

Proposal to include antibacterial drugs for treating upper and lower respiratory infections in Children

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1. Summary statement

Community acquired acute upper and lower respiratory infections (LRI) are common in children. Although viruses cause a proportion of these infections, bacterial infections of the respiratory tract are important preventable causes of mortality and morbidity among children.

In children aged 1m to 5yrs, pneumonia is responsible for 19% of deaths and is the single most common cause of mortality. Evidence shows that prompt therapy with appropriate antimicrobials can significantly reduce mortality associated with community acquired pneumonia (CAP). Reducing mortality among children is on of the Millennium Development Goals.

Acute streptococcal tonsillo – pharyngitis and bacterial otitis media are other common infections in children with possibility of serious complications. Penicillin therapy can prevent development of long term complications following streptococcal infections. Treatment of acute otitis media can reduce complications like mastoiditis, chronic otitis media and deafness especially in children from poorer communities.

Since majority of these infections are caused by *S pneumoniae* and *H influenzae*, empirical therapy of community acquired respiratory infections in children is mainly aimed at these two bacteria. However, resistance has appeared among these bacteria to several commonly used antimicrobials and so there is a need for alternative choices. Other bacteria, requiring different drugs, can also be responsible for community and hospital acquired respiratory infections. Hence several antimicrobials have to be available on the essential drug list for effective management of respiratory infections in childhood. Most often, therapy for respiratory infections are initiated based on clinical findings, especially at primary care facilities. Drugs being requested include those for use at community level and also those required for treatment of severe community and hospital acquired respiratory infections.

2. Name of the focal point in WHO submitting or supporting application

3. Names of organizations consulted and or supporting the application

4. International non – propriety name (INN generic name) of the medicines

5. Information supporting public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Lower respiratory infections

In children aged 1m to 5yrs, pneumonia is responsible for 19% of deaths and is the single most common cause of mortality [1]. About 26% of neonatal deaths are caused by severe bacterial infections, a large proportion of which is pneumonia/sepsis. The burden of acute respiratory infections and the mortality due to this is significantly more in developing countries. 150 million episodes of pneumonia occur per year among children below five years in developing countries, accounting for 95% of new cases. Pneumonia related mortality is 2% in developed countries compared to 21% each in South Asia and Sub Saharan Africa. Risk of infection is more for undernourished children, children suffering from infections like AIDS, measles etc and for those living in overcrowded situations.

Effective interventions are available but reach too few children. Less than 20% of children with pneumonia receive antibiotics. Main reason is the health seeking behaviour. If treatment for pneumonia is universally delivered, 600,000 lives can be saved every year at a cost of \$600 million [1]. Reducing mortality among children is one of the millennium development goals.

Simple guidelines based on respiratory rates and chest in drawing while breathing are available and popularised for clinical diagnosis of pneumonia and for assessing severity of infection. A meta-analyses of 9 studies on community based management of pneumonia using these guidelines showed that overall mortality could be reduced by 27%, 20% and 24% respectively among neonates, infants and children up to 4yrs of age [2]. The larger than expected benefit in these studies underscore the need for treating children with pneumonia effectively at a primary health care level.

Choice of therapy depends on the aetiology of infection. Data on relative frequencies of pathogens causing LRI including pneumonia in children in different parts of the world is limited. *Streptococcus pneumoniae* is responsible for more than 50% cases of pneumonia and proportionately more of fatal cases in most developing countries. In developed countries incidence of this infection has fallen after introduction of pneumococcal vaccines, but still continues to be the most important cause [3]. This is followed by *Haemophilus influenzae* which causes about 20% of cases. [1]. Other bacteria include *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae* and others. A recent Cochrane review [4] on therapies for CAP, report 10 studies were aetiological agents were identified. Only 324/4009 (8%) had bacteria isolated from blood cultures- 169 (52%) *S. pneumoniae*, 102 (32%) *H. influenzae*, 11 (3%) *S. aureus* and 42 (13%) other pathogens. Most bacteria isolated were susceptible to commonly used antimicrobials, but the studies were done over 10yrs ago. Since majority of infections are caused by *S pneumoniae* and *H influenzae*, empirical therapy should cover these two pathogens. Atypical pathogens were also identified in some studies - 213/885 (24%) were positive for *M. pneumoniae* (under five years 57 / 388 (15%)) and 151/ 825 (18%) for *Chlamydia spp* (under five years 41/ 388 (11%)). Viruses also cause LRI in children. In neonates Gram negative bacilli are common causes of pneumonia.

Immediate antimicrobial therapy is recommended for children diagnosed to have pneumonia [1]. The drugs recommended for use at primary care level are Co-trimoxazole and amoxicillin. However, with increasing prevalence of resistance, other drugs may need to be used in certain situations. Similarly, in children with severe infections and in those with

underlying disorders like severe malnutrition or HIV infections, the choice of antibacterial therapy may differ. Antibacterial drugs that are shown to be effective and recommended for use in these alternative regimes include macrolides, cloxacillin, penicillin, gentamicin, chloramphenicol and second and third generation cephalosporins [5].

Prophylactic use of co-trimoxazole, in HIV infected children and in infants born to HIV positive mothers, is shown to prevent pneumonia and significantly reduce mortality [1]. Routine anti bacterial therapy is not recommended for acute bronchitis, bronchiolitis [6-8] , cough associated with viral upper respiratory infections and wheeze [9]. 90% of croup has viral aetiology and antibacterial therapy is of no use. However, epiglottitis mostly due to *H influenzae* require antimicrobials[10].

Some of these drugs should be available at the community level. With this comes the responsibility to prevent misuse of antimicrobials. Training of health workers to diagnose infections requiring antibacterial therapy, guidelines for clinical management of acute respiratory infections in different settings and supervision will help in this regard.

Sore throat

Sore throat or acute tonsillo-pharyngitis is a very common condition in the community and many seek treatment even though it is self curing. Majority of throat infections are caused by viruses and so require no antibiotics. Those caused by Group A β haemolytic streptococci can lead onto complications like Rheumatic fever and heart disease (RF/RHFD) and glomerulonephritis. It is however, difficult to clinically differentiate streptococcal tonsillo-pharyngitis from viral infections and guidelines have low sensitivity (<15%) for specifically diagnosing this infection [9]. A recent Cochrane review on antibiotic therapy for clinically diagnosed sore throat showed that therapy reduces incidence of rheumatic fever by two thirds and that incidence of suppurative complications like otitis media and quinsy are also reduced [11]. Although there was a trend towards reduction in glomerulonephritis, numbers were not sufficient. There was not much difference in time to recovery from sore throat itself between treated and untreated patients. Therefore treatment of sore throat is basically to prevent complications especially RF/RHD. Where facilities exist, diagnosis of streptococcal pharyngitis is to be made based on antigen detection tests or culture[12, 13]. Since specific clinical diagnosis of streptococcal sore throat is very difficult, physicians in settings where facilities for culture or rapid diagnostic tests do not exist, can decide to treat sore throat with antibiotics based on the prevalence of RF/RHD in the community[9]. This tends to be higher in developing countries. Penicillin has the most evidence for this effect.

Otitis media

Acute otitis media (AOM) is another common infection in children for which antibiotics are prescribed. Most cases occur in children between 6 months to 36 months[10]. Upto 71% of children suffer at least one attack. Bacteria responsible are *S pneumoniae*, *H influenzae* and *M catarrhalis*. About 40% of cases are due to viruses[14]. In about 80% of children the infection resolves without antibiotics in a few days time[14]. A review [15] of eight placebo controlled trials in developed countries showed that antibiotics do not significantly affect outcomes like pain or incidence of complications like mastoiditis. However there are geographic differences in the incidence of mastoiditis. While in the US it is only 0.4%[14] the complication is common in developing countries[16]. The authors of the Cochrane review state that antibiotic treatment may play an important role in reducing the risk of mastoiditis in populations where it is common. Acute infections can also lead to chronic otitis media

(COM) which is a preventable cause of deafness. COM is a public health problem and is more common in developing countries and in poor communities. Early diagnosis and management of AOM helps to prevent COM. So in developing countries antibiotics are usually recommended for AOM to prevent complications like mastoiditis and COM[17, 18]. Children below 2 yrs and those with severe infections are more likely to benefit from antibiotic therapy[14]. In countries where mastoiditis is rare, children over 2 without high fever or vomiting could generally be treated with analgesia, and antibiotic use can be delayed to those requiring it [15].

There are also issues related to diagnosis of AOM[9]. These include consensus on guidelines (clinical and use of otoscope), feasibility etc.

For children at risk of future episodes of AOM, the available evidence suggests that antibiotics given once or twice daily will reduce the probability of AOM while the child is on treatment [19]. In most cases of COM systemic antibiotic therapy is not required[20, 21], but may be of benefit in some cases[18].

Sinusitis

Sinusitis develops in about 5-10% of children with Upper respiratory infections[22]. The condition is usually diagnosed clinically by the presence of purulent nasal discharge especially from middle meatus, pain on pressure over sinuses etc. The bacteria responsible are similar to that causing otitis media – *S. pneumoniae* and *H influenzae*. *M. catarrhalis*, *S aureus* and anaerobes are also causative agents. Here again, there is no conclusive evidence to recommend routine antibiotic therapy. However, antibiotic therapy is recommended in some cases [22, 23].

The antibacterial drugs required for treating common upper and lower respiratory infections are discussed in detail below.

Amoxicillin Ampicillin	First line therapy for community acquired pneumonia, otitis media
Penicillin	For severe pneumonia including those in neonates, streptococcal sore throat
Amoxicillin plus Clavulanic acid	For penicillinase producing <i>H influenzae</i> infections – LRI and otitis media
Cloxacillin	For staphylococcal lung infection
Co - trimoxazole	Alternative therapy for community acquired pneumonia in resource poor settings
Erythromycin Azithromycin	Alternative in those with penicillin hypersensitivity and for LRI caused by organisms like mycoplasma, otitis media
Chloramphenicol	For epiglottitis caused by <i>H influenzae</i> , severe community acquired pneumonia
Gentamicin	For severe pneumonias of unknown aetiology in new born and children, to be used together with penicillin
Ceftriaxone / Cefotaxime	Severe community acquired pneumonia, hospital acquired pneumonia

Amoxicillin and ampicillin

Trials summarized in tables

Amoxicillin

[Addo Yobo 2004](#)

[Catchup, 2002](#)

[Harris,1998](#)

[Jibril,1989](#)

[Kogan, 2003](#)

[Strauss,1998](#)

[Tsarouhas,1998](#)

[APPIS group 2004](#)

[Appleman, 1991](#)

[Burke, 1991](#)

[Damoiseaux, 2000](#)

[Kaleida,1991](#)

[Van Buchem, 1981\(a\)](#)

[Van Buchem, 1981 \(b\)](#)

[Leelarasamee, 2000](#)

[Taylor, 1977](#)

Ampicillin

[Campbell,1988](#)

[Deivanayagam,1996](#)

[Campbell,1988](#)

[Halsted, 1968](#)

[Howie, 1972](#)

[Laxdal, 1970](#)

1. Formulation proposed for inclusion

[Amoxicillin](#) 250mg tab-cap for per oral use

Amoxicillin 125 mg/5ml suspension for per oral use

On WHO essential drug list – strength may be different

[Ampicillin](#) 250mg/vial or 500 mg/vial for injection

When parenteral therapy is indicated, ampicillin is used and is on WHO EDL

2. International availability (sources)

[Amoxicillin](#)

Tab-cap - UNFPA, MISSION, IMRES, JMS, MEDS, IDA, DURBIN, ORBI, ACTION

Powder for suspension -UNFPA, MEDS, MISSION, IDA, IMRES, JMS, DURBIN, ACTION, ORBI

[Ampicillin](#)

250 mg/vial –MEDS

500mg/vial – ACTION, IDA, IMRES, MEDS, UNFPA, JMS, ORBI, MISSION, DURBIN

3. Whether listing is requested as individual drug or as an example of a therapeutic group

Individual drugs

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Amoxicillin and ampicillin[24, 25] are amino penicillins and act by inhibiting synthesis of cell walls in bacteria. They are penicillinase susceptible and have similar antibacterial spectrum. They are active against most bacteria causing respiratory infections like *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* which do not

produce β lactamase. So they are used for a variety of respiratory tract infections. The drug also has activity against a few aerobic Gram negative bacilli and enterococci and so is also used for other infections including urinary infections.

Amoxicillin is acid stable and is absorbed rapidly and completely from GIT. Peak plasma concentrations are reached at 2 hours. Food does not interfere with absorption. Perhaps because of more complete absorption, incidence of diarrhea is less than that following administration of ampicillin. Effective concentrations of orally administered amoxicillin are detectable in the plasma for twice as long as with ampicillin and so require only less frequent dosing. Therefore this is the preferred oral agent[25]. Ampicillin is preferred for parenteral use –IM or IV. These drugs are distributed well in tissues and reaches therapeutic levels in pleural fluid and middle ear fluid. Drug entry into CSF is minimal when the meninges is normal. Most of the antibiotic is excreted in an active form in the urine.

Bacterial resistance to these antibiotics are already high in most areas. Resistance may be due to production of β -lactamases that destroy the antibiotics or due to alterations in or acquisition of novel penicillin-binding proteins (PBP). Decreased drug entry into the bacterium and/or active efflux of the antibiotic, as seen mostly in Gram negative bacteria, can also cause resistance. β lactamase mediated resistance, found in *H influenzae* can be overcome using a combination of amoxicillin and clavulanic acid which is a β lactamase inhibitor . Prevalence of this resistance varies and can be approximately 2-15% [26-28]. Resistance in *S. pneumoniae*, is PBP mediated and so cannot be overcome using clavulanic acid combination. Up to about 35% of *S. pneumoniae* isolated from community acquired pneumonias in the US show resistance to penicillins[3]. The prevalence varies in different areas[29-31]. In vitro resistance however, does not have a consistent relationship with clinical treatment failures[9]. Infections due to penicillin resistant pneumococci, especially the ones with intermediate resistance may respond to amoxicillin or ampicillin therapy but dosage may need to be increased [3, 25].

Mycoplasma pneumoniae, another agent of LRI in children does not have cell walls and so are naturally resistant to β lactam antibiotics. Amoxicillin may be of use in treating lung infections where anaerobes may be involved.

Therapeutic uses in respiratory infections

1. Community acquired pneumonia . For severe infections also oral amoxicillin is found to be effective
2. Otitis media where antibiotics are indicated [14, 32]
3. Sinusitis where antibiotics are required [22, 33]
4. Streptococcal tonsillo pharyngitis as an alternative to penicillin
5. Cystic fibrosis for bacterial infection

It is also used for prophylaxis during oral and respiratory procedures to prevent endocarditis in those at risk.

Dosage

Amoxicillin – 45 -90 mg/kg per day - depending on site of infection, severity of infection and possibility of penicillin resistant pneumococci [22, 25]- as 2-3 divided doses. Maximum dose is 2gm per day. For CAP, IMCI recommends 5 days [21]. Recent data shows that three days may be sufficient [9]

Ampicillin - IM or IV – 25mg/kg four times daily (three times daily for neonates)

When there is severe renal impairment (creatinine clearance < 10ml/min/1.73m²) dose or frequency is to be reduced. Can change to amoxicillin after clinical response.

Therapy for pneumonia, otitis media, sinusitis and sore throat can be initiated based on clinical diagnosis. Chest x-ray will help in confirming diagnoses and assessing severity of LRI. For documenting specific microbial pathogen and resistance patterns laboratory facility for culture and susceptibility testing is required.

Amoxicillin is recommended as an alternative for CAP and ear infections in WHO IMCI guidelines[21, 34]. Amoxicillin is also recommended for secondary bacterial infections following bronchiolitis[34]. It is recommended for AOM and sinusitis[10]. Other guidelines [3, 5, 14]also recommend this drug for these indications. Parenteral ampicillin is recommended for neonatal sepsis and in serious bacterial infections in malnourished children along with gentamicin[34]. Amoxicillin can be used for acute streptococcal pharyngitis[12]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection, /exclusion of particular data)

A recent Cochrane review has found amoxicillin [4] to be better than co- trimoxazole for community acquired pneumonia in two multicenter studies published in 2002 and 1998 respectively and involving 2054 children (1132 in the co-trimoxazole group and 922 in the amoxicillin group) between 2 months and 59 months of age. The diagnosis of pneumonia was based on clinical evidence. Both the studies were double-blinded and scored five points on the Jadad scale. The failure rate was significantly higher in the co-trimoxazole group compared to the amoxicillin group (OR 1.33; 95% CI 1.05 to 1.671). In one study involving 170 children aged 6 months to 18 years and comparing Amoxicillin with procaine penicillin (three on Jadad scale) failure rates were similar in the two groups (OR 0.75; 95% CI 0.17 to 3.25). On comparing amoxicillin with co-amoxiclavulanic acid, one open-label study involving 100 children between 2 and 12 years of age (two on Jadad scale) found that cure rate was better with co-amoxiclavulanic acid (OR 10.44; 95% CI 2.85 to 38.21). In a trial (2 on Jadad scale) involving 47 children aged between 1 m and 14 years with classical pneumonia comparing azithromycin with amoxicillin, all recovered in both groups[4]. Indirect comparisons done by the authors showed that cure rates were better in the amoxyiillin group compared to the chloramphenicol group (OR 4.26; 95% CI 2.57 to 7.08) and failure rates were lower in the amoxicillin group (OR 0.64; 95% CI 0.41 to 1.00).

The review [4] also compared treatment in hospitalised patients. Penicillin and amoxicillin performed equally well (as detailed in next para). On comparing Ampicillin with chloramphenicol plus penicillin, one trial involving 115 children between 5 months and 4 years of age (three on Jadad scale), showed cure rates (OR 0.48; 95% CI 0.15 to 1.51) and

duration of hospitalization to be similar in the two groups (weighted mean difference (WMD) 0.1; 95% CI -1.13 to 0.93)

Studies included in the review are summarised in table 1

Another Cochrane review to compare oral versus parenteral antibiotics for treatment of severe community acquired pneumonia, report on two studies[35]. Both found oral therapy to be as effective as parenteral therapy. One of those studies reported in 2004 evaluated 1702 patients comparing oral amoxicillin with intravenous penicillin for two days followed by oral amoxicillin. After 48 hours, treatment failure occurred in 161/845 (19%) in the amoxicillin group and 167/857 (19%) in the parenteral penicillin group. Recovery was similar in both groups at 5 and 14 days. Characteristics of these studies are in table 2.

To find out whether clinical failure rates due to increasing MIC of amoxicillin among *S pneumoniae* and *H influenzae* can be reduced, a randomised clinical trial was undertaken to compare standard dosage with double doses of amoxicillin. There was no significant difference in cure rates between the two regimes in children aged 2m to 59m with non – severe pneumonia. This recent report shows that treatment was effective in both groups[36], with a clinical failure rate of 5.9% on day 14 in the group receiving standard dosage. Another recent study reported that failure rates with amoxicillin is higher among HIV infected children with severe pneumonia compared to non infected and the authors have called for alternate empirical therapy regimens in areas with high HIV prevalence[37]

Otitis media

A Cochrane review found that all children with otitis media do not require antibiotic therapy, but antibiotics can benefit some groups [15]. Studies included in this review are summarised in table 3 Amoxicillin is effective for otitis media [38]. High dose (90mg/kg) amoxicillin is found useful for treating children with otitis media even when resistant bacteria were isolated[32]. High dose therapy is as effective as azithromycin treatment [39]

Sinusitis

There is no conclusive evidence to show that routine antibiotic therapy is useful[23, 40]. However, amoxicillin is recommended if one decides on antibiotic therapy[22, 23, 33].

There is also some evidence to show that amoxicillin use can facilitate colonisation with non susceptible organisms[41]

6. Summary of comparative evidence on safety

It is a safe drug in children[25].Hypersensitivity reactions are by far the most common adverse effects noted with the penicillins. The overall incidence of such reactions to the penicillins varies from 0.7% to 10% in different studies. Anaphylaxis occurs in less than 0.05%. Children who are allergic to one penicillin will be allergic to all other penicillins and may also be hypersensitive to cephalosporins and other β lactam antibiotics. A patient with manifest allergy to one penicillin is at a greater risk of reaction if another is given. Reactions may appear in the absence of a previous known exposure to the drug and with any dosage or form of penicillin. Manifestations include maculopappular rash, urticarial rash, fever, bronchospasm, and anaphylaxis. Rashes can occur due to reasons other than hypersensitivity and so has to be carefully evaluated before making a diagnosis of penicillin hypersensitivity. Chances of rash and severity are more in those suffering from EBV infection.

Diarrhoea and vomiting can occur and are more common in children. Antibiotic associated diarrhoea can also occur. Very large doses can cause CNS toxicity and convulsions.

7. Summary of available data on comparative cost

Tab –cap- US\$ 0.0147per 250 mg cap

Powder for suspension - 0.0037/ml ie 0.0185 for 5ml of 125 mg

Ampicillin injection – 250 mg- 0.1048/vial

500mg 0.1057/vial

8. Comparative cost effectiveness presented as range of cost per routine outcome (cost per case, cost per outcome etc)

Amoxicillin therapy with capsules is cheaper than with suspension and is only about one tenth the cost of parenteral therapy. Cost for one day with capsule is around US \$ 0.1

9. Summary of regulatory status

FDA approved

10. Availability of pharmacopoeial standards

Ampicillin is listed in US, European and International pharmacopoeias

Amoxicillin is listed in US and European pharmacopoeia

11. Proposed text for WHO model formulary

Amoxicillin/Ampicillin for oral/ parenteral use respectively

These have action against common pathogens causing community acquired pneumonia, acute otitis media and sinusitis

Uses in respiratory infections

Community acquired pneumonia, as first line therapy.

Otitis media as first line therapy

Sinusitis where antibiotics are required

Streptococcal tonsillo-pharyngitis as an alternative to penicillin

Dosage

Amoxicillin – 45 -90 mg/kg per day as 2-3 divided doses. Maximum dose 2gm/d.

Ampicillin - IM or IV – 25mg/kg four times daily (three times daily for neonates)

Contraindication

Hypersensitivity

Precautions

Check for hypersensitivity

When there is severe renal impairment (creatinine clearance < 10ml/min/1.73m²) dose or frequency is to be reduced

Adverse reactions - Low incidence

Hypersensitivity

Rash

Diarrhoea and vomiting

Antibiotic associated diarrhoea.

CNS toxicity and convulsions with large doses

Penicillin

Trials summarized in tables

[Addo Yobo 2004](#)

[Camargos,1997](#)

[Campbell,1988](#)

[Cetinkaya,2004](#)

[Deivanayagam,1996](#)

[Duke,2002](#)

[Keeley, 1990](#)

[Sidal,1994](#)

[Tsarouhas,1998](#)

[APPIS group 2004](#)

[Campbell,1988](#)

[Laxdal, 1970](#)

[Mygind, 1981](#)

[Thalin, 1985](#)

[Bennike, 1951](#)

[Chapple, 1956](#)

[Dagnelie, 1996](#)

[De Meyere, 1992](#)

[El Daher, 1991](#)

[Krober, 1985](#)

[Middleton, 1988](#)

[Nelson, 1984](#)

[Pichichero, 1987](#)

[Siegel, 1961](#)

[Whitfield, 1981](#)

[Zwart, 2003](#)

1. Formulation proposed for inclusion

Parenteral use

Benzyl Penicillin (Penicillin G sodium) 1mu as powder for reconstitution

Benzathine benzyl penicillin 1.2mu as powder for reconstitution

Procaine benzyl penicillin 1mu as powder for reconstitution

Oral use

Phenoxy methyl penicillin (Penicillin V)

Tab-cap - 250 mg

Suspension - 250 mg/5ml is available, but tab-cap maybe better

All drugs on WHO essential drug list – strength may be different

2. International availability (sources)

Penicillin G 1mu powder -IDA, UNFPA, MEDS, MISSION, IMRES, JMS, DURBIN, ORBI, ACTION

Procaine penicillin 1mu powder- UNFPA, MISSION, IMRES, IDA

Benzathine penicillin 1.2 mu powder– MISSION, IDA, IMRES, ORBI

Phenoxy methyl penicillin 250 mg tab –cap - IDA, UNFPA, MEDS, MISSION, IMRES, JMS, DURBIN, ORBI, ACTION

Phenoxy methyl penicillin 250 mg/5ml suspension

3. Whether listing is requested as individual drug or as an example of a therapeutic group

Individual drug

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Penicillin is a β lactam antibiotic which acts by inhibiting synthesis of bacterial cell wall[24]. It is susceptible to β lactamases produced by bacteria. Penicillin G is destroyed by gastric acid and is not recommended for oral use. After IM injection, peak plasma concentrations are obtained in 15 to 30 min. half life is only about 30 min. The drug diffuses well into tissues and fluids, but penetration into CSF is low when there is no meningeal inflammation. It is excreted in urine. To prolong therapeutic levels in the body, repository preparations are employed. Two such compounds in use are penicillin G procaine and penicillin G benzathine. Such agents release penicillin G slowly from the injection site and produce persistent concentrations of antibiotic in the blood. After an injection of procaine penicillin, peak levels are achieved in 1-3hrs and falls to very low levels in 24 hrs. After benzathine penicillin, antibiotic effect remains for an average of 26 days. Penicillin V is not destroyed by gastric acid and so can be administered orally.

Penicillin has activity against most Streptococci including *S. pyogenes* and *S. pneumoniae*. However, penicillin-resistant *S. pneumoniae* are becoming more common and are common in paediatric populations but prevalence varies [3, 29-31]. Penicillin resistance is PBP mediated in *S pneumoniae* and so cannot be overcome using β lactamase inhibitors. Many penicillin-resistant pneumococci are also resistant to third-generation cephalosporins. However, they still may respond to β lactam therapy.

More than 90% of Staphylococci are now resistant to penicillin. Among respiratory pathogens, *Corynebacterium diphtheriae* are susceptible to penicillin. With the exception of a few anaerobic Gram negative bacteria (eg *Bacteroides fragilis*) anaerobes are susceptible and so lung infections where anaerobes are involved may respond.

Therapeutic uses of penicillin in respiratory infection

Severe community acquired pneumonia (with gentamicin in some cases)

Empirical therapy of sepsis/pneumonia in neonates along with gentamicin

Streptococcal pharyngitis – there is virtually no resistance to penicillin among *S pyogenes* and it brings about 98% cure

Otitis media as an alternative to amoxicillin (penicillin G or V)

Diphtheria

Prophylactic use to prevent rheumatic fever after streptococcal infection

Dosage

Penicillin G

50,000units/kg every 6 hours. Change to oral after about 3 days

Can be administered intramuscular or slow intravenous or intravenous infusion. Intravenous route is recommended for infants and neonates. Use is in severe infections.

Penicillin V

125mg, 250 mg or 500mg orally 4 times a day – based on age and weight

This should not be used for severe infections. It is used for prophylaxis to prevent recurrent streptococcal infection in rheumatic fever. It can also be used for streptococcal tonsillo-

pharyngitis, otitis media and for continuing therapy after clinical response with benzyl penicillin. Cure rate may be lower than with benzathine penicillin for tonsillo-pharyngitis[10].

Prophylaxis – 1m to 6yrs-125 mg; 6yrs to 18 yrs-250 mg - twice daily

Procaine penicillin – is added in some areas to benzathine penicillin[10]

Benzathine penicillin – 1.2 mu IM once for therapy of acute streptococcal tonsillo-pharyngitis. Single dose therapy ensures compliance and decreases cost. For prophylaxis, the drug is given every 3-4 wks. (for children less than 6yrs 0.6mu is used)[10]

Reduce dose if severe renal impairment

Treatment with penicillin is initiated based on clinical diagnosis for pneumonia, tonsillo-pharyngitis, neonatal pneumonia/sepsis and for diphtheria.

Penicillin G is recommended as first line therapy for children with severe CAP and second line along with gentamicin for very severe CAP [34]. It is also recommended for use as pre referral single dose [21]. It is recommended along with gentamicin for children aged 1wk to 2m with serious bacterial infections (including pneumonia) and in neonatal sepsis [21, 34]. It can be used in secondary bacterial infections following bronchiolitis[34]. Penicillin – oral or parenteral (benzathine G or mixture of benzathine and procaine as single dose) – is recommended for acute streptococcal pharyngitis [12, 13]. It is also an alternative for treating AOM [10]. BNF C also recommends penicillin for severe community acquired lobar pneumonia and in neonates [5]. For diphtheria procaine penicillin is recommended for 7 days[34]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection, /exclusion of particular data)

Pneumonia

The Cochrane review found that penicillin is a good option for hospitalised patients with pneumonia [4] and performance is similar to amoxicillin. Failure rates were similar in children treated either with amoxicillin or procaine penicillin. For severe pneumonia also injectable penicillin and amoxicillin performed equally well. Comparison between procaine penicillin and benzathine penicillin showed that cure rates were not significantly different between the two groups (OR 0.53; 95% CI 0.27 to 1.01), but failure rates were lower in the procaine penicillin group (OR 3.31; 95% CI 1.45 to 7.55). Two studies in this review showed that procaine penicillin is significantly better than co-trimoxazole for cure (OR 2.64; 95% CI 1.57 to 4.45). On comparing chloramphenicol with penicillin and gentamicin for severe pneumonia, need for change in antibiotics, death rates and adverse events were similar in the two groups. However, re-admission rates before 30 days favoured the penicillin-gentamicin combination (OR 1.6; 95% CI 1.02 to 2.55).

Another Cochrane review to compare oral versus parenteral antibiotics for treatment of severe community acquired pneumonia, report on a study which evaluated 1702 patients comparing oral amoxicillin with intravenous penicillin for two days followed by oral amoxicillin. After 48 hours, treatment failure occurred in 161/845 (19%) in the amoxicillin group and 167/857 (19%) in the parenteral penicillin group. Recovery was similar in both groups at 5 and 14 days [35].

Tonsillo -pharyngitis

A Cochrane review has concluded that antibiotic treatment of sore throat significantly reduces incidence of acute rheumatic fever and suppurative complications like otitis media, sinusitis and quinsy, although effect on recovery from sore throat itself is minimal [11]. Characteristics of studies included in this review are summarised in table 4. Acute rheumatic fever was reduced to about one quarter that in the placebo group (RR 0.27; 95% CI 0.12 to 0.60). Few studies examined antibiotics other than penicillin. Confining the analysis to penicillin alone resulted in no difference in estimated protection (RR 0.27; 95% CI 0.14 to 0.50). This review included both adults and children.

For neonatal sepsis penicillin is used with gentamicin. For treatment of sepsis, β lactams alone are as effective as combination with aminoglycosides [42]

6. Summary of comparative evidence on safety

Penicillin is a relatively safe drug. Hypersensitivity is the major adverse event and can occur in upto 10% exposed individuals. Anaphylaxis occurs in <0.05%. Children who are allergic to one penicillin will be allergic to all other penicillins and may also be hypersensitive to cephalosporins and other β lactam antibiotics. Reactions may appear in the absence of a previous known exposure to the drug and with any dosage or form of penicillin. Manifestations include maculopapular rash, urticarial rash, fever, bronchospasm, and anaphylaxis.

CNS toxicity including convulsions can occur with high doses or renal impairment. Interstitial nephritis, haemolytic anaemia, leucopenia, thrombocytopenia, coagulation disorders etc are also described

Antibiotic associated diarrhoea can follow oral preparations

Procaine related toxicity like dizziness, tinnitus, and head ache can occur with this formulation

IM injections cause local pain

7. Summary of available data on comparative cost

Penicillin G 1 mu – US\$ 0.0655/vial

Procaine penicillin 1mu – US\$ 0.0781/vial

Benzathine penicillin 1.2 mu – US\$ 0.1010/vial

Phenoxy methyl penicillin 250 mg tab –cap – US\$ 0.0120

Phenoxy methyl penicillin 250 mg/5ml suspension– buyer price US \$ 0.0082/ml

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

Benzathine penicillin for a course (one injection) is US\$ 0.1010. Oral penicillin for a similar course is at least US \$ 0.24

9. Summary of regulatory status

FDA approved

10. Availability of pharmacopoeial standards

All formulations listed in US and European pharmacopoeias. International pharmacopoeia has penicillin V listed

11. Proposed text for WHO model formulary

Penicillin – benzyl, procaine benzyl, benzathine benzyl, phenoxymethyl penicillin

Has action on several pathogens causing acute upper and lower respiratory infections

Therapeutic uses of penicillin in respiratory infection

Severe community acquired pneumonia

Empirical therapy of sepsis/pneumonia in neonates

Streptococcal pharyngitis

Otitis media as an alternative to amoxicillin (penicillin G or V)

Diphtheria

Prophylactic use to prevent rheumatic fever after streptococcal infection

Dosage

Penicillin G- 150,000units/kg/day in four divided doses IM or IV

Intravenous route is recommended for infants and neonates.

Penicillin V- 125mg, 250 mg or 500mg PO 4 times a day – based on age and weight

Prophylaxis – 1m to 6yrs-125 mg; 6yrs to 18 yrs-250 mg – twice daily

Procaine penicillin – 25,000 to 50,000 units/kg/day IM or (0.6 or 1.2mu IM/day)

Benzathine penicillin – 1.2 mu IM once for therapy of acute streptococcal tonsillo-pharyngitis.
For prophylaxis, every 3-4 wks.

Contraindications

Hypersensitivity

Precautions

Check for hypersensitivity

Reduce dose if severe renal impairment

Adverse events - Low incidence

Hypersensitivity

CNS toxicity including convulsions with high doses or renal impairment

Antibiotic associated diarrhoea can follow oral preparations

Interstitial nephritis, haemolytic anaemia, leucopenia, thrombocytopenia, coagulation disorders are reported

Procaine related toxicity- dizziness, tinnitus, and head ache

IM injections cause local pain

Cloxacillin

1. Formulation proposed for inclusion

Cloxacillin

250 mg capsule for oral use

125mg/5ml – as powder for reconstitution as syrup or elixir for oral use

250 mg vial – as powder for reconstitution for parenteral use

Listed on WHO EDL as example of a therapeutic group

2. International availability (sources)

250 mg tab-cap – IDA, UNFPA, MEDS, MISSION, IMRES, JMS, DURBIN, ORBI, ACTION

125mg/5ml suspension – IDA, UNFPA, MEDS, MISSION, DURBIN

250 mg vial for injection – MEDS

3. Whether listing is requested as individual drug or as an example of a therapeutic group

As example of a therapeutic group – penicillinase resistant penicillin

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Cloxacillin is a penicillinase resistant anti staphylococcal penicillin [24]. This narrow spectrum penicillin is not destroyed by gastric acid and is well absorbed from GIT especially on empty stomach. However, the absorption may be variable and so parenteral route is used for severe infections. Dicloxacillin is better absorbed than cloxacillin. This difference does not seem to have any clinical significance. The drug is excreted mainly through the kidneys – but dose adjustments are not usually required in renal failure.

About 90% of staphylococci produce penicillinase and are penicillin resistant. Penicillinase resistant penicillins like cloxacillin is the drug of choice for treating penicillin resistant methicillin susceptible *S aureus* infections[43].

S aureus is responsible for a small proportion of severe CAP in children in different parts of the world[4, 44]. This may be associated with viral infections like influenza[45] and measles[46]. *S aureus* can cause pneumonia/sepsis in the new borns also[47]. It is a nosocomial pathogen involved in ventilator associated pneumonias as well. Without appropriate antimicrobial therapy, these infections progress rapidly. MRSA is resistant to this group of drugs. The prevalence of MRSA varies and is now known to cause community acquired infections as well [45].

Indications for use in respiratory illnesses

Staphylococcal pneumonia

1. Empyema due to *S aureus*

Otitis externa due to staphylococci

Staphylococcal lung infection in cystic fibrosis

Dosage

Oral or parenteral – 50mg/kg every 6 hrs for 3 weeks[34]

For neonates frequency is reduced

Staphylococcal infections are diagnosed based on culture. Lung infections due to staphylococci can be suspected based on x ray findings[34]. Cloxacillin is recommended for staphylococcal lung infection and empyema, along with gentamicin[34]. If there is no response to penicillin plus gentamicin, then penicillin is replaced with cloxacillin in children with severe pneumonia[34]. Therapy in severe infection is initiated with parenteral preparation and later changed to oral[34]. Neonatal staphylococcal sepsis also cloxacillin is recommended[34].

It is recommended as second line therapy, if amoxicillin fails, in pneumonias occurring in children with measles[46]. BNF C recommends flucloxacillin for staphylococcal pneumonia[5]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection, /exclusion of particular data)

Cloxacillin is has proven use in treating staphylococcal infections. It is found useful for treating pneumonia due to methicillin susceptible *S aureus* as well[48]

6. Summary of comparative evidence on safety

Incidence of adverse events is low[49]. Cholestatic jaundice and hepatitis with elevation of AST, ALT, bilirubin, and LDH can occur even several weeks after therapy. Therefore, it has to be used with caution in hepatic diseases. Avoid if previous cloxacillin related hepatic events have occurred.

Other events recorded include glossitis, stomatitis, gastritis, nausea/vomiting, rash, hemolytic anemia, superinfection, pseudomembranous colitis, seizures, interstitial nephritis, vaginitis, anorexia, hyperthermia and itchy eyes.

Risk of hypersensitivity is similar to other β lactams.

7. Summary of available data on comparative cost

250 mg tab-cap – US \$ 0.0147

125mg/5ml suspension –US \$ 0.0037/ml

250 mg vial – US \$ 0.1048/vial

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

This drug has only limited use in treatment of respiratory infections, but where it is specifically required there is no alternative. Oral therapy is cheaper than parenteral therapy. Cost per day for 250 mg cap will be US \$ 0.06 compared to 0.15 for suspension.

9. Summary of regulatory status

FDA approved

10. Availability of pharmacopoeial standards

Listed in US, International and European pharmacopoeias.

11. Proposed text for WHO model formulary

Cloxacillin – for oral and parenteral use

This is a narrow spectrum antimicrobial effective against methicillin susceptible staphylococci

Use in respiratory infections

Staphylococcal lung infections, including those in cystic fibrosis

Otitis externa due to staphylococci

Dosage

>20 kg - 250- 500mg every 6 hrs;

<20 kg – 50-100mg every 6 hrs

For neonates frequency is reduced

Contra indication

Hypersensitivity to penicillin group of drugs

Previous cloxacillin related hepatic events

Precaution

Check for hypersensitivity

Use with caution in hepatic diseases

Adverse events - Low incidence

Hypersensitivity

Cholestatic jaundice and hepatitis can occur even several weeks after therapy.

Co-amoxiclavulanic acid

Trials summarized in tables

[Wubbel,1999](#)

1. Formulation proposed for inclusion

Amoxicillin (as trihydrate or sodium salt) + Clavulanate as potassium salt

125mg+31mg per 5ml suspension

250mg+125mg tablets

Other combinations of strength are available. Parenteral preparations are also available

It is listed on WHO EDL – but another strength

2. International availability (sources)

125/31 suspension - MEDS, ORBI

250/125 tab - MEDS, DURBIN, JMS

3. Whether listing is requested as individual drug or as an example of a therapeutic group

Individual drug

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Combining amoxicillin with clavulanic acid, a β lactamase inhibitor, protects amoxicillin from destruction by β lactamases produced by amoxicillin resistant bacteria like *S aureus*, *H. influenzae*, and some strains of *E coli* and *K pneumoniae* Clavulanic acid itself has minimal antibacterial action[24].

Therapeutic use in respiratory infections

LRI, otitis media and sinusitis due to β lactamase producing organisms like *H influenzae*. Decision to use this drug is usually taken using culture and susceptibility data or following clinical failure with first line drugs. It is an alternative to azithromycin or erythromycin in this situation.

For staphylococcal infections - cloxacillin is a better option.

Dosage

45mg/kg/day of amoxicillin (max 2gm)

Maximum dose of clavulanate not to exceed 6.4 mg/kg/day[14].

If higher doses of amoxicillin are required, amoxicillin alone can be given to a dose of up to 90mg/kg/day along with the combination.

To be used only as second line therapy for clinical failure or for proven infections due to resistant organisms.

Recommended as alternative to amoxicillin for sinusitis[10] and otitis media[14] and for CAP as an alternative[5]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection, /exclusion of particular data)

Cure rate was better with co-amoxiclavulanic acid (OR 10.44; 95% CI 2.85 to 38.21) as compared to amoxicillin, in one open-label study involving 100 children between 2 and 12 years of age suffering from clinically diagnosed bacterial pneumonia [4]. Co-amoxyclovulanic acid was compared with azithromycin in two studies involving 283 children below five years of age. The cure rates, failure rates (OR 1.21; 95% CI 0.43 to 3.43) and improvement rates (OR 0.85; 95% CI 0.43 to 1.71) were similar in the two groups. There were fewer side effects reported in the with azithromycin group (OR 0.17; 95% CI 0.09 to 0.32). Comparison with cefpodoxime in one multicenter study on 348 children between 3 months and 11.5 years of age, showed that the response rate at the end of 10 days of treatment was comparable in the two groups for pneumonia (OR 0.69; 95% CI 0.18 to 2.6).

Amoxicillin is the first line drug when antimicrobials are required for treating otitis media. Several trials have shown that Co-amoxiclav is effective and at least equal to azithromycin [50-52] for this condition.

6. Summary of comparative evidence on safety

Adverse events including hypersensitivity may be similar to that found with amoxicillin. Diarrhoea is more frequent with the combination as compared to amoxicillin alone[53] Cholestatic jaundice can occur and liver toxicity which is reversible is more common with the combination than with amoxicillin alone. Serious complications, however, are very rare in children

There were fewer side effects reported in the azithromycin group (OR 0.17; 95% CI 0.09 to 0.32) compared to Co- amoxiclav in a Cochrane review [4]. Adverse events were less in Azithromycin (11-14%) treated groups compared to co- amoxiclav (17-67%)in another Cochrane review also[54]. The majority of adverse events were related to the gastrointestinal tract (diarrhoea, vomiting, abdominal pain, nausea, anorexia) and were more common in children under five years of age.

Dose or frequency may need to be reduced in renal impairment

7. Summary of available data on comparative cost

125+31/5ml suspension – US \$ 0.0336/ml

250 +125 tab –cap – US \$ 0.3136/tab

8. Comparative cost effectiveness presented as range of cost per routine outcome (cost per case, cost per outcome etc)

For a daily dose of 1gm, the cost per day will be about US\$ 1.3 for tab and 1.4 for suspension. For azithromycin which is used for similar indications, cost of therapy (250 mg) for a day is approximately US \$ 0.3 for tab and suspension.

9. Summary of regulatory status

FDA approved

10. Availability of pharmacopoeial standards

Amoxicillin and clavulanate are listed separately in US and European pharmacopoeias

11. Proposed text for WHO model formulary

Amoxicillin and clavulanic acid for oral use

Amoxicillin is the active ingredient and has action against several respiratory pathogens. Because of the presence of clavulanate the combination is active against β lactamase producing organisms as well.

Therapeutic use in respiratory infections

Pneumonia, otitis media and sinusitis due to β lactamase producing organisms, based on susceptibility data or following clinical failure with first line drugs.

Dosage

45mg/kg/day of amoxicillin (max 2gm)

Maximum dose of clavulanate not to exceed 6.4 mg/kg/day

Contra indications

Hypersensitivity

Precautions

Check for hypersensitivity

Reduce dose in severe renal impairment

Adverse events

Hypersensitivity

Diarrhoea, vomiting, nausea

Antibiotic associated diarrhoea

Cholestatic jaundice

Erythromycin/azithromycin

[Block 1995](#)

[Kogan, 2003](#)

[Roord, 1996](#)

[Roord, 1996](#)

[Howie, 1972](#)

[Wubbel,1999](#)

[Harris,1998](#)

1. Formulation proposed for inclusion

Erythromycin

For oral use stearate or ethyl succinate

250 mg tab –cap

125mg/5ml powder for reconstitution for suspension

Parenteral preparations available as lactobionate

Azithromycin

Capsule 250 mg

Oral suspension – 200mg/5ml powder for reconstitution

Erythromycin is listed on WHO EDL. Azithromycin is listed for treating chlamydia infections only.

2. International availability (sources)

Erythromycin

250 mg tab –cap – UNFPA, MEDS, IMRES, IDA, MISSION, ORBI, DURBIN, ACTION, JMS

125mg/5ml powder - UNFPA, MEDS, IMRES, IDA, MISSION, DURBIN, ACTION, JMS

Azithromycin

Capsule 250 mg -MISSION

Oral suspension – 200mg/5ml - MISSION

3. Whether listing is requested as individual drug or as an example of a therapeutic group

As individual drugs

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Erythromycin and azithromycin are macrolide antibiotics and act by inhibiting protein synthesis in bacteria. Their spectrum of activity is similar to that of penicillin and so is used as an alternative to penicillin in those hypersensitive. About 15% of *S pneumoniae* isolated in the US from community acquired pneumonia are resistant to macrolides[3]. Macrolide resistance is usually found in penicillin resistant strains. About 40% of *S. pyogenes* are also macrolide resistant. Macrolides are active against other bacteria that cause respiratory infections like Mycoplasma, Chlamydiae and Legionella. Most penicillin resistant staphylococci are also susceptible. Action of erythromycin on *H influenzae* is poor.

Azithromycin has better activity against *H influenzae* but action is slightly lesser against Gram positive bacteria as compared to erythromycin.

Upto 40% of LRI in children are believed to be due to Mycoplasma and are more common in children above 5 yrs. However problems with specific diagnosis of mycoplasma infections make estimates of prevalence variable and sometimes unreliable.

Both erythromycin and azithromycin are absorbed well from GIT. Azithromycin has a long tissue half life and so once daily dose is used. Compliance is better with this drug because of dosing schedule and fewer side effects.

Indications for use

1. Alternative to penicillin/amoxicillin in those hypersensitive
2. LRI -

In some guidelines, azithromycin is recommended as first line therapy for children above 5 yrs with non severe CAP [3]. For those below five years, this drug is added if there is no clinical response with amoxicillin after 48 hrs.

3. Otitis media – this is one of the second line drugs, if there is no response to amoxicillin[14]
4. Pertussis

Dosage

Erythromycin -Neonate – 20-40mg/kg/d in 4 divided doses

Azithromycin- Child over 2months – 10mg/kg once a day (max 500mg)

The drug is used following clinical diagnoses.

WHO recommends erythromycin for pertussis[34]. Erythromycin/ azithromycin is recommended for otitis media[14] and sinusitis[10] as an alternative. It is also recommended for CAP in those allergic to penicillin and if there is clinical failure with amoxicillin [3]. According to this guideline, azithromycin may be used as first choice in children above 5 yrs. BNF C also has similar recommendations [5]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection, /exclusion of particular data)

In a trial involving 47 children aged between 1 m and 14 years with classical pneumonia, comparing azithromycin with amoxicillin, all recovered in both groups[4]. Co-amoxyclovulanic acid was compared with azithromycin in two studies involving 283 children below five years of age. The cure rates, failure rates (OR 1.21; 95% CI 0.43 to 3.43) and improvement rates (OR 0.85; 95% CI 0.43 to 1.71) were similar in the two groups. Comparing erythromycin with azithromycin or clarithromycin also showed no significant differences[4].

A Cochrane review attempted to evaluate therapy for mycoplasma infections in children[54]. Aetiological diagnosis was not stated in most included studies (only 38 children with mycoplasma infection identified) but compared macrolides with β lactam antibiotics for LRI in 1352 children. There were no major differences between treatment groups. No conclusion is drawn on effective therapy for mycoplasma infections.

Macrolides can also be used for prophylaxis in those with cystic fibrosis. A review on this issue including both children and adults found that there is a small but significant improvement in respiratory function following treatment with azithromycin[55].

It is shown to be effective for treating otitis media and comparable to Co-amoxiclav [39, 50, 51]

6. Summary of comparative evidence on safety

Incidence of adverse events is low. Macrolides can cause GI disturbances like nausea, vomiting and diarrhoea.

QT interval prolongation and ventricular tachycardia are serious complications. Electrolyte disturbances, anaemia, leucopenia, renal and hepatic toxicity, allergy, reversible hearing loss, cholestatic jaundice, pancreatitis, myasthenia, Steven Johnson's syndrome, super infection with Candida etc are also recorded. Rashes and generalised exanthematous pustular eruptions can also occur.

There were fewer side effects reported in the with azithromycin group (OR 0.17; 95% CI 0.09 to 0.32) compared to Co- amoxiclav in a Cochrane review [4]. Another Cochrane review showed adverse events in 11-14% of Azithromycin treated children compared to 25 % in erythromycin; both drugs were better tolerated than co- amoxi clav where 17-67% had adverse events [54]. Majority of adverse events were related to the gastrointestinal tract (diarrhoea, vomiting, abdominal pain, nausea, anorexia) and were more common in children under five years of age.

7. Summary of available data on comparative cost

Erythromycin

250 mg tab –cap –US \$ 0.0236

125mg/5ml powder – US \$ 0.0091/ml

Azithromycin

Capsule 250 mg – US \$ 0.2417

Oral suspension – 200mg/5ml – US \$ 0.0500/ml

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

For azithromycin, cost of oral therapy (250 mg) for a day is approximately US \$ 0.3. Single daily dose of this drug may facilitate compliance.

Erythromycin tab – cap will cost less than US \$0.1 per day. For Co-amoxiclav, which is used for similar indications, a daily dose of 1gm will cost about US\$ 1.3 for tab and 1.4 for suspension.

9. Summary of regulatory status

Both erythromycin and azithromycin are FDA approved

(Azithromycin is licensed for respiratory infection, otitis media and cystic fibrosis)

10. Availability of pharmacopoeial standards

Erythromycin is listed in US, International and European pharmacopoeias

Azithromycin is listed in US and European pharmacopoeias

11. Proposed text for WHO model formulary

Erythromycin/azithromycin

These are active against several respiratory pathogens including *Mycoplasma pneumoniae*, *Legionella* spp and *Chlamydia* spp.

Indications for use

1. Alternative to penicillin/amoxicillin in those hypersensitive
2. Community acquired LRI if there is no response to first line therapy
3. Otitis media if there is no response to first line therapy
4. Pertussis

Dosage

Erythromycin -Neonate – 20-40mg/kg/d in 4 divided doses

Azithromycin- Child over 2months – 10mg/kg once a day (max 500mg)

Contraindication

Precaution

Co-administration of drugs that can cause QT prolongation

Adverse events

GI disturbances like nausea, vomiting and diarrhoea.

QT interval prolongation

Electrolyte disturbances, renal and hepatic toxicity, allergy, reversible hearing loss, cholestatic jaundice, pancreatitis, myasthenia, Steven Johnson's syndrome etc are also recorded.

Chloramphenicol

Trials summarized in tables

[Cetinkaya,2004](#)

[Mullholland,1995](#)

[Deivanayagam,1996](#)

[Shann,1985](#)

[Duke,2002](#)

1. Formulation proposed for inclusion

Chloramphenicol 250mg capsules for oral use

1gm vial for parenteral use

This is listed on WHO EDL – strength may be different

2. International availability (sources)

250 mg cap - UNFPA, MEDS, IMRES, IDA, MISSION, ORBI, DURBIN, ACTION, JMS

1 gm vial - UNFPA, MEDS, IMRES, IDA, MISSION, DURBIN, ACTION, JMS

3. Whether listing is requested as individual drug or as an example of a therapeutic group

Individual drug

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Chloramphenicol is a broad spectrum antibiotic which acts by inhibiting bacterial protein synthesis. It is active against *H. influenzae*, *S. pneumoniae* and *Bordetella pertussis*. Most anaerobic bacteria, including gram-positive cocci, *Clostridium* spp., and gram-negative rods including *B. fragilis* are susceptible. Chloramphenicol is active against *Mycoplasma*, *Chlamydia*, and *Rickettsia*. It is absorbed rapidly from the gastrointestinal tract, and peak concentrations occur within 2 to 3 hours. The drug is widely distributed in body fluids.

Bone marrow suppression is a major adverse event and so the drug is generally used only for severe infections.

Uses in respiratory infections [34]

First line therapy for very severe CAP in children

First line therapy for empyema

Alternative for neonatal sepsis

Alternative for pertussis

CAP and child is unconscious or cannot tolerate oral antimicrobials

Severe secondary bacterial infections following bronchiolitis

Dosage

25mg/kg every 8hrs Initiate with parenteral therapy and change to oral later. In neonates dose and frequency is reduced.

Total duration of therapy for severe infections is 10 days. For empyema, 4 wks treatment is recommended [34]

Treatment with this drug can be initiated based on clinical diagnosis of severe pneumonia and sepsis [34]. WHO also recommends that one doze of chloramphenicol is given to children with CAP who are unconscious, in shock or vomiting incessantly [21] before referring. Chloramphenicol is recommended as alternative or second line therapy for pneumonia [46] and for epiglottitis[5, 10]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection, /exclusion of particular data)

On comparing chloramphenicol with penicillin and gentamicin for severe pneumonia, need for change in antibiotics, death rates and adverse events were similar in the two groups. However, re-admission rates before 30 days favoured the penicillin-gentamicin combination (OR 1.6; 95% CI 1.02 to 2.55)[4]. On comparing chloramphenicol with co-trimoxazole in 111 malnourished children below five yrs in the year 1995, cure rates (OR 1.06; 95% CI 0.47 to 2.40), failure rates (OR 1.03; 95% CI 0.45 to 2.33), number of patients requiring a change in antibiotics (OR 1.42; 95% CI 0.46 to 4.40), relapse rates (OR 1.02; 95% CI 0.24 to 4.30) and death rates (OR 2.21; 95% CI 0.63 to 7.83) were similar in the two groups.

6. Summary of comparative evidence on safety

Bone marrow suppression is the most serious adverse event. Therefore blood count has to be monitored. Risk may be more in hepatic impairment. It is better to avoid it in severe renal impairment. Neonates, especially if premature, may develop gray baby syndrome.

Other side effects include nausea, vomiting, unpleasant taste, and diarrhoea. Rarer toxic effects include blurring of vision, digital paresthesias, encephalopathy and cardiomyopathy.

Chloramphenicol inhibits hepatic cytochrome P450 isozymes and prolongs the half-lives of drugs like warfarin, dicumarol, phenytoin, chlorpropamide, antiretroviral protease inhibitors, rifabutin, and tolbutamide. Concurrent administration of phenobarbital or rifampin, shortens the half-life of the antibiotic.

7. Summary of available data on comparative cost

250 mg cap – US \$ 0.0119/cap

1gm vial for parenteral use – 0.2238/vial

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

Cost for one day oral therapy is less than US \$ 0.1

9. Summary of regulatory status

FDA approved

10. Availability of pharmacopoeial standards

Chloramphenicol is listed in US, International and European pharmapoeias

11. Proposed text for WHO model formulary

Chloramphenicol for oral and parenteral use

Chloramphenicol has a broad spectrum of activity and is active against several respiratory pathogens

Use in respiratory infection

Very severe CAP

Empyema

Children in shock, unconscious or vomiting as a pre referral dose

Epiglottitis

Pertussis

Dosage

50-100mg/kg/day in four divided doses

Contraindications

Severe renal and hepatic impairment

Precaution

Monitor blood count.

Consider drug interactions

Adverse events

Bone marrow suppression - risk may be more in hepatic impairment.

Gray baby syndrome

Nausea, vomiting, unpleasant taste, and diarrhoea

Rarer toxic effects - blurring of vision, digital paresthesias, encephalopathy and cardiomyopathy

Co-trimoxazole

Trials summarized in tables

[Catchup, 2002](#)

[Campbell, 1988](#)

[Keeley, 1990](#)

[Mullholland, 1995](#)

[Sidal, 1994](#)

[Strauss, 1998](#)

[Taylor, 1977](#)

1. Formulation proposed for inclusion

Sulphamethoxazole- trimethoprim – 100 + 20 mg tablets

Oral suspension – 200 + 40 mg/5ml

Other strengths are also available

It is listed in WHO EDL

2. International availability (sources)

100+20 tab – MISSION, IDA, IMRES, DURBIN, ORBI, JMS

200+40/5ml – MISSION, IDA, IMRES, ORBI, JMS, MEDS, UNFPA, DURBIN, ACTION

3. Whether listing is requested as individual drug or as an example of a therapeutic group

As individual drug

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Combination of sulpha methoxazole and trimethoprim (co – trimoxazole) is synergistic since the two drugs act on sequential steps of an enzymatic reaction necessary for synthesis of tetrahydrofolic acid. The drug has activity against Staphylococci, Streptococci including *S pneumoniae*, *H.influenzae* and a variety of Gram negative bacilli. A good proportion of isolates belonging to these species are now resistant to this drug limiting its clinical utility.

After a single oral dose of the combined preparation, trimethoprim is absorbed more rapidly than sulfamethoxazole. Peak blood concentrations of trimethoprim usually occur by 2 hours, whereas peak concentrations of sulfamethoxazole occur by 4 hours after a single oral dose. The half-lives of trimethoprim and sulfamethoxazole are approximately 11 and 10 hours, respectively.

Use in bacterial respiratory infection

1. This drug is used for LRI. However, there is mounting resistance to this drug among respiratory pathogens and so many authorities do not recommend this for empirical therapy of bacterial infections in the respiratory tract. It can be used if there is bacteriological evidence for susceptibility. However, in resource poor settings, where other superior drugs are not accessible, this drug is still used. WHO recommend this drug for community management of non severe pneumonia. In this situation, children should be closely monitored for response.

2. Other uses include therapy of acute otitis media and secondary bacterial LRI following bronchiolitis
3. It is currently recommended as drug of choice for prophylaxis and treatment of *pneumocystis jiroveci* pneumonia, treatment of toxoplasmosis and nocardiosis.
4. Using this drug for prophylaxis in children with HIV infection reduced mortality, mainly from respiratory infections, in one study in a developing country[56, 57]. Such prophylaxis may be of use in neonates born to HIV infected mothers also.

Dosage for bacterial infections

20 + 4mg/kg twice daily for 5 days

For respiratory infections, antibiotic therapy is initiated based on clinical evidence.

Co trimoxazole is recommended as first line therapy for non severe CAP and acute ear infections [20, 21]. It is also recommended as an alternative for sinusitis[10]. It can be used for secondary bacterial infections following bronchiolitis[34]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection, /exclusion of particular data)

A recent Cochrane review has found amoxicillin [4] to be better than co- trimoxazole for community acquired pneumonia. Two multicenter double blinded studies in children between 2 m and 59m of age showed that failure rate was significantly higher in the co-trimoxazole group compared to the amoxicillin group (OR 1.33; 95% CI 1.05 to 1.671). Two studies in this review also showed that procaine penicillin is significantly better than co-trimoxazole for cure (OR 2.64; 95% CI 1.57 to 4.45). In 111 malnourished children, co-trimoxazole and chloramphenicol showed similar results.

In a more recent study, failure rate was 11.6% with Co-trimoxazole [58]. But the authors conclude that this is an acceptable drug for management of non severe pneumonia at first level health facility. Co-trimoxazole along with monitoring for treatment failures using tested criteria [59] may be an option for community level management of pneumonia.

A Cochrane review identified one study on 534 children, which met the criteria for inclusion, on effect of prophylaxis in HIV infected children. Prophylaxis with Co trimoxazole significantly reduced mortality[56]. The excess mortality in the placebo group was mainly due to respiratory infections [57]. Bacterial resistance to Co-trimoxazole is high in the study area. Antimicrobial use for serious infections was also significantly higher in the placebo group.

6. Summary of comparative evidence on safety

There is very little toxicity and is mostly skin related. Exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis are reported, mostly in older individuals.

GI events like nausea and vomiting can occur. Glossitis, stomatitis, mild and transient jaundice, headache, depression, and hallucinations are reported. It is better to avoid this drug in those with hepatic impairment.

Hematological effects include anemias, coagulation disorders and granulocytopenia. Renal dysfunction can also occur. Dose may be reduced if there is renal dysfunction

It should be avoided in children below 1m of age [21] because of risk of kernicterus. Use in HIV prophylaxis is an exception.

7. Summary of available data on comparative cost

100+20 tab – 0.0027/tab

200+40 suspension – 0.0037/ml

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

For one day the cost of treatment is approximately US\$ 0.04 compared to US\$ 0.1 for amoxicillin

9. Summary of regulatory status

FDA approved

(According to BNF C it is not licensed for use in children under 6 wks)

10. Availability of pharmacopoeial standards

Sulfamethoxazole and trimethoprim are listed separately in US, International and European pharmacopoeias

11. Proposed text for WHO model formulary

Co trimoxazole for oral use

Co-trimoxazole has action on bacteria causing respiratory infections. However, resistance is increasing.

Indications for use (bacterial respiratory infections)

Community management of non severe pneumonia

Acute otitis media

Prophylaxis for children with HIV infection

Dosage for bacterial infections

20 + 4mg/kg twice daily

Precautions

Children with pneumonia should be monitored for response.

Use with caution in hepatic impairment

Dose may be reduced if there is renal dysfunction

Avoid in children below 6 wks of age (except for pneumocystis prophylaxis) because of risk of kernicterus

Contraindications

Adverse events

Low incidence- skin related mostly -rash, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis

Nausea, vomiting, glossitis, stomatitis, mild and transient jaundice, headache, depression, hallucinations, anaemia, coagulation disorders, granulocytopenia

Gentamicin

Trials summarized in tables

[Duke,2002](#)

1. Formulation proposed for inclusion

40mg/ml for parenteral use

10mg/ml for parenteral use

Listed in WHO EDL

2. International availability (sources)

10mg/ml – MEDS, UNFPA, MISSION, IDA

40mg/ml – UNFPA, IDA, IMRES, MEDS, MISSION, JMS, DURBIN, ORBI, ACTION

3. Whether listing is requested as individual drug or as an example of a therapeutic group

Individual drug

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Gentamicin is an aminoglycoside and acts by inhibiting protein synthesis. This drug is not absorbed from the gut and is to be given parenterally. Excretion is predominantly via the kidneys and can accumulate if there is renal dysfunction. Clearance is rapid in children with cystic fibrosis and so higher doses are required.

Gentamicin is active against several Gram negative bacilli including pseudomonas. Although gentamicin is active against some Gram positive cocci, its activity against *S pyogenes* and *S pneumoniae* is poor and is inactive against anaerobes. Therefore gentamicin alone should not be used for treating pneumonia.

Use in respiratory infections

For empirical therapy of serious LRI of unknown aetiology including nosocomial pneumonia and pneumonia/sepsis in the new borns, this drug is used along with a β lactam antibiotic, usually penicillin. If staphylococcal infection is suspected, cloxacillin is used instead of penicillin.

Because of the high probability of dose related toxicity, drug level monitoring is recommended. Prolonged use also should be prevented.

Dosage

Although gentamicin can be given as 2-3 divided doses, once daily dosage is more convenient and ensures adequate serum concentration. Authors of a recent Cochrane review[60] have stated that there is insufficient evidence to conclude whether 'once a day' or 'multiple doses a day' regimen is superior in treating bacteriologically confirmed neonatal sepsis. However, the pharmacokinetic properties of 'once a day' regimen are superior to 'multiple doses a day' since it achieves higher peak levels while avoiding toxic trough levels.

There was no change in nephrotoxicity or auditory toxicity. 'Once a day' regimen may be therefore superior in treating neonatal sepsis. For infants less than 32 week gestation with their decreased glomerular filtration rates, a further extended regimen of once in 36 to 48 hours may be appropriate.

Loading and maintenance doses are calculated based on body weight and renal function. Doses are then adjusted based on serum concentrations. Usual starting dosage is 7mg/kg/day. Higher dose may be required in those with cystic fibrosis.

Treatment with gentamicin can be initiated based on clinical diagnosis. Monitoring of drug levels require laboratory facility.

It is recommended in combination with a β lactam antibiotic for very severe CAP, neonatal sepsis and staphylococcal infections[34]. This combination is also recommended as pre referral single dose [21]. BNF C also recommended it for severe bacterial infections (including pneumonia) in neonates and infants [5].

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection, /exclusion of particular data)

There are not many trials comparing Penicillin + gentamicin combinations with other drugs for severe pneumonia. The Cochrane review on therapy for pneumonia in children, found on comparing chloramphenicol with penicillin and gentamicin for severe pneumonia, need for change in antibiotics, death rates and adverse events were similar in the two groups. However, re-admission rates before 30 days favoured the penicillin-gentamicin combination (OR 1.6; 95% CI 1.02 to 2.55)[4].

A recent Cochrane review on management of sepsis did not find any additional advantage when β lactam aminoglycoside combinations were used compared to β lactam monotherapy[42]. Nephrotoxicity is significantly more with combination therapy RR 0.30 (95% CI 0.23-0.39).

6. Summary of comparative evidence on safety

Major adverse events like ototoxicity (vestibular and auditory) and nephrotoxicity can occur in up to 25% of those receiving therapy. These adverse events are dose related and so monitoring is recommended. Dose or frequency is reduced based on drug levels. Renal, auditory and vestibular functions also need to be monitored. Prolonged use and concomitant use of other drugs that can increase toxicity should be avoided. Toxicity is more in children with renal impairment.

The drug can impair neuromuscular transmission and so is to be avoided in children with myasthenia.

One study in a Cochrane review reported 2 of 13 and 1 of 11 neonates receiving once a day or multiple doses a day respectively developed ototoxicity. Three other studies which looked for ototoxicity did not find any[60].

7. Summary of available data on comparative cost

10mg/ml – 0.0347/vial

40mg/ml-0.0331/vial

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

For one day therapy cost is less than US \$ 0.1

9. Summary of regulatory status

FDA approved

10. Availability of pharmacopoeial standards

Listed in US, European and international pharmacopeia

11. Proposed text for WHO model formulary

Gentamicin for parenteral use

Gentamicin has action against Gram negative bacilli.

Indications in respiratory infection

For empirical therapy of serious pneumonia of unknown aetiology including nosocomial pneumonia and pneumonia/sepsis in the new borns to be used along with a β lactam antibiotic, usually penicillin

Dosage

7mg/kg/day as single daily dose or as 2-3 divided doses

Loading and maintenance doses are calculated based on body weight and renal function. Doses are then adjusted based on serum concentrations.

Precautions

Should not be used as mono therapy for respiratory infections

Drug level monitoring is recommended. Prolonged use and concomitant use of other drugs that can increase toxicity should be prevented.

Renal, auditory and vestibular functions need to be monitored.

Contraindications

Can impair neuromuscular transmission and so avoid in children with myasthenia

Adverse events

Ototoxicity (vestibular and auditory)

Nephrotoxicity

Toxicity is more in children with renal impairment.

Impairment of neuromuscular transmission

Ceftriaxone/cefotaxime

Trials summarized in tables

[Cetinkaya,2004](#)

1. Formulation proposed for inclusion

Ceftriaxone 250 mg vial for parenteral use

500 mg vial for parenteral use

It is listed on WHO EDL as an example of a therapeutic group

2. International availability (sources)

MISSION, IDA, DURBIN, MEDS

3. Whether listing is requested as individual drug or as an example of a therapeutic group

Example of third generation cephalosporins

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Cefotaxime and Ceftriaxone[24], are third generation cephalosporins with good activity against Enterobacteriaceae and *H influenzae* including those producing penicillinase. Their action on Gram positive cocci like *S. aureus*, *S pneumoniae*, and *S. pyogenes* is comparable to that of first-generation agents. Achievable serum concentrations exceed MICs for most penicillin-resistant isolates of *S pneumoniae*, *H. influenzae* and *S. aureus*. The antimicrobial spectrum of cefotaxime and ceftriaxone is therefore suited for the treatment of pneumonia, when cause is not identified. It is also useful for other severe infections caused by *H influenzae*, like epiglottitis.

Ceftriaxone has a half-life of about 8 hours and so once daily administration is effective for treating most infections. About half the drug can be recovered from the urine and the remaining from bile.

Use in respiratory infections

Severe community acquired pneumonia [61]

May be of use in hospital acquired pneumonia [62]

Epiglottitis

Dosage

50-75mg/kg/d IV or IM (max 2gm/day)

BNF C recommends this drug for epiglottitis [5]. It is recommended for severe CAP and otitis media[3, 14] . It may be of use in treating hospital acquired pneumonias[62].

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection, /exclusion of particular data)

In the Cochrane review on therapy of CAP[4] one double-blind study involving 97 children between 2 to 24 months of age diagnosed with severe CAP was identified comparing ceftriaxone with penicillin and chloramphenicol combination. Cure rates in the two groups were similar (OR 1.36; 95% CI 0.47 to 3.93).

6. Summary of comparative evidence on safety

Adverse events are rare[63, 64]. Hypersensitivity can occur. A proportion of individuals hypersensitive to penicillin will be hypersensitive to cephalosporins also

These drugs can also cause nephrotoxicity, diarrhoea, vomiting and skin rash[63, 64]

Super infection with *Candida* spp can occur

7. Summary of available data on comparative cost

250 mg vial –US \$ 1.0141/vial

500 mg vial – US \$ 1.4460/vial

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

It is an expensive drug, to be used only for selected indications where there are few other options

9. Summary of regulatory status

FDA approved

10. Availability of pharmacopoeial standards

Listed in US and European pharmacopoeia

11. Proposed text for WHO model formulary

Ceftriaxone for parenteral use

Its spectrum o activity is suitable for treating severe pneumonias

Use in respiratory infections

Severe community acquired pneumonia

Epiglottitis

Dosage

50-75mg/kg/d IV or IM (max 2gm/day)

Contraindications

Hypersensitivity

Precautions

Those hypersensitive to penicillin may be hypersensitive to cephalosporins

Adverse reactions

Diarrhoea, vomiting, skin rash

Superinfection with candida spp

Hypersensitivity

Nephrotoxicity

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Table 1 Studies included in the Cochrane review on therapy of community acquired pneumonia in children[4]

Author, year, centre	Design	Subjects	Interventions	Outcome
Addo Yobo 2004 Concealment – D not used	RCT	3 to 59 months with severe pneumonia	1. Daily IM penicillin 200,000 IU/kg 2. PO amoxicillin 45 mg/kg/day	Failure rate at 48 hours, 5 days and 14 days and death rate
Block 1995 B unclear	RCT	3 to 16 years with radiographically diagnosed pneumonia	1.PO clarithromycin (15 mg/kg/day) for 10 days 2. PO erythromycin 40 mg/kg/day for 10 days	Cure rates, resolution of signs and symptoms, improvement, failure or worsening
Catchup, 2002 A- Adequate	RCT	2 to 59 months with non-severe pneumonia	1.PO amoxicillin 25 mg/kg/day for 5 days 2.Co-trimoxazole 20/4 mg/kg/day for 5 days	Cure rate, failure rate, change of antibiotics
Camargos,1997 D	RCT	2 years to 12 years with non severe pneumonia	1.Single dose of benzathine penicillin (600,000 U for patients below 20 kg weight and 1,200,000 U for those above 20 kg), 2.Procaine penicillin 300,000 IU/kg/day IM for 7 days	Cure rate, failure rate, lost to follow up
Campbell,1988 D	RCT	1 month to 4 years of age with non-severe pneumonia	1.Daily cotrimoxazole PO for 5 days 2. Single dose procaine penicillin with daily PO ampicillin	Cure rate, hospitalisation rate, death rate

Author, year, centre	Design	Subjects	Interventions	Outcome
Cetinkaya,2004 A	RCT	6 months to 16 years with clinical or radiological evidence of pneumonia	1. IV chloramphenicol 15 mg/kg every 6 hours plus penicillin 25,000 IU/kg every 4 hours for 10 days 2. ceftriaxone 50 mg/kg every 12 hours	Clinical recovery
Deivanayagam,1996 D	RCT	5 months to 4 years with pneumonia admitted to hospital	1. IM/ IV ampicillin (100 mg/kg/day) for 48 hours then PO, 2. IV penicillin (100000 IU/kg/day) plus chloramphenicol (100 mg/kg/day)	Cure rate, failure rate
Duke,2002 D	RCT	1 to 59 months age, with severe pneumonia	1.IM chloramphenicol (25 mg/ kg 6 hourly for at least 5 days) 2. penicillin (50 mg/ kg 6 hourly) and gentamicin (7.5 mg/ kg/d single dose) for at least 5 days	death, change in antibiotics, absconded, readmission within 30 days), rate of hospitalization, duration of hospital stay
Harris,1998 D	RCT	6 months to 16 years with clinical or radiological evidence of pneumonia	1. PO azithromycin (10 mg/kg/day 1 followed by 5 mg/kg/day for 4 days) 2. amoxicillin clavulanic acid (40 mg/kg/day) for 10 days 3. erythromycin (40 mg/kg/day) for 10 days	Cure rate (15,19d) improvement rate, failure rate
Jibril,1989 D	RCT	2 years to 12 years age, with non-severe pneumonia	1. Amoxicillin and clavulanic acid (250 + 62.5 mg or 500 + 125 mg tds) for 19 days 2. amoxicillin (250 mg or 500 mg tds) for 10 days	Cure rate, poor or no response

Author, year, centre	Design	Subjects	Interventions	Outcome
Keeley, 1990 D	RCT	3 months to 12 years with non severe pneumonia	1.Co-trimoxazole per oral for 5 d. 2.Procaine penicillin IM daily for 5 days	Cure rate, treatment failure, hospitalization, well at final follow up and death rate
Klein,1995 B	RCT	3 months to 11.5 years	1. Cefpodoxime 5 to 12 mg/kg/day PO for 10 days 2. co-amoxiclavulanic acid 6 to 13 mg/kg/day for 10 days	Response rate
Kogan, 2003 D	RCT	1 month to 14 years with non severe pneumonia	1. Azithromycin (10 mg/kg/day) PO for 3 daysr 2. amoxicillin PO 75 mg/kg/day for 7 days	Clinical and radiological cure rates, fever on day 3 and day 7, chest x-ray on day 14
Mullholland,1995 A	RCT	below 5 years of age with malnutrition and clinical or radiological evidence of pneumonia	1. Cotrimoxazole for 1 week 2. Chloramphenicol for 1week	Cure rate, failure rate, relapse rate, death rate
Roord, 1996 D	RCT	2 months to 16 years with non severe pneumonia (acute LRTI)	1. Azithromycin 10 mg/kg/day for 3 days 2. erythromycin 40 mg/kg/day for 10 days	Cure rate, failure rate at day 10 to 14, improvement at day 10, and between days 25 to 30
Shann,1985 D	RCT	children	1.IM chloramphenicol daily until switched over to oral 2. IM chloramphenicol with benzyl penicillin until switched over to oral	Good improvement, discharge from hospital

Author, year, centre	Design	Subjects	Interventions	Outcome
Sidal,1994 D	RCT	3 months to 14 years with non severe pneumonia (including moderate pneumonia)	1.PO cotrimoxazole (40 mg/kg/day) for 10 days 2. IM procaine penicillin (50,000 IU/kg/day) for 10 days	Cure rate and improvement at days 5 and 10, failure rate
Strauss,1998 A	RCT	2 months to 59 months with non severe pneumonia	1.PO cotrimoxazole 20 mg/kg/day for 5 days 2. amoxicillin 45 mg/kg/day for 5 days	Clinical and radiological failure rate
Tsarouhas,1998 D	RCT	6 months to 18 years with pneumonia	1. PO amoxicillin (50 mg/kg/day) 2. procaine penicillin IM (50,000 IU/kg/day)	Hospitalization rate, failure rate, temperature more than 38.5, ill appearance, increased respiratory rate
Wubbel,1999 D	RCT	6 months a 16 years with pneumonia	1. PO azithromycin (10mg/kg on day one followed by 5 mg/kg/day for next 4 days) 2. PO co-amoxiclavulanic acid 40 mg/kg/day for 10 days in children under 5 years of age; and erythromycin 40 mg/kg/day for 10 days in children over 5 years	Cure rates, failure rates, improvement clinically diagnosed

Table 2 Studies included in the Cochrane review on oral versus parenteral therapy for CAP in children[35]

Author, year	Design	Subjects	Interventions	Outcome
APPIS group 2004 A	Multicentre, randomized, open-label, equivalency study Intention-to-treat analysis for the main outcome	Children, admitted to tertiary-care centres in eight developing countries in Asia, Africa and South America aged 3 to 59 months WHO defined severe pneumonia	1. Oral: amoxicillin syrup 45 mg/kg per day in three doses (857) 2. Parenteral: intravenous penicillin G crystalline 200.000 IU/kg per day in four doses (845)	Treatment failure up to 48 hours, serious adverse drug reaction, necessity of other antibiotic or death
Campbell,1988 C-inadequate 7th day follow up was blinded and 14th day outcome evaluation was unblinded	Multi-centre, controlled Intention to treat analyses	Age mean =22 months Children from seven rural villages of The Gambia WHO defined severe pneumonia	Oral: co-trimoxazole, five days course of WHO recommended doses (66) Parenteral + Oral: procaine penicillin (4 mega units) + benzylpenicillin (1 mega unit) one dose, followed by five day course of oral ampicillin - WHO recommended doses (68)	Treatment failure at seven days and 14 days Incomplete recovery. Requirement for further treatment

Table 3 Studies included in the Cochrane review on otitis media in children [15]

Author, year	Design	Subjects	Interventions	Outcome
Appleman, 1991 Netherlands A	Randomised Double blind	121 children in a general practice aged 6 months to 12 years with AOM and a previous episode of otitis media within 1 to 12 m	1. Amoxicillin/clavulanate (weight tailored dose) 2. Placebo. Duration: 7 days	3 d fever and otalgia; 14 d otorrhoea; 1 m otoscopy and tympanometry. failure = either otalgia or fever or both at 3 d.
Burke, 1991 UK A	Randomised Double blind	Aged between 3 and 10 years Acute earache and at least one abnormal eardrum	1. Amoxicillin 250mg tds 2. Placebo tds Duration: 7 days.	Symptoms at 24 hrs, 5-7days
Damoiseaux, 2000 Netherlands A	Randomised	240 children between 6 m and 2 yrs attending general practice. Diagnosis according to Dutch guidelines	1. Amoxicillin suspension 40mg/kg/d in 3 divided doses 2. Placebo suspension Duration: 10 days	Symptoms at 4 days (ear ache, fever, crying irritably)
Halsted, 1968 USA B	Randomised Blinded	Clinical diagnosis of acute otitis media, excluded if rupture or recent antibiotics	1. Ampicillin 100mg/kg/day 2. phenethicillin 30mg/kg/day + sulfisoxazole 150mg/kg/d 3. placebo	Culture results, clinical improvement
Howie, 1972 USA A	Randomised	Age 2.5 years or less clinical diagnosis of acute otitis media	1. Erythromycin, ampicillin, or triple sulphonamide plus erythromycin 2. placebo	culture

Author, year	Design	Subjects	Interventions	Outcome
Kaleida, 1991 USA A	Randomised Double blind	Age between 7 m and 12 yrs Acute otitis media: otoscopic middle ear effusion plus general symptoms or signs	1. Amoxycillin 40mg/kg/day in 3 doses 2. Placebo in 3 divided doses Duration: 14 days	Treatment failure
Laxdal, 1970 Canada C	Not clear	Clinical diagnosis of acute otitis media for at least one ear; excluded if rupture had occurred	1. Penicillin 250mg/sq.m./day qid or ampicillin 250mg/sq.m./day qid 2. symptomatic therapy only	Treatment failure – middle ear inflammation 7 th day
Mygind, 1981 Denmark A	Randomised, double blind	Age - one to ten years, Acute otitis media, who had had earache for 1-24 hours.	1. PenV 55mg/kg/d in 3 doses 2. Placebo Duration: 7 days	Symptoms Tympanometry Otoscopy
Thalin, 1985 Sweden A	Randomised, double blind	Age - 2 to 15 years Acute otitis media = clinical diagnosis	1. Penicillin 50mg/kg/d in 3 doses 2. Placebo Duration: 7 days	clinical examination – 0, 3- 4, 8-10, 30 d Audiogram on day 30
Van Buchem, 1981 (a) Netherlands A Without myringotomy	Randomised, double blind	Age 2-12 years acute otitis media - clinical diagnosis	1. Amoxicillin 250mg tds 2. placebo; sham myringotomy Duration: 7 days	Parent report of pain Clinical assessment: day 2, 7, 14, 28, 56. Audiogram at > 2 weeks
Van Buchem, 1981 (b) Netherlands A With myringotomy	Randomised	Children aged 2-12 years acute otitis	1. Amoxicillin 250mg tds and myringotomy 2. Placeb, myringotomy Duration: 7 days	Parent report of pain Clinical assessment: day 2, 7, 14, 28, 56. Audiogram at > 2 weeks

Table 4 Studies included in Cochrane review on sore throat [11]

(Studies where only adults were included are not listed below)

Author, year	Design	Subjects	Interventions	Outcome
Bennike, 1951 C	Open, non randomised	669 patients aged from less than one year to greater than 50 years	1. Penicillin 2. No treatment	Incidence of rheumatic fever, otitis media, quinsy, sinusitis and symptoms of sore throat and headache
Chapple, 1956 A	Randomised, double blind	308 subjects aged greater than two years old. Data from 283 subjects included in analyses	1.Oral penicillin 2. sulphadimidine 3. barium sulphate (placebo) for five days	Incidence of rheumatic fever, otitis media, and symptom of sore throat
Dagnelie, 1996 A Netherlands	Randomised double blind	239 patients aged 4 to 60, presenting to general practices who were clinically suspected of GABHS sore thraot	1. Penicillin V 2. Placebo	Resolution of sore throat, fever, and return to daily activities (assessed for 7 d)
De Meyere, 1992 A	Double blind	173 patients aged 5 to 50 yrs Belgium	1. Oral penicillin 2. Oral placebo	Symptoms of sore throat
El Daher, 1991 A	Randomised, double blind	229 children with positive culture for GABHS	1. Oral penicillin for 10 d 2. Placebo for 2 d, then oral penicillin for 8 d	Symptoms of sore throat and headache on day 3
Krober, 1985 A	Randomised double blind	44 children presenting to a paediatric clinic. 26 yielded group A BHS from throat swabs	1.Oral penicillin 2. Oral placebo 3 times a day for 3 days	Symptom of fever

Author, year	Design	Subjects	Interventions	Outcome
Leelarasamee, 2000 A	Randomised double blind	1217 patients aged over 5 years presenting to community -based medical centres with complaints of fever or sore throat of less than ten days duration	1. Amoxicillin 2. placebo for seven days	Duration of sore throat and fever. incidence of complications and adverse reactions
Little, 1997 C	Randomised, Not blinded	716 patients aged 4 years and over, presenting to their GP with a sore throat, with an abnormal physical finding localised to the throat (e.g. inflamed tonsils or pharynx, etc)	1. Antibiotic for 10 days; 2.No prescription 3. Offer of antibiotic prescription if symptoms were not starting to settle after 3 days	Duration of symptoms, satisfaction, compliance with and perceived efficacy of antibiotics, time off school or work. Temperature
Middleton, 1988	Multicentre, randomised, double blind	178 patients aged 4 to 29 yrs with streptococcal pharyngitis; symptom duration < 4 days. Results reported for 57 with severe illness only	1.Eight individual doses of penicillin 2. Unmedicated placebo	Symptoms of sore throat and fever
Nelson, 1984 C		51 children aged 5 to 11 years. 16 were excluded because throat swabs were negative for Group A BHS. (i.e. n=35) Children with history of penicillin hypersensitivity were also excluded	1. IM penicillin 2. Oral syrup placebo	Symptoms of sore throat and fever
Pichichero, 1987 A	Randomised, double blind	114 Group A Beta Haemolytic Streptococcus positive children aged 4 to 18 years. Children were excluded if, allergic to penicillin; had received penicillin in past 7 days; had another acute illness within 7 days, had a Group	1. Oral penicillin for forty eight hours 2. Oral placebo used	Incidence of otitis media, quinsy, sinusitis

Author, year	Design	Subjects	Interventions	Outcome
		A BHS positive swab in past month, or had another concurrent infection that required antibiotics		
Siegel, 1961 C	Randomised, open	1213 patients aged 3-16 years. Suppurative complications occurring in the control group were treated with sulphonamides. Subjects were excluded if there was a complication.	1. IM penicillin 2. No treatment	Incidence of rheumatic fever
Taylor, 1977 A	Double blind, randomised	122 children aged 2-10 years. Children with positive Streptococcus throat swabs were excluded. Nine children were excluded because of pre-existing suppurative complications	1.Oral amoxicillin 2. Oral cotrimoxazole 3. Oral placebo 3 times a day for 5 days	Incidence of otitis media and sinusitis and symptoms of sore throat and fever
Whitfield, 1981 A	Double blind, randomised	745, Age >10yrs, presenting to general practitioner with sore throat. Only 528 returned questionnaires. Subjects were excluded if poor compliance was suspected; previous reaction to penicillin; a previous episode of rheumatic fever or acute nephritis	1. Oral penicillin 4 times a day for 5 days 2. Oral lactose placebo 4 times a day for 5 days	fever
Zwart, 2003 A	Randomised, double blind	165 children aged 4 to 15 years presenting with sore throat of less than 7 days duration	1.Penicillin V for 7 days 2. Penicillin V for 3 days and placebo for 4 days 3.Placebo for 7 days	Duration of symptoms of sore throat, occurrence of streptococcal sequelae

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