

# What are appropriate first-line antibiotics for septicaemia in children in developing countries?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: [http://www.who.int/child-adolescent-health/publications/CHILD\\_HEALTH/PB.htm](http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm)

This review addresses the question: *What are appropriate first-line antibiotics for septicaemia in children in developing countries?*

The **WHO Pocketbook of Hospital Care for Children** recommends for antibiotic therapy – where blood cultures are available, obtain blood cultures before starting antibiotics – Give ampicillin (or penicillin) and gentamicin – Give cloxacillin (if available) instead of penicillin if extensive skin pustules or abscesses as these might be signs of staphylococcus infection.(Pocketbook chapter 6.5, page 158).

## Introduction:

Infections are the most common cause of death in infants and children, causing over 5 million child deaths every year worldwide [1]. There is much overlap in the common clinical syndromes of pneumonia, meningitis and other bacterial infections. Indeed, WHO defines pneumonia with cyanosis, inability to feed or convulsions as “very severe disease” in recognition of this overlap, and in recognition of the common occurrence of occult bacteraemia or infection (such as urinary tract infection). Empiric treatment of presumed serious bacterial infection is highly effective. Improved outcomes have been noted for several of the major severe disease categories without primary bacterial aetiology (severe malnutrition, severe malaria & measles), indicating secondary

bacterial infection as a common ‘end point’ in these conditions.

Septicaemia is a clinical syndrome characterized by a systemic inflammatory response. The clinical features invariably include fever or hypothermia, tachypnoea, and may progress to cardiovascular instability (hypotension) and major organ dysfunction (septic shock). Purpura or petechiae may be present. The systemic inflammatory response is due to a complex cascade of immune activation and cytokine release. The inciting aetiology may be bacterial, viral, fungal or other stimuli. Children most at risk are young infants and those with severe malnutrition.

## Methodology

The clinical search strategy employed was: (septicaemia OR sepsis) AND (children OR paediatric OR pediatric) AND developing (country OR countries). The clinical filter was ‘therapy’ was used and 71 articles were found. 10 systematic reviews were found using the same search strategy.

A further search was conducted using the search strategy: Antibiotics AND (septicaemia OR sepsis) AND (children OR paediatric OR pediatric). This search resulted in 30 articles and 15 reviews.

All abstracts were read and relevant articles sourced.

Articles were excluded if they related to chemotherapy or pharmacological immunosuppression, if they related specifically to sickle cell disease, dealt with predictors of illness or related specifically to nosocomial infection.

No RCT's were found. Two retrospective cohort studies, and six prospective cohort studies were found that were relevant. One review article was found, however this concentrated mainly on

North America with only one study from a developing country included. For this reason it was not felt to be of sufficient value to be included.

## Results

All eight included studies examined patients with suspected sepsis and collected data on the infecting organism and subsequent antibiotic sensitivities. Six studies included recommendations on empiric antibiotic therapy for sepsis [3,4,5,6,7,9].

One study focused specifically on disease due to *Streptococcus pneumoniae* in rural West Africa [10]. The authors of this study isolated 103 cases of pneumococcal infection over a 2-year period (8% pneumonia, 35.5% meningitis, 5% sepsis).

Antibiotic resistance was not found to be a significant problem in this study; only 3/34 isolates obtained showing reduced susceptibility to oxacillin, 3/34 resistant to chloramphenicol, and 1/34 resistant to trimethoprim-sulfamethoxazole (TMP-SMX). This resistance pattern may have changed significantly in the 10 years since this study, however.

Two studies [3,7] demonstrated an increased incidence of bacteraemia in malnourished children (Wellcome Class of Malnutrition); 9.6% and 7.7% malnourished hospitalized children having bacteraemia at presentation compared with 4.9% of well nourished hospitalized children.

Infecting organisms in children with malnutrition were similar in both studies, with *Strep. Pneumoniae* (19% & 19%) the most common bacteria isolated, followed by *Salmonella* (19% & 6.4%), *S. aureus* (18% & 16%) and *E. Coli* (17% & 9.6%). Gram Negative enteric aerobes were 2.6 times more frequent in malnourished than in well nourished children [3]. Antibiotic sensitivity data was also similar in both studies, with a recommended combination of ampicillin and gentamicin covering 86% of community acquired infection in one study [3], and 90.3% in the other [7]. Overall rates of resistance to penicillin by *S. aureus* were also similar (33% vs. 40%).

Two studies focused on sepsis in young infants [5,6]. In both studies *S. pneumoniae* was identified as the most common pathogen in children with bacteraemia (13% & 27%). One study, based in the Gambia, showed a 9.4% infection rate with Group A streptococcus [5] while another in Papua New Guinea, showed a 27% infection rate with this organism [6].

Infection with *S. aureus* remained prevalent in this group (32% & 21%), with the first study identifying 41% of staphylococcal infected infants presenting with a typical skin rash.

Sensitivities were not fully reported in one study [5] although all *Salmonella* spp. isolated during the study period were resistant to penicillin, but sensitive to ampicillin and chloramphenicol.

Another study of young infants [6] showed that 27% of pneumococci isolated had intermediate resistance to penicillin. Ten of the 12 staphylococcal isolates were penicillin resistant; all were sensitive to gentamicin *in vitro*.

Two further studies [4, 9] included children of all ages and levels, malnourished and well nourished. The most common infecting organism in the first study was *S. pneumoniae*, followed by *Salmonella*, *Haemophilus influenza* and *Escherichia coli*. There was a 24% resistance to penicillin in the pneumococci, and all *S. aureus* isolates were fully resistant to penicillin. 98% of *E. coli* isolates were susceptible to gentamicin and 89% of *Salmonella* spp. were susceptible to ampicillin. The authors of this study recommend ampicillin and gentamicin as first line antibiotics in the treatment of suspected bacteraemia.

The second study [9] focused on bacteraemia in children in Malawi and found *non-typhi Salmonella* was the most common infecting organism (38.4%), followed by enteric Gram-negative bacilli (24.9%) and *S. pneumoniae* (16.2%). Resistance was common to current first line antibiotics (ampicillin and TMP-SMX) and one-fifth of all isolates also resistant to chloramphenicol. Enteric Gram-negative bacilli had a high rate of resistance to all antibiotics including a 20% resistance to gentamicin, but the authors acknowledge that half of these isolates were from infants on the neonatal special care unit and nosocomial infection was probable. The authors of this study recommend chloramphenicol as the first line treatment for septicaemia, with the addition of gentamicin if no improvement is seen in 48 hours.

One further study conducted in Papua New Guinea [8] concentrated mainly on disease-specific causes of death in children. Sepsis was found to be the cause of death in 35.7% of children, and accounted for 42.9% of neonatal death. The most common pathogen identified was again *S. pneumoniae*. The study authors noted the higher than expected rate of enteric Gram-negative bacillus infection in this group – accounting for almost a quarter of all deaths.

## Discussion

Despite a variety of locations in the studies reviewed, it is clear that two main issues emerge:

- Infecting organisms in septicaemia in infants and children are similar across locations in the developing world, and include Gram-positive (*S. pneumoniae*, *S. aureus*, Group A streptococci) and Gram negative bacteria (*H. influenzae* and enteric Gram negative bacilli).
- There is established resistance to penicillin in *S. aureus* infections, and increasing penicillin resistance among pneumococcal infections in most developing countries.

## Summary

A combination of ampicillin and gentamicin as first line therapy for suspected non-meningitic septicaemia in children is appropriate first-line therapy. Ampicillin should be given in high dose (200-300mg/kg/day) to overcome penicillin-resistance among pneumococci. Once daily gentamicin has been proven to be safe, effective and associated with less toxicity than more frequent doses.

Where meningitis is suspected, the options are chloramphenicol or a third-generation cephalosporin. A third-generation cephalosporin (e.g. ceftriaxone) will be preferable to chloramphenicol where resistance to chloramphenicol and penicillin among *H. influenzae* and *S. pneumoniae* is common.

Anti-staphylococcal antibiotics (such as beta-lactamase stable penicillins flucloxacillin or cloxacillin) should be given as first-line treatment if there are suggestive skin lesions, abscesses, bone or joint infection, or if other signs of staphylococcal infection (such as pneumatoceles or empyema) are present. If flucloxacillin or cloxacillin are not available, chloramphenicol will have some anti-staphylococcal activity.

Further studies are needed to follow antimicrobial susceptibility in developing countries so that empirical treatment recommendations maintain a strong evidence base. Restricting the use of third-generation cephalosporins and beta-lactamase stable penicillins to where there are specific indications will reduce the development of antibiotic resistance.

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