (–0.6%, –3.1 to 2.0), and 46 (5%) in group D (–2·7%, –5·1 to 0·3). Treatment failure in groups B, C, and D was within the similarity margin compared with group A.	*Death between days 9 and 15 after enrolment relapse and adherence to the allocated treatment between days 1 and 8.* PP: During the 15 days after random allocation, 12 (1%) infants died in group A, compared with 10 (1%) infants in group B, 20 (2%) infants in group C, and 11 (1%) infants in group D. An infant in group A had a serious adverse event other than death (injection abscess). More parents withdrew their infants from group A (49 [5%] of 894 infants) than did parents in the other three groups, with 23 (3%) of 884 infants in group B, 13 (1%) of 896 infants in group C, and 11 (1%) of 890 infants in group D being withdrawn. During the second week after enrolment, 24 (1%) of 3564 infants relapsed.	The three simplified regimens were as effective as injectable procaine benzylpenicillin–gentamicin for 7 days on an outpatient basis in young infants with clinical signs of severe infection, without signs of critical illness, and whose caregivers did not accept referral for hospital admission.	Trial was not fully blinded. Only clinical criteria were used to make the diagnosis, with no confirmatory microbiological or other supportive laboratory data. Renal function was not assessed
AFRINEST group, 2015 [2]	Infants were randomly allocated to receive:	*Treatment failure by day 8 after enrolment, defined as clinical deterioration, development of a serious adverse event including*	*Death 9 – 15 days after enrolment; relapse, and*	Young infants with fast breathing alone can be effectively treated with oral amoxicillin on an	Trial was not fully blinded. Only clinical criteria were used to make the

Author and year of publication	Intervention	Outcome 1	Outcome 2	Conclusion	Limitations / Confounding
	– either injectable procaine benzylpenicillin–gentamicin once per day – or oral amoxicillin treatment twice per day for 7 days	*death, persistence of fast breathing on day 4, or recurrence up to day 8:* PP: In the procaine benzylpenicillin–gentamicin group, 234 infants (22%) failed treatment, compared with 221 (19%) infants in the oral amoxicillin group (risk difference –2.6%, 95% CI –6.0 to 0.8).	*adherence to the study therapy on days 1 – 8:* PP: During the second week after enrolment, 18 (2%) of 827 infants who had not already failed treatment relapsed in the injectable procaine benzylpenicillin – gentamicin group compared with 22 (2%) of 914 infants in the oral amoxicillin group (0.2%, 95% CI-1.2 to 1.6). Few infants died (n=4) or developed signs of critical illness or severe infection (25 [2%] infants in the injectable procaine benzylpenicillin – gentamicin group and 22 [2%] infants in the oral amoxicillin group). Adherence to oral amoxicillin (98%) was better than adherence to injectable therapy (91%). No drug-related serious adverse events	outpatient basis when referral to a hospital is not possible.	diagnosis, with no confirmatory microbiological or other supportive laboratory data. Renal function was not assessed
Baqui, 2015 [3]	Infants were randomly allocated to receive: – intramuscular procaine benzylpenicillin and gentamicin once per day for 7 days (group A, reference group)	*Treatment failure by day 8 after enrolment defined as treatment failure as death at any time before the day 8 assessment; clinical deterioration at or before the day 8 assessment, change of antibiotic or addition of another antibiotic on / or before day 8, hospital admission for*	*Proportions of infants who died and of those who had non-fatal relapse, defined as young infants who were deemed to be cured within 7 days but developed any of the clinical signs of severe*	Alternative regimens (im gentamicin once per day and oral amoxicillin twice per day for 7 days OR im procaine benzylpenicillin and gentamicin once per day for 2 days, then oral amoxicillin twice per day	Trial was not fully Blinded. Only clinical criteria were used to make the diagnosis, with no confirmatory microbiological or other

Author and year of publication	Intervention	Outcome 1	Outcome 2	Conclusion	Limitations / Confounding
	– intramuscular gentamicin once per day and oral amoxicillin twice per day for 7 days (group B) – or intramuscular procaine benzylpenicillin and gentamicin once per day for 2 days, then oral amoxicillin twice per day for 5 days (group C)	*any reason at or before the day 8 assessment, occurrence of new clinical signs of severe infection at or after day 3, presence of at least two of the signs that were present on enrolment at day 4 in infants with multiple signs at enrolment, presence of the sign on day 4 in infants with a single sign on enrolment; recurrence of any one of the five inclusion signs on or after day 5, persistence of any one of the five signs of severe infection that was present at enrolment on day 8.* In group A, 78 (10%) infants had treatment failure, compared with 65 (8%) infants in group B and 64 (8%) infants in group C. Risk difference between groups C and A was -1.5% (95% CI 4.3 to 1.3) and risk difference between groups B and A was -1.7% (-4.5 to 1.1). Therefore, the upper bound of both confidence intervals was less than the predefined 5% equivalence margin. In group A, 14 (2%) infants died before day 15, compared with 12 (2%) infants in group B and 12 (2%) infants in group C. Hospital admission and deaths in the first week were slightly more common in group A than in groups B and C.	*infection after 7 days and within 14 days* Death in the second week was slightly more common in group C than in groups A and B, but risk of death at any time before the day 15 follow-up was less than 2% in all treatment groups. This risk was similar to that of infants who opted for hospital admission (5 [2%] of 272 infants for whom we had data died during hospital admission and another 3 [1%] infants died within 1 week of discharge). Non-fatal relapse rates were similar in all three groups (12 [2%] infants in group A vs 13 [2%] infants in group B and 10 [1%] infants in group C).	for 5 days) were efficacious and safe for outpatient treatment of clinical signs of severe infection in young infants whose caregivers did not accept hospital care.	supportive laboratory data Regimens not assessed in young infants with critical illnesses or in infants with clinical signs of severe infection whose caregivers accepted hospital admission. The study sample included few infants aged 0 – 6 days (10%)

Author and year of publication	Intervention	Outcome 1	Outcome 2	Conclusion	Limitations / Confounding
		Non-fatal severe adverse events were rare. Three infants in group A, two infants in group B, and three infants in group C had severe diarrhoea.			
Zaidi, 2012 [4]	Infants were randomly allocated to receive: (1) procaine penicillin and gentamicin, reference arm, (2) ceftriaxone, or (3) oral trimethoprim-sulfamethoxazole (TMP-SMX) and gentamicin for 7 days	*Treatment failure, defined as death, deterioration in clinical condition during therapy or no improvement after 2 days* 13 of 145 failures with penicillin-gentamicin, 22 of 145 with ceftriaxone and 26 of 143 with TMP-SMX-gentamicin. Treatment failure was significantly higher with TMP-SMX-gentamicin compared with penicillin-gentamicin [relative risk 2.03, 95% confidence interval: 1.09 – 3.79] by intention-to-treat analysis. Differences were not significant in the ceftriaxone versus penicillin-gentamicin comparison [relative risk 1.69, 95% confidence interval 0.89–3.23) ITT: By 14 days, there were 2 deaths in the penicillin-gentamicin group, 3 in the ceftriaxone group and 11 in the TMP-SMX-gentamicin group [relative risk 5.58, 95% confidence interval: 1.26–24.72 (group 3 versus 1)].	*Case fatality rates at 7 and 14 days after enrollment, relapse, withdrawal, therapy completion rates and adverse events* ITT: On 14 days after enrollment, there were no additional deaths between 7 and 14 days of treatment in the penicillin plus gentamicin group or the ceftriaxone group; however, there were 4 additional deaths among babies who had failed therapy in the TMP-SMX plus gentamicin group, totaling 11 (7.7%) in this group (Table 1). The RR of death at 14 days after enrollment in the ceftriaxone group compared with the penicillin plus gentamicin group was 1.50 (95% CI: 0.25–8.84); the RR of death in the TMP-SMX plus gentamicin group at 14 days after enrollment compared with the penicillin plus gentamicin group was statistically significant at 5.58 (95% CI: 1.26–24.72)	When hospitalization of sick infants is unfeasible, outpatient therapy with injectable antibiotics is an effective option. Procaine penicillin-gentamicin was superior to TMP-SMX-gentamicin. Ceftriaxone is a more expensive option, and may be less effective, although this requires further research.	Trial was not fully Blinded. Only clinical criteria were used to make the diagnosis

Author and year of publication	Intervention	Outcome 1	Outcome 2	Conclusion	Limitations / Confounding
			PP: the TMP-SMX plus gentamicin group still had a higher treatment failure rate than the penicillin plus gentamicin group after 7 days of therapy (RR 1.84, 95% CI: 0.98–3.44), but did not reach statistical significance. However, at 14 days, the relative risk of death in infants treated with TMP-SMX and gentamicin was significantly higher (RR 4.78, 95% CI: 1.07–21.41) than those treated with procaine penicillin and gentamicin in the modified per-protocol analysis There were significantly more withdrawals [14 (9.7%)] in the penicillin plus gentamicin group compared with the ceftriaxone group [5 (3.4%)] (RR 2.80, 95% CI: 1.04–7.57) and the TMP-SMX plus gentamicin group [5 (3.5%)] (RR 2.76, 95% CI: 1.02–7.47).		
Berkowitz, 2015 [5]	Empiric therapy with a β-lactam agent alone (n = 101) superior to combination therapy of a β-lactam agent with an aminoglycoside agent (n = 103) for at least 48 hours before the	*Time required for achieving a negative blood culture:* No statistical significant difference in the time to culture-negative between the 2 groups. The mean antimicrobial therapy duration to negative blood culture was 3 days	*Mortality among patients given monotherapy was compared with those given combination therapy:* No significant difference in 7-day and 30-day mortality or in the rates of intensive care	Combination therapy consisting of a β-lactam agent and an aminoglycoside agent was not superior to monotherapy with a β-lactam agent alone for managing	Patients with cancer were more likely to receive combination therapy (38% vs. 16%; P < 0.001); patients with gastrointestinal disease and those receiving total parenteral

Author and year of publication	Intervention	Outcome 1	Outcome 2	Conclusion	Limitations / Confounding
	susceptibility data were known	(sd 1.1 days for monotherapy and 1.2 days for combination therapy.	unit admission between the groups	Enterobacteriaceae bacteremia in children and young adults (P = 0.86).	nutrition were more likely to receive monotherapy (58% vs. 39%; P = 0.006 and 54% vs. 37%; P = 0.013, respectively). patients with coinfection with other Enterobacteriaceae were statistically associated with clinical outcome
Cantey, 2015 [6]	Empiric antibiotic regimens for infants. They were either ampicillin/gentamicin (n = 116; 44%) or third-generation cephalosporin-based (n = 149; 56%). For 126 infants 28 days or younger with SBI, ampicillin/gentamicin was used more frequently (n = 98; 78%); for the 139 infants older than 28 day, empiric therapy was predominantly third-generation cephalosporin-based (n = 121; 87%). Twelve infants (5%) received vancomycin.	*Antibiotic effective susceptibility:* − When meningitis was not suspected, ampicillin/gentamicin and third-generation cephalosporin-based regimens were effective empiric coverage for 96% and 97% of infants, respectively (P = 0.78). − Ampicillin and gentamicin, with third generation cephalosporins reserved for cases where meningitis is suspected, would have provided effective coverage for 98.5% of infants and unnecessarily broad therapy for 4.3%. − Third-generation cephalosporins with ampicillin would have been effective for 98.5% of infants and unnecessarily broad for 83.8%.	*Unnecessary antibiotic course based on drug susceptibility*: − Based on in vitro susceptibilities and infected compartment(s), 67% of third-generation cephalosporin use and 12 of 12 (100%) courses of vancomycin were unnecessarily broad relative to ampicillin / gentamicin. − 57% of third-generation cephalosporin courses were continued despite susceptibility results which would have allowed a de-escalation of therapy, resulting in 511 extra days of therapy with third-generation cephalosporins.	Ampicillin/gentamicin remains an effective empiric regimen for infants 60 days or younger with suspected SBI. Use of a third generation cephalosporin for suspected meningitis is appropriate, but cerebrospinal fluid must be obtained promptly to guide appropriate therapy	Third-generation cephalosporin monotherapy would have been a less efficacious regimen for the infants in this cohort. This difference is because of the 20 *Enterococcus faecalis* isolates (7.5% of identified pathogens), which are intrinsically resistant to cephalosporins

Author and year of publication	Intervention	Outcome 1	Outcome 2	Conclusion	Limitations / Confounding
		– Third-generation cephalosporin monotherapy was less effective than either combination (P < 0.001).			
Sick, 2014 [7]	Children receiving empirical combination therapy versus empirical monotherapy	Mortality within 10 days of the first day positive blood culture was obtained: – Ten-day mortality was similar between the groups (odds ratio, 0.84; 95% CI, 0.28 to 1.71) – There was no survival benefit when evaluating 10-day mortality for the severely ill (pediatric risk of mortality III score ≥15) or profoundly neutropenic patients (absolute neutrophil count ≤100 cells/mL) receiving combination therapy – A survival benefit was observed when empirical combination therapy was prescribed for children growing multidrug-resistant Gram-negative organisms (n=46) from the bloodstream (odds ratio, 0.70; 95% CI, 0.51 to 0.84).	*Duration of bacteremia:* – The median duration of bacteremia for children in the monotherapy and combination therapy arms was 1.9 and 2.1 days: no significant difference in the duration of bacteremia in the matched samples, even after adjusting for time to central line removal or drainage of intraabdominal abscesses (20.51 days; 95% CI,22.22 to 1.48 days) – Nonsignificant trend toward longer durations of bacteremia for patients receiving b-lactam monotherapy (0.85 days; 95% CI, 20.04 to 2.10 days) who had MDRGN bacteremia	No improvement in 10-day mortality of children who have Gram-negative bacteremia receiving empirical beta-lactam and aminoglycoside combination therapy compared with b-lactam monotherapy, unless the bacteremic episode was attributable to a multidrug-resistant organism.	Children receiving combination therapy were more likely to be immunocompromised, profoundly neutropenic, have a central line on the first day of bacteremia, and continue to receive combination therapy after antibiotic susceptibilities were finalized. Aminoglycoside side effects not assessed.
Tamma, 2013 [8]	Definitive therapy with a β-lactam agent alone (n = 342) superior to combination therapy of a β-lactam agent with an aminoglycoside agent (n = 537) for at least	*30-day mortality:* 41 deaths (7.6%) in the combination therapy and 23 (6.7%) in the monotherapy group (P = .61)	*Nephrotoxicity classified according to the pediatric RIFLE criteria* There were 170 patients (19.3%) with evidence of acute kidney injury, including	The risk of mortality is similar in pediatric patients with gram-negative bacteremia treated with β-lactam monotherapy and those	Patients receiving combination therapy were more likely to require ICU admission, vasopressors, or mechanical ventilation;

Author and year of publication	Intervention	Outcome 1	Outcome 2	Conclusion	Limitations / Confounding
	48 hours before the susceptibility data were known	no association between combination therapy and 30-day mortality (odds ratio, 0.98; 95%CI, 0.93-1.02; P = .27)	135 (25.1%) and 35 (10.2%) in the combination therapy and monotherapy arms, respectively. Patients receiving combination therapy had approximately twice the odds of nephrotoxicity compared with those receiving monotherapy (odds ratio, 2.15; 95%CI, 2.09-2.21).	treated with combination (β-lactam and aminoglycoside) therapy The use of β-lactam monotherapy for gram-negative bacteremia in pediatric patients reduces subsequent nephrotoxicity without compromising survival.	to have a central venous line that remained in place for more than 72 hours after obtaining the first positive blood culture result (OR, 2.11; 95%CI, 2.07-2.15 adjusted model) to have an underlying cancer; and to have Pseudomonas bacteremia. Patients with urosepsis as their source of bacteremia were much more likely to receive monotherapy (P = .01).
Tewari, 2014 [9]		*Treatment failure (blood culture isolate resistant to the allocated antibiotic or progression of the illness necessitating change of antibiotic identified by unresolved shock, worsening of respiratory distress, coagulopathy, abdominal distension, hypoglycemia, poor activity and temperature instability)* Treatment failure with use of amikacin or piperacillin-tazobactum was very low (n =3 (3.2%) and n=2 (2.1%), respectively (p = 0.44))	*second infection necessitating antibiotics within 1 week of stopping the study antibiotic, all-cause mortality by day 7 and day 28 since birth and episode of proven fungal infection within 28 days since birth* no increased risk or significant difference in the incidence of second infection within 7 days of stopping the study antibiotic, no difference in the incidence of fungal sepsis and no difference in the all-cause mortality at day 7 and day 28	Authors conclude that amikacin monotherapy did not result in a higher treatment failure rate as compared with piperacillin-tazobactum (p>0.01). Both antibiotics were effective as monotherapy in babies at risk for EOS.	Only few confirmed bacteremia (n=5)

Author and year of publication	Intervention	Outcome 1	Outcome 2	Conclusion	Limitations / Confounding
			between the two study groups (p > 0.4)		
Ramsamy, 2014 [10]	Infants were randomly allocated to receive: – Cloxacillin + Amikacin (n = 40, group I) – Or Cefotaxime + Gentamicin (n = 50, group II) For 10 days	*mortality before discharge from hospital and complications including shock, DIC, acidosis, renal failure and re-hospitalization within 2 weeks of discharge* Complications, duration of hospital stay, treatment failure, re-hospitalization and cost were essentially similar in both the groups and were not statistically significant in relation to the outcome. – There was increased mortality in cases with septicaemia, meningitis and pneumonia in group II compared with group I, but the difference was not statistically significant. – The number of babies with complications in group II was more than that in group I, but the difference was not statistically significant	*Treatment failure, subsequent fungal infections, duration of hospital stay, cost analysis and problems on follow-up* – 3 blood for fungal culture of 18 babies were positive for candida nonalbicans – Of the 36 discharged babies in group II, nine (25%) had evidence of sequelae in the form of either tone abnormalities or hydrocephalus or evidence of chronic lung disease compared with only two (5.5%) in group I. (p<0.05). – Average antibiotic cost per baby in groups I and II was Rupees 70 and 72.50, respectively	Authors conclude that there was no significant difference between the two antibiotic regimens with regard to outcome of LOS.	Results are not clear and do not address the stated primary outcome. Low quality of report.
Bibi, 2012 [11]	181 patients received ampicillin + gentamicin first line 2 patients received ceftriaxone + gentamicin first line 46 (25%) received ceftriaxone + gentamicin second line	*mortality rate* 7 patients died who received injection ampicilin and gentamicin (survival rate 96%). None died among the other two patients who received injection ceftriaxone and injection gentamicin combination (p=1.00) as the first-line antibiotics.	46 (25%) patients required a change of antibiotics to the combination of intravenous ceftriaxone plus gentamicin after non-response of injection ampicilin and injection gentamicin combination	Authors conclude that the combination of injection ampicilin and injection gentamicin as the first-line antibiotics for the management of sepsis in children even beyond the neonatal age is very effective, resulting in lower mortality.	Low study quality of and interpretation. Method not specified. Statistics on 2 patients provided on two patients (no method specified). Design is also questionable, since no

Author and year of publication	Intervention	Outcome 1	Outcome 2	Conclusion	Limitations / Confounding
		All patients who died received second-line therapy due to clinical deterioration.			clear outcome was specified
Chong, 2013 [12]	Change to Piperacillin/Tazobactam vs Ampicillin-gentamicin as empiric therpy for suspected sepsis at birth (EOS) in neonates ≤ 1500 g	*Cohorts were evaluated for composite morbidities and mortalities, incidence of sepsis, patent ductus arteriosus treated with indomethacin, ibuprofen or ligation, NEC, ventilator-associated pneumonia (defined as per Vermont Oxford Network) and types of rash (diaper rash and systemic rash – rash outside the diaper area):* − Significant improvement in incidence of NEC with PT treatment compared with AG treatment in both the unmatched and matched analyses − Fewer diaper rashes in PT exposed infants − More late-onset infections during the Ampicillin and Gentamicin epoch than Piperacillin / Tazobactam epoch but neither group reached statistical significance after the Bonferroni correction.	*Neutropenia, thrombocytopenia, elevated or critically low glucose, abnormal calcium, abnormal sodium , creatinine, direct bilirubin, aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase on Days 1, 2 and 7:* − Significant increase in mean alkaline phosphatase associated with PT use (but not incidence of elevated alkaline phosphatase) − Lower mean calcium values in both the unmatched and matched cohorts. It met significance for hypocalcemia in the unmatched analysis, but was just above significance in the matched cohort.	Use of Piperacillin/ Tazobactam as the initial empiric antibiotic for very low birth weight infants was not associated with adverse microbiological outcomes. There was no increase in major morbidities. Outcomes were superior in ≤ 1500 g infants treated with Piperacillin / Tazobactam when compared with Ampicillin-gentamicin.	Patients with MRSA colonization were to be excluded from this study if they were treated with vancomycin during the empiric phase of therapy Retrospective, historically controlled observational study The timing of intervention correlated with a reduction in NEC and diaper rash

Author and year of publication	Intervention	Outcome 1	Outcome 2	Conclusion	Limitations / Confounding
Rodriguez-Guerineau, 2013 [13]	Addition of rifampicin to vancomycin for persistent CoNS LOS *(The therapeutic efficacy of this combination lies in the ability of vancomycin to prevent the emergence of resistance to rifampicin and the effect of intracellular rifampicin that would act synergistically with vancomycin, improving its bactericidal activity)*	*Infection resolution, negative blood culture:* Bacteremia persisted for a median of 9 (range 6–19) days until rifampicin initiation. Bacteremia was resolved in all cases on vancomycin–rifampicin with no serious side effects. In all patients, the blood cultures became negative on vancomycin–rifampicin, taken between 24 to 72 h after the initiation of rifampicin. The average duration of treatment with vancomycin–rifampicin was 9.4 days (median 10 days, range 5–13)	*Side effects (for vancomycin were nephrotoxicity, ototoxicity, neutropenia, red man syndrome after rapid infusion, and local phlebitis and for the rifampicin abnormal liver function tests, rash or elevated blood urea nitrogen)* No serious side effects	Authors conclude that data supports the safety and efficacy of vancomycin–rifampicin combination for the treatment of persistent coagulase negative staphylococcal bacteremia in preterm neonates. Further research is guaranteed	Retrospective study Antibiotic coverage before rifampicin initiation: Vanco + amikacin + in some patient: Cefotaxime, meropenem for Gram negative suspicion, + metronidazole for the 3 neonates with NEC signs. 8 males / 2 female Most of the infections were considered central venous catheter-related bloodstream infections after ruling out other sources of infection

ITT: Intention treat; **PP**: Per protocol; **NEC**: Necrotizing enterocolitis; **CI**: confidence interval; **EOS**: Early-onset sepsis; **LOS**: Late-onset sepsis; **MDRGN**: Multidrug resistant Gram negative; **RR**: Risk ratio; **CoNS**: Coagulase negative staphylococcus; **TMP-SMX**: trimethoprim-sulfamethoxazole

Table 1.c. Pathogens distribution and resistance

Author and year of publication	Pathogens	Resistance and susceptibility
AFRINEST group, 2015[1]	NA	NA
AFRINEST group, 2015 [2]	NA	NA
Baqui, 2015 [3]	NA	NA
Zaidi, 2012 [4]	Positive blood culture (11 of 218 (5%)) Gram-negative bacilli (8) *Pseudomonas aeruginosa* (4)	
Berkowitz, 2015 [5]	*Klebsiella* spp	Multidrug-resistant (MDR) was identified in 11 of 78 (14%) *Klebsiella* spp, which included 7 ESBL producers, 1 presumed ampC cephalosporinase (ampC) producer and 3 presumed carbapenemase (KPC) producers by Clinical and Laboratory Standards Institute criteria
	E. coli	11 of 73 (15%) *E. coli* as ESBL producers were identified
	Enterobacter spp	13 of 53 (25%) *Enterobacter* spp, which included 10 ampC producers and 3 that were both ESBL- and ampC producers were identified
Cantey, 2015 [6]	-	No MRSA, no VRE, no penicillin-resistant streptococcus pneumoniae
	ESBL Gram-negative (n = 4)	
	E. coli and GBS (predominant)	
	Enterococcus faecalis (n = 20)	Intrinsically resistant to cephalosporins
Sick, 2014 [7]	MDRGN (46%) *E. coli* or *Klebsiella* spp (n = 12) *Pseudomonas* spp (n = 15) *Enterobacter* spp (n = 14) *Citrobacter* spp (n =2) *Serratia marcescens* (n = 3)	83% susceptibility for meropenem, 38% susceptibility for ceftriaxone, 66% susceptibility for cefepime
Tamma, 2013 [8]	*Klebsiella* spp (27.5%)	
	Pseudomonas spp (22%)	
	E. coli (16.6%)	
	Acinetobacter baumannii (5.9%)	
	Serratia marcescens (5.9%)	

Author and year of publication	Pathogens	Resistance and susceptibility
	Citrobacter spp (3.8%)	
	Proteus mirabilis (5%)	
Tewari, 2014 [9]	*K. pneumoniae* (n=1)	Sensitive to allocated antibiotic (NS)
	E. coli (n=1)	Sensitive to allocated antibiotic (NS)
	Enterobacter cloacae (n=2)	Not sensitive to allocated antibiotic (NS)
	P. aeruginosa (n=1)	Sensitive to allocated antibiotic (NS)
Ramasamy, 2014 [10]	CoNS (26.67%)	Sensitive to vancomycin, tetracycline, ceftriaxone, oxacillin
	E. coli (13.33%)	
	S pneumoniae (13.33%)	
	K. pneumoniae, *P. aeruginosa*, *S aureus*, micrococci, enterococci, MRSA, *Enterobacter* species (6.7%)	*K. pneumoniae* and *P. aeruginosa* were sensitive to amikacin and meropenem
Bibi, 2012 [11]	CoNS (2)	Patients died; were sensitive to ceftriaxone + gentamicin regimen
	Streptococcus spp (3)	
	Staphylococcus aureus (1)	
	Streptococcus pneumoniae (1)	
	Pseudomonas spp (2)	
	Klebsiella spp (1)	
	Salmonella typhi (1)	
	Acinetobacter spp (1)	
	Moraxella spp (1)	
Chong, 2013 [12]	Group B streptococcus	All sensitive to Piperacillin/Tazobactam
	E. coli	All resistant to Ampicillin. All sensitive to Piperacillin/Tazobactam
	Citrobacter spp.	All resistant to Ampicillin. All sensitive to Piperacillin/Tazobactam
	Pseudomonas spp	1 isolate was resistant to Ampicillin and Gentamicin regimen. All sensitive to Piperacillin/Tazobactam
Rodriguez-Guerineau, 2013 [13]	*Staphylococcus epidermidis* (3)	
	CoNS not typified (7)	

NA: Not Applicable; **MRSA**: methicillin-Resistant S. Aureus; **MRSE**: Meticillin Resistant Staphylococcus Epidermidis; **VRE**: Vancomycin Resistant Enterococcus **CoNS**: coagulase-negative staphylococci**; ESBL**: Extended Spectrum Beta-Lactamase; **MDRGN**: Multidrug resistant Gram negative**.**

Table 1.d. Drug details and dose

Author and year of publication	Drug 1 (%) [route, dose, frequency]	Drug 2 (%) [route, dose, frequency]	Drug 3 (%) [route, dose, frequency]	Drug 4 (%) [route, dose, frequency]	Drug 5 (%) [route, dose, frequency]	Drug 6 (%) [route, dose, frequency]	Drug 7 (%) [route, dose, frequency]
AFRINEST group, 2015[1]	Gentamicin IM Neonates < 7 days: 4 mg/kg Neonates ≥ 7 days: 7.5 mg/kg Once daily	Procaine Benzylpenicillin IM 50 000 units/kg once daily	Amoxicillin PO Neonates < 2 kg: 75 mg/kg/day Neonates ≥ 2 kg: 100 mg/kg/day Divided twice a day				
AFRINEST group, 2015 [2]	Gentamicin IM Neonates < 7 days: 4 mg/kg Neonates ≥ 7 days: 7.5 mg/kg Once daily	Procaine Benzylpenicillin IM 50 000 units/kg once daily	Amoxicillin PO Neonates < 2 kg: 75 mg/kg/day Neonates ≥ 2 kg: 100 mg/kg/day Divided twice a day				
Baqui, 2015 [3]	Gentamicin IM 4 mg/kg to 6.5 mg/kg Once daily	Procaine Benzylpenicillin IM 40 000 - 50 000 units/kg once daily	Amoxicillin PO 75 mg/kg/day to 100 mg/kg/day Divided twice a day				
Zaidi, 2012 [4]	Gentamicin IM 5 mg/kg, once daily	Procaine penicillin IM 50,000 units/kg, once daily	Ceftriaxone IM 50 mg/kg, once daily	Trimethoprim-sulfamethoxazole (TMP-SMX) PO 10 mg/kg/day divided twice daily			
Berkowitz, 2015 [5]	meropenem (31%) [NS] [NS, NS]	ceftazidime (28%) [NS] [NS, NS]	cefotaxime (17%) [NS] [NS, NS]	ceftriaxone (15%) [NS] [NS, NS]	piperacillin/tazobactam (7%) [NS] [NS, NS]	cefuroxime (2%) [NS] [NS, NS]	Aminoglycoside without specification [NS] [NS, NS]
Cantey, 2015 [6]	Ampicillin [NS] [NS, NS]	Gentamicin [NS] [NS, NS]	Third generation cephalosporin [NS]				

Author and year of publication	Drug 1 (%) [route, dose, frequency]	Drug 2 (%) [route, dose, frequency]	Drug 3 (%) [route, dose, frequency]	Drug 4 (%) [route, dose, frequency]	Drug 5 (%) [route, dose, frequency]	Drug 6 (%) [route, dose, frequency]	Drug 7 (%) [route, dose, frequency]
			[NS, NS]				
Sick, 2014 [7]	Gentamicin (90%) 2.5 mg/kg every 8 hours	Amikacin (10%) 5 to 7.5 mg/kg every 8 hours	Piperacillin-tazobactam *According to Guidelines for the Management of Bloodstream Infections in Neonatal and Pediatric Patients*	Ceftriaxone *According to Guidelines for the Management of Bloodstream Infections in Neonatal and Pediatric Patients*	Cefepime *According to Guidelines for the Management of Bloodstream Infections in Neonatal and Pediatric Patients*	Meropenem *According to Guidelines for the Management of Bloodstream Infections in Neonatal and Pediatric Patients*	
Tamma, 2015 [8]	Piperacillin-tazobactam (37.3%) [NS] [NS, NS]	ceftriaxone(30.8%) [NS] [NS, NS]	And cefepime hydrochloride (15.0%) [NS] [NS, NS]				
Tewari, 2014 [9]	Piperacillin-tazobactam (50%) [NS] [NS, NS]	Amikacin (50%) [NS] [NS, NS]					
Ramasamy, 2014 [10]	Cloxacillin [NS] [NS, NS]	Amikacin [NS] [NS, NS]	Cefotaxime [NS] [NS, NS]	Gentamicin [NS] [NS, NS]			
Bibi, 2012 [11]	Ampicillin [NS] [NS, NS]	Gentamicin [NS] [NS, NS]	Ceftriaxone [NS] [NS, NS]				
Chong, 2013 [12]	Ampicillin [NS] [NS, NS]	Gentamicin [NS] [NS, NS]	Piperacillin / Tazobactam [NS] [NS, NS]				
Rodriguez-Guerineau, 2013 [13]	Vancomycin: 10 mg/kg, every 8 hours 10 mg/kg, every 12 hours 10 mg/kg, every 18 hours	Rifampicin: 5 mg/kg, every 12 hours					

Author and year of publication	Drug 1 (%) [route, dose, frequency]	Drug 2 (%) [route, dose, frequency]	Drug 3 (%) [route, dose, frequency]	Drug 4 (%) [route, dose, frequency]	Drug 5 (%) [route, dose, frequency]	Drug 6 (%) [route, dose, frequency]	Drug 7 (%) [route, dose, frequency]
	depending on Post-conceptional age and Post-natal age						

IV: Intravenous, **IM**: intramuscular injection, **PO**: Per Os; **NS**: Not specified

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