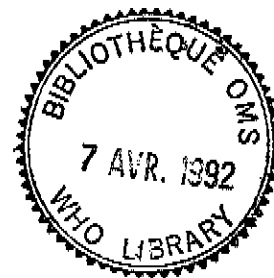


Antibiotics
in the treatment of
acute respiratory
infections in
young children



**Programme for the Control of
Acute Respiratory Infections**

World Health Organization
Geneva



**ANTIBIOTICS IN THE TREATMENT OF ACUTE RESPIRATORY
INFECTIONS IN YOUNG CHILDREN**

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1. INTRODUCTION

Acute respiratory infections (ARI) are one of the commonest causes of death in children in developing countries. They are responsible for 4 of the estimated 15 million deaths that occur in children under 5 years of age each year; two-thirds of these deaths are in infants (especially young infants).¹ Almost all ARI deaths in young children are due to acute lower respiratory infections, in particular pneumonia(1). Lung puncture studies in developing countries indicate that most cases of severe pneumonia in children are caused by bacteria, usually *Streptococcus pneumoniae* or *Haemophilus influenzae*(2).

Neonates and one-month-old infants with pneumonia are at particularly high risk of mortality. In this age group, bacterial infections may present with non-specific clinical signs only, making it difficult to distinguish pneumonia from sepsis and meningitis. These infections can be rapidly fatal in young infants,¹ who are best treated in hospital with parenteral antibiotics. The following bacteria are important causes of pneumonia in young infants in developed countries: group B streptococci, *Chlamydia trachomatis*, *Listeria monocytogenes*, *Streptococcus faecalis*, and enteric Gram-negative bacilli such as *Escherichia coli* and *Klebsiella* spp.(3, 4). The organisms that cause pneumonia in this age group in developing countries are less well known.

Clinical experience and intervention studies in developing countries have indicated that early treatment with antibiotics can reduce mortality from pneumonia. Many pneumonia deaths occur at home, some after only a few days of illness. The key to reducing ARI mortality is to ensure better access to and timely use of correct case management of pneumonia. This requires the strengthening of health services to enable them to provide early treatment with appropriate antibiotics.

Acute upper respiratory infections result in few deaths in children but cause considerable disability. Otitis media is the leading preventable cause of deafness in developing countries and is a significant contributor to developmental and learning problems in children. In addition, acute rheumatic fever may follow streptococcal pharyngitis. While the main age group of concern for the detection and treatment of streptococcal pharyngitis to prevent acute rheumatic fever (and chronic rheumatic heart disease) is 5-15 years, similar clinical management is appropriate for younger children since rheumatic fever cases also occur in this age group.

In acute pharyngitis the two most important pathogens are *Streptococcus pyogenes* and *Corynebacterium diphtheriae*. In acute otitis media *S. pneumoniae* or *H. influenzae* are usually involved(5).

¹ The term young infants relates to infants under 2 months of age.

The ARI case management guidelines of the WHO Programme for the Control of Acute Respiratory Infections are based on the assumption that there is a substantial incidence of bacterial pneumonia in children visiting the facility, and that risk factors for pneumonia, such as undernutrition and low birth weight, are relatively common, resulting in high rates of pneumonia-specific mortality. Accordingly, they recommend antibiotic therapy in situations where bacterial pneumonia is a significant possibility.

The WHO ARI Programme recommends four first-line antibiotics for the outpatient treatment of pneumonia in children 2 months up to 5 years of age: cotrimoxazole (trimethoprim-sulphamethoxazole), amoxycillin, ampicillin, and procaine penicillin. Benzathine penicillin and phenoxymethylpenicillin (penicillin V) are not recommended for the treatment of pneumonia.

A further group of antibiotics are recommended for the inpatient treatment of severe or very severe pneumonia: benzylpenicillin, chloramphenicol, oxacillin or (flu)cloxacillin, and gentamicin.

The antimicrobial activity, pharmacology, mode of administration, dosage, toxicity, and clinical use of these antibiotics in the treatment of ARI are considered in detail in this document. Erythromycin is included because it is specifically indicated in the treatment of pertussis (and infections due to *Chlamydia* and *Mycoplasma*). More expensive antibiotics such as third generation cephalosporins, which would be the treatment of choice for certain conditions in settings with ample resources (yet usually low mortality) are not discussed. The spectrum of activity of each antibiotic is summarized in Annex 1, and the recommended dosage schedules are presented in Annex 2.

A detailed presentation of the WHO ARI Programme case management guidelines and antibiotic treatment recommendations can be found in "Acute Respiratory Infections in Children: Case Management in Small Hospitals in Developing Countries - A Manual for Doctors and other Senior Health Workers" (unpublished document WHO/ARI/90.5).

2. BENZYLPENICILLIN, PROCAINE PENICILLIN, BENZATHINE PENICILLIN

Benzylpenicillin is a rather unstable acid and the following relatively stable salts are used clinically.

Sodium benzylpenicillin. This is a highly soluble salt and can be administered both intramuscularly (IM) or intravenously (IV). The dosages of this and other benzylpenicillin preparations can also be expressed in units. One unit of activity is equivalent to 0.6 µg of pure sodium benzylpenicillin.

Potassium benzylpenicillin. One unit of activity of this very soluble salt is equivalent to 0.625µg of pure potassium benzylpenicillin.

The terms "penicillin G" or "crystalline penicillin" are often used as synonyms for either of the above benzylpenicillin salts.

Procaine penicillin. This is a much less soluble salt of benzylpenicillin, and it is administered IM as a suspension of crystal particles, which dissolve slowly so that the absorption of liberated benzylpenicillin takes place over a prolonged period. One unit of activity is equivalent to 1.0 µg of pure procaine penicillin.

The terms "procaine penicillin G" or "procaine benzylpenicillin" are sometimes used as synonyms.

Benzathine penicillin. This is an even less soluble salt of benzylpenicillin than procaine penicillin and is absorbed more slowly from an IM injection site producing prolonged but low serum levels of benzylpenicillin. One unit of activity is equivalent to 0.75 µg of the pure substance. Procaine and benzathine salts of penicillin are known as "long-acting" or "depot" forms. They must never be given IV.

2.1 Antimicrobial activity

Benzylpenicillin is very active against *S. pyogenes*. It is equally so against *S. pneumoniae*, except that relatively resistant strains are being encountered with increasing frequency throughout the world. The minimum inhibitory concentrations (MICs) for these strains are 0.1-1.0 µg per ml, compared with 0.006-0.008 µg per ml for fully sensitive strains. (6)

Pneumococci that were completely resistant to benzylpenicillin were detected in South Africa in 1977 (7) and in Spain in 1984 (8), but fortunately these have not spread widely throughout the world.

H. influenzae, with an MIC of 1 µg per ml, is moderately sensitive to benzylpenicillin. Beta-lactamase-producing strains are completely resistant. Most *Staphylococcus aureus* strains are now resistant, since they produce beta-lactamase. Group B streptococci and *L. monocytogenes* are penicillin-sensitive. *S. faecalis* is also sensitive, but to a lesser degree (MIC 2 µg per ml). The Gram-negative enteric bacteria are penicillin-resistant.

2.2 Pharmacology

After IM administration of benzylpenicillin high peak serum levels are obtained. With an IM dose of 35 000 units per kg (approximately 21 mg), a peak serum level of 10-15 µg per ml is attained in 30 minutes in children. The level then falls to zero in 4-6 hours (9). If benzylpenicillin is administered IV by short (20-minute) intermittent infusions, the peak serum levels and half-life are about the same as those observed after IM administration of the same dose.

When IM procaine penicillin in a dose of 48 000 units per kg (nearly 50 mg per kg) is given to children, the peak serum level 3-6 hours later is 4-6 µg per ml and the serum level remains above 1 µg per ml for 26 hours (9). Ginsburg, McCracken, and

Zweighaft (10) studied the serum levels of penicillin after IM administration of benzathine penicillin to children aged 1.8 to 10.7 years. Seven children who weighed less than 27 kg received a single dose of 600 000 units (0.45 g). The mean peak serum concentration attained at 24 hours was 0.16 µg per ml and the subsequent mean serum levels were 0.075, 0.04, and 0.01 µg per ml on days 5, 10, and 18, respectively.

If renal function is normal, over 70% of an injected dose of benzylpenicillin is excreted *via* the kidneys within 6 hours, mainly as the active drug, and high urinary concentrations result. Most of the drug is excreted by tubular secretion. This secretion can be partly blocked by probenecid. In newborn infants excretion is predominantly by glomerular filtration, because tubular function is immature at that age; as a result, the serum half-life of benzylpenicillin is prolonged (11). A small amount of penicillin is eliminated *via* the bile and the remainder is inactivated in the liver.

2.3 Mode of administration and dosage

Benzylpenicillin. The usual dosage is 50 000 units (30 mg) per kg every 6 hours.

In developing countries the drug is usually administered by the IM route, but it can also be given IV in the same dosage. Since inappropriate secretion of antidiuretic hormone is a known complication of pneumonia, it would seem prudent to avoid IV administration in these circumstances unless bolus antibiotic injections can be given through an indwelling IV cannula. Experimental studies suggest that drugs such as benzylpenicillin can be administered twice daily, the total daily dose remaining the same (12, 13). Data from controlled studies in man are not yet available.

In newborn infants a smaller dosage is necessary, because of decreased renal clearance. For infants 0-7 days old, a dosage of 50 000 units (30 mg) per kg body weight, administered every 12 hours, is usually adequate for most infections caused by susceptible bacteria, including group B streptococci. For infants older than 7 days, the usual dosage is 50 000 units (30 mg) per kg every 6 hours.

Procaine penicillin. This can only be administered by the IM route. The dosage is 50 000 units (50 mg) per kg daily once. The dosage is the same for neonates.

Benzathine penicillin. This also can only be administered IM. In children 2 months up to 5 years of age it is given in a single dose of 300 000 - 600 000 units (225-450 mg). Children 5 years of age or older should receive a single dose of 1200 000 units (900 mg).

2.4 Toxicity

Hypersensitivity reactions. (14). Mild hypersensitivity reactions are common, occurring in 5-10% of patients treated with penicillin, and result from previous contact with penicillin. The most serious manifestation of penicillin hypersensitivity is anaphylaxis. This

is rare (4-15 cases of non-fatal anaphylaxis occur in every 100 000 patients) but may result in death within minutes (1-2 deaths in every 100 000 patients). Health personnel should always inquire whether the patient has had a reaction to a prior dose of penicillin since severe reactions are more common in children with a history of any type of prior reaction. Reactions are more likely in young adults than in children.

Skin testing using benzylpenicillin alone as the reagent is inaccurate and may also cause sensitization. Therefore it is not recommended. In special research laboratories, where modern testing reagents - namely, penicilloyl-polylysine and minor determinant mixture - are available, skin testing can be of value. If these tests are negative in patients with a history of possible benzylpenicillin allergy, the risk of an immediate reaction to the drug is very low. However, these tests are not practicable at this stage, even in hospitals in developed countries, and they certainly cannot be recommended for use in developing countries (15).

The onset of pallor, dyspnoea due to bronchospasm, circulatory failure, and angioneurotic oedema within 30 minutes of giving penicillin should alert the clinician; immediate administration of epinephrine (adrenaline) is required at the following doses:

Initial treatment therapy (epinephrine 1:1000, aqueous):

infants less than 1 year:	0.1 ml per dose
children 1-2 years:	0.2 ml per dose
children 2-4 years:	0.3 ml per dose

Administer by IM injection in the arm that did not receive antibiotics. The dose can be repeated every 15 to 30 minutes.

The IV administration of hydrocortisone and an antihistamine agent will help to prevent deterioration after primary treatment has been given. IV infusion of a plasma substitute such as dextran may be necessary to combat shock. Serum sickness occurs as a late reaction in approximately 2% of patients who are treated with benzylpenicillin. This is manifested by fever, urticaria, joint pains, and occasionally angioneurotic oedema. It is usually not serious and resolves when the drug is withdrawn.

Reactions peculiar to procaine penicillin. Occasionally, severe reactions, including convulsions and even death, may result from the accidental IV injection of this preparation. Less severe side-effects such as anxiety, tachycardia, disorientation, or psychotic behaviour may occur within a few minutes of an injection. These probably result from direct procaine toxicity (16); however, they are a very uncommon occurrence in children.

Nerve and muscle injury. The danger of sciatic nerve injury from IM benzylpenicillin injections in the buttock is well known, and so the drug is usually given in the lateral aspect of the thigh. Rarely, muscle contractures may result from repeated injections in the thigh.

Intra-arterial injection of procaine or benzathine penicillin. This is a rare but serious complication of IM injections of procaine or benzathine penicillin. As the drug is injected under pressure, retrograde distribution in the arteries may occur, resulting in ischaemic changes in muscles and even transverse myelitis of the spinal cord (17).

Other complications. These are unlikely when the above three penicillin preparations are used IM to treat acute respiratory disease in children. Jarisch-Herxheimer reaction occurs only when specific diseases such as syphilis are treated with benzylpenicillin. Other complications, such as direct benzylpenicillin toxicity and convulsions, interstitial nephritis, and haemolytic anaemia, occur only if large doses (greater than 10 million units or 6 g daily) of benzylpenicillin are given IV (18, 19).

2.5 Clinical uses

Benzylpenicillin. This is used for the treatment of severe pneumonia in children 2 months up to 5 years of age. Such children have chest indrawing, but they have no cyanosis and they are still able to drink. Pneumonias due to pneumococci and *H. influenzae* respond to this treatment. The most likely cause of treatment failure is if the responsible organism is *S. aureus* or beta-lactamase-producing *H. influenzae*. In combination with gentamicin, benzylpenicillin is recommended for the treatment of pneumonia in infants under 2 months of age.

Procaine benzylpenicillin. A single daily IM injection can be used for home treatment of pneumonia in children who have fast breathing but no chest indrawing. The recommended alternative treatments in this situation are oral ampicillin, amoxycillin or cotrimoxazole. Procaine penicillin in single daily doses for 7 days is used as an adjunct to antitoxin for the treatment of diphtheria.

Benzathine benzylpenicillin. This is not suitable for the treatment of pneumonia or otitis media since the low serum levels do not exceed the MICs for *H. influenzae*. One injection of this drug can be used to treat streptococcal pharyngitis.

3. PHENOXYMETHYLPENICILLIN

Phenoxyethylpenicillin also known as penicillin V (and phenoxyethylpenicillin also known as phenethicillin) are acid-stable and can be administered by mouth. The antimicrobial spectra of these drugs are similar to that of benzylpenicillin, but some organisms are less susceptible. For instance, *H. influenzae* with an MIC of 5 µg per ml is some ten times less sensitive to penicillin V than to benzylpenicillin. The drug is not suitable for the treatment of otitis media or pneumonia, because the serum levels are not high enough to inhibit *H. influenzae*. Penicillin V is suitable for the treatment of streptococcal pharyngitis. A 10-day course should be given (20). The dosage is 12.5 mg per kg every 6 hours. Recent clinical trials suggest that, for the treatment of streptococcal pharyngitis, the drug is just as effective if the total

daily dose is administered in 2 divided doses (i.e., 25 mg per kg every 12 hours) (21). With the usual doses the peak serum level is only about 2 µg per ml. The side-effects are the same as with benzylpenicillin, except that anaphylaxis is even rarer and the complications that arise only when large doses of benzylpenicillin are given IV do not occur.

4. CLOXACILLIN, OXACILLIN, FLUCLOXACILLIN, NAFICILLIN, METHICILLIN

4.1 Antimicrobial activity These are closely related semisynthetic isoxazolyl penicillins which combine the property of resistance to staphylococcal beta-lactamase with resistance to gastric acidity. Although other bacteria are sensitive to them, they are used only for the treatment of staphylococcal infections. Methicillin-resistant staphylococci are resistant to these drugs. Methicillin and nafcillin are ineffective if given orally and therefore are only given by the intramuscular or intravenous route. The dose in children is 25-50 mg per kg every 6 hours. Further remarks will be confined to the isoxazolyl penicillins: cloxacillin, oxacillin and flucloxacillin with cloxacillin taken as the specific example.

4.2 Mode of administration and dosage The usual dosage is 25-50 mg per kg every 6 hours. The drug can be administered orally, IM or IV. Newborn infants require a reduced dosage owing to their slower rate of renal excretion. During the first 7 days of life a dose of 25 mg per kg, administered every 12 hours, is recommended. Infants 8-30 days old require 25 mg per kg every 8 hours (3). In older children and adults, the peak serum level after the usual oral dose is reached one hour later and is approximately 8 µg per ml. With IM administration, the peak level is reached in 30 minutes and is nearly doubled. With both modes of administration the serum level returns to zero in 4 hours. Like benzylpenicillin, cloxacillin is excreted mainly *via* the kidneys, both by glomerular filtration and tubular secretion.

4.3 Toxicity Hypersensitivity reactions similar to those that occur with benzylpenicillin, and gastrointestinal disturbances, are the main side-effects. Fever, vomiting, and abnormal liver function tests have been observed, but they resolve when the treatment is stopped. Reversible neutropenia can also occur rarely.

4.4 Clinical uses Parenteral cloxacillin is used for the treatment of proven or suspected staphylococcal infections. If very severe pneumonia fails to respond to IM chloramphenicol, or a chest X-ray shows a pneumatocele or empyema, a course of cloxacillin plus gentamicin should be given for a minimum of 3 weeks. Cloxacillin will give better cover for possible *S. aureus* pneumonia and gentamicin will be useful in the unlikely event that pneumonia is caused by Gram-negative rods such as *E. coli*.

In young infants, if the response to the usual benzylpenicillin plus gentamicin combination is poor, cloxacillin plus gentamicin may be used to cover the possibility of staphylococcal pneumonia.

5. AMPICILLIN AND AMOXYCILLIN

These two semisynthetic penicillins are similar in all respects, except that amoxycillin is better absorbed after oral administration and only ampicillin is available in a parenteral preparation. Therefore, amoxycillin is recommended when oral treatment is indicated, whereas ampicillin is used when parenteral administration is necessary.

5.1 Antimicrobial activity

Both drugs are potent against the same bacteria as benzylpenicillin, but against most Gram-positive cocci benzylpenicillin is slightly more active. Ampicillin and amoxycillin are somewhat more active against *H. influenzae* (MICs 0.05-0.25 µg per ml); beta-lactamase-producing strains are resistant. These drugs are also active against some Gram-negative enteric bacilli, such as *E. coli* and *Proteus mirabilis*, but others such as *Klebsiella* spp. are resistant.

5.2 Pharmacology

Amoxycillin is well absorbed after oral administration. Its absorption, unlike that of ampicillin, is only slightly affected by food (22). In adults, after a single oral dose of 500 mg, an average peak serum level of about 3 µg per ml is reached in 1-2 hours and the serum level usually returns to zero in 6 hours. Oral ampicillin attains only half of these levels whereas IM ampicillin reaches levels that are very similar to those of oral amoxycillin.

Like benzylpenicillin, these drugs are excreted from the body mainly by renal glomerular filtration and tubular secretion.

5.3 Mode of administration and dosage

Amoxycillin is given orally in a dosage of 15 mg per kg every 8 hours. The dosage of IM ampicillin is 50 mg per kg every 6 hours (the usual dose of oral ampicillin is 25 mg per kg every 6 hours).

For newborn infants, only parenteral ampicillin is suitable. A dosage of 50 mg per kg body weight is recommended every 12 hours for young infants less than 7 days old and every 8 hours for young infants 8-30 days old.

5.4 Toxicity

Ampicillin and amoxycillin may be "cross allergenic" with other penicillins and in sensitized patients may evoke any of the hypersensitivity reactions that are caused by benzylpenicillin. Rashes are more common with ampicillin and amoxycillin than with other penicillins and do not usually represent true penicillin hypersensitivity. The rash usually appears 8-10 days (range 4-14 days) after the start of therapy, is urticarial or macular, and often subsides even if treatment is continued. The risk of developing a rash is increased if the patient has glandular fever, cytomegalovirus infection, lymphatic leukaemia, or lymphoma (23).

Gastrointestinal adverse effects, particularly diarrhoea but also nausea and vomiting, occur quite frequently, usually following oral administration, and are associated with marked changes in

the faecal flora. These are found more commonly with ampicillin than with amoxycillin. Often children experience mild diarrhoea but occasionally it is more severe and necessitates the discontinuation of therapy. Rarely, ampicillin-related diarrhoea is caused by the production of toxin by *Clostridium difficile*.

5.5 Clinical uses

Ampicillin. This drug, given IM, may be used as a substitute for benzylpenicillin for the treatment of severe pneumonia in children 2 months up to 5 years of age on the grounds that the MIC for *H. influenzae* is lower than with benzylpenicillin. However, benzylpenicillin is effective and preferred. A combination of IM ampicillin and gentamicin may be used for pneumonia in young infants, but the benzylpenicillin and gentamicin combination is usually preferred.

Amoxycillin. This antibiotic, administered orally, can be used for the home treatment of pneumonia. It is also a useful drug for the treatment of otitis media.

6. COTRIMOXAZOLE

Trimethoprim was synthesized in 1956. It has a broad spectrum of antibacterial activity. It interrupts bacterial purine synthesis and acts on the same metabolic pathway as the sulfonamides. The combination of trimethoprim with a sulfonamide therefore has some synergistic effect against certain bacteria (24). In the period 1968-78, trimethoprim was available for general use only as a mixture with a medium-acting sulfonamide, sulfamethoxazole. Commercial formulations contain a mixture of sulfamethoxazole and trimethoprim in a fixed ratio of 5:1. The name cotrimoxazole is used to describe this combination.

Many of the advantages originally claimed for cotrimoxazole have since been challenged; for most infections, trimethoprim is the more active drug and has fewer side-effects than the combination. Most clinicians now accept that, for simple urinary tract infections, trimethoprim can be used alone (25). However the efficacy of trimethoprim alone in the treatment of childhood pneumonia has not yet been proved.

6.1 Antimicrobial activity

Both cotrimoxazole and trimethoprim are active against important respiratory pathogens such as *S. pneumoniae*, *S. aureus*, and *H. influenzae*, including beta-lactamase-producing strains. Gram-negative enteric bacilli are also susceptible, e.g., *E. coli*, *Klebsiella*, *Enterobacter*, and *Proteus* spp. Resistant strains have emerged among the latter but are still uncommon. Clinical experience suggests that *Pneumocystis carinii* is susceptible to cotrimoxazole (26).

6.2 Pharmacology

Trimethoprim is well absorbed after oral administration. In adults, after the usual oral dose of 160 mg, a peak serum level of about 2 µg per ml is reached in 1-2 hours; this is maintained for

about 6 hours and then falls progressively. The serum half-life of the drug is about 13 hours and detectable serum levels are still present 24 hours after this dose (27). Recently, it has been shown that the drug attains the same peak serum levels in children as in adults, but thereafter is eliminated more rapidly, resulting in a shorter serum half-life (28). Sulfamethoxazole is also well absorbed from the gastrointestinal tract and its half-life is almost identical to that of trimethoprim.

Both trimethoprim and sulfamethoxazole are eliminated from the body *via* the kidneys either as active drug or as metabolites.

6.3 Mode of administration and dosage

The usual dosage of cotrimoxazole for children has been sulfamethoxazole/trimethoprim 15/3 mg per kg every 12 hours. However, recent studies (28) suggest that the dose of trimethoprim for children should be higher, and approximately 3 mg per kg every 8 hours; thus 20/4 mg per kg every 12 hours is recommended. The slightly elevated sulfamethoxazole dose is acceptable. For the treatment of *P. carinii* pneumonia, a high-dose sulfamethoxazole/trimethoprim regimen is necessary, i.e., 10 mg of trimethoprim per kg every 12 hours (29). The use of cotrimoxazole is in general not recommended in developed countries during the first 4 weeks of life. However, it has occasionally been used for the treatment of severe infections in infants 2-3 weeks of age without any evidence of toxicity (30). Sulfonamides such as sulfisoxazole displace bilirubin from albumin-binding sites and may cause kernicterus (31). However, sulfamethoxazole is a weak displacer of bilirubin. Springer, Eyal, and Michel (32) found no bilirubin displacement from albumin with sulfamethoxazole concentrations of up to 300 µg per ml. There have not been any reports linking sulfamethoxazole to a case of kernicterus (31), however experience with this drug in this age group is limited.

Parenteral benzylpenicillin plus gentamicin is preferred to cotrimoxazole for the treatment of pneumonia in young infants under 2 months of age. Cotrimoxazole should not be used in young infants who are premature or jaundiced. Only limited pharmacokinetic data are available on the use of cotrimoxazole in this age group. Current dosage recommendations are shown in Annex 2.

6.4 Toxicity

Most of the toxic effects of cotrimoxazole are attributable to the sulfamethoxazole component. Mild hypersensitivity reactions are common, but rarely they may take the form of serious or even fatal Stevens-Johnson syndrome. Bone marrow depression with neutropenia and thrombocytopenia may also occur. Nephrotoxicity and hepatotoxicity are less common. These reactions are more common in older patients and relatively rare in children (33). Data were published in 1985 on deaths in the United Kingdom that were associated with cotrimoxazole and ampicillin. Sixty-four deaths (1.4 per million prescriptions), of which 50 were due to blood dyscrasias and 14 to skin reactions, were attributable to cotrimoxazole therapy. Thus the overall incidence of fatal reactions, though higher than that found to be associated with ampicillin (0.18 per million prescriptions), is still relatively low (34).

6.5 Clinical uses

Cotrimoxazole can be used as an alternative to daily procaine penicillin or oral amoxycillin or ampicillin for the home treatment of pneumonia (35, 36). It is considerably cheaper than either procaine penicillin or amoxycillin and beta-lactamase-producing *H. influenzae* strains are sensitive to it. Cotrimoxazole is a possible alternative to the IM benzylpenicillin/gentamicin combination for pneumonia in young infants when this is not available.

7. CHLORAMPHENICOL

Chloramphenicol, isolated in 1947, was the first-broad spectrum antibiotic. Despite more than four decades of use, the drug retains *in-vitro* and *in-vivo* activity against a wide variety of bacterial and rickettsial species.

7.1 Antimicrobial activity

Chloramphenicol is active against nearly all the bacterial species that cause pneumonia in young infants and children. These include *S. pneumoniae*, *S. aureus*, *S. pyogenes*, Group B streptococcus, *L. monocytogenes*, *H. influenzae* (including beta-lactamase-producing strains), and Gram-negative enteric bacteria such as *E. coli* and *Klebsiella* spp. Chloramphenicol-resistant *H. influenzae* strains occur, but are rare: a recent survey of 426 isolates of *Haemophilus* spp. in 11 developing nations showed that 1.6% were resistant to the drug (37).

7.2 Pharmacology

Absorption and serum levels: Chloramphenicol is difficult to dissolve and bitter. In adults and older children it can be given orally as capsules. The peak serum level in adults after an oral dose of 1.0 g is about 13 µg per ml, attained 2 hours after administration. The half-life of active chloramphenicol in serum is 1.6-3.3 hours. When serum levels of chloramphenicol are monitored, the aim is to achieve trough concentrations of about 5 µg per ml and peak levels just below 20 µg per ml (38). Young children can neither swallow capsules nor tolerate the bitter taste of the drug; the tasteless ester, chloramphenicol palmitate, is therefore used. This must be hydrolysed by enzymes in the gut before liberated active chloramphenicol can be absorbed. In neonates it gives variable blood levels, probably because of prolonged and erratic absorption of the drug (39). In older children, chloramphenicol from this ester is well absorbed and the resulting serum concentrations are similar to or higher than those achieved with IV chloramphenicol succinate (40, 41).

The pharmacodynamics of oral chloramphenicol in severely malnourished children requires further study. Two studies have suggested that the absorption of oral chloramphenicol palmitate may be normal (42, 43), however a larger third study showed erratic oral absorption with 30% of children achieving only low serum levels (44). For IM and IV administration, the soluble ester chloramphenicol succinate is used. This has no antibacterial activity, but is rapidly hydrolysed in the body to produce active chloramphenicol. Hydrolysis of the ester varies greatly from

person to person and some chloramphenicol succinate is excreted unchanged in urine (41). The peak blood level after an IV dose of this ester is similar to or lower than that attained after oral administration. This preparation has been extensively used for serious infections for many years, in the same doses as are used for oral administration, and the treatment results have been satisfactory.

In one study in adults it was found that the serum levels of chloramphenicol after IM administration of the succinate ester were only about half those attained after identical doses were given by mouth (45). About one-third of the IM dose circulated in the serum as the antimicrobially inactive ester. Although the IM route was not compared with the IV route, this study brought IM chloramphenicol into disrepute. However, plasma levels of chloramphenicol are also higher after oral administration than after IV administration, so it cannot be concluded that IV administration is superior to IM administration merely on this basis. It has been shown (46) that the bioavailability of chloramphenicol, whether given IM or IV, is only 60-70% of that of oral chloramphenicol.

IM administration has several advantages, particularly in less developed countries (it is cheaper, takes less time, and carries less risk of sepsis and overhydration).

Shann et al. (47) showed that there was no difference between IM and IV administration of chloramphenicol sodium succinate. With both methods, some succinate may circulate in the body as such and be excreted unchanged. These authors studied 70 children who were given IM (53 cases) or IV chloramphenicol (17 cases). All were given 25 mg per kg 4 times daily. The peak levels were similar in the two groups after the first dose and higher in the IM group after subsequent doses. All children achieved adequate peak levels of $>13 \mu\text{g}$ per ml.

If the clinical condition of the child improves after the first few days of IM or IV administration, chloramphenicol should then be given orally so long as it is well tolerated.

Excretion: About 90% of a dose of chloramphenicol is excreted in urine, but only 5-10% is in active form. Chloramphenicol is rapidly conjugated with glucuronic acid in the liver. These conjugates have no antibacterial activity. The active drug does not accumulate in the serum of uraemic patients. The immature liver of the newborn is deficient in chloramphenicol conjugating mechanisms, and the active drug accumulates in these patients unless smaller amounts are given.

7.3 Mode of administration and dosage

The dosage is the same for all three modes of administration: 25 mg per kg every 6 hours.

For newborn infants, a dose of 25 mg per kg every 12 hours has been recommended (48, 49). However, individual dosage adjustment with serum level monitoring is strongly recommended, where possible, in this age group.

7.4 Toxicity

Aplastic anaemia. The risk of this complication is about one in 40 000 and the aplastic anaemia is usually irreversible and fatal. It was suggested in the past that parenteral chloramphenicol might not be the cause of this complication. However, several cases of aplastic anaemia apparently caused solely by parenterally administered chloramphenicol have been reported (50).

Haemopoietic toxicity. This effect on the bone marrow reflects the pharmacological action of the drug. It occurs during treatment and is usually dose-related and reversible. This unwanted effect can be detected early if regular blood examinations, including reticulocyte counts, are performed during therapy. A falling haemoglobin and a low reticulocyte count are early warning signs. However, when chloramphenicol is given for 5-10 days only, clinically significant toxicity is uncommon.

Grey syndrome. This is an acute circulatory collapse, often fatal, which was originally described in neonates who had received excessive doses (greater than 100 mg/kg/day) of chloramphenicol. This syndrome has been clearly related to high levels of the active drug (51). Lately, a similar picture has been seen in adults and older children after an accidental overdosage of chloramphenicol

Other side-effects. Gastrointestinal symptoms may occasionally arise after oral administration. Chloramphenicol interferes with the biotransformation of tolbutamide, diphenylhydantoin, and dicoumarol. Conversely, both phenytoin and phenobarbitone may increase the rate of metabolism of chloramphenicol by the induction of hepatic microsomal enzymes; thus abnormally low serum levels of chloramphenicol may result (52).

7.5 Clinical uses

Chloramphenicol is the drug of choice for the treatment of children 2 months up to 5 years of age with very severe pneumonia, i.e., those who are cyanosed or unable to drink. Initially the drug is given by the IM route, but when the child improves, oral administration can be substituted. Chloramphenicol is also the best drug for the treatment of acute epiglottitis.

8. GENTAMICIN

Gentamicin is structurally related to other aminoglycosides (e.g., streptomycin, kanamycin, amikacin).

8.1 Antimicrobial activity

Of the Gram-positive bacteria only *S. aureus* and *S. epidermidis* are gentamicin-sensitive. *L. monocytogenes* is moderately sensitive (MIC 0.25-1.0 µg per ml) (53). The main advantage of gentamicin is that it is active against nearly all the enteric Gram-negative

bacilli such as *E. coli*, and *Enterobacter*, *Klebsiella*, *Proteus*, *Providencia*, *Serratia*, *Citrobacter*, and *Yersinia* species. Other sensitive Gram-negative bacteria include *Pseudomonas aeruginosa*, *Pasteurella multocida*, *Acinetobacter* spp., *Francisella tularensis*, and *Campylobacter jejuni*. *H. influenzae* is relatively resistant. Resistant strains of all these bacteria do occur, but are still relatively uncommon.

8.2 Pharmacology

The drug can only be given by the IM or IV route. In developing countries it is usually given IM. If a single dose of 2.5 mg per kg is given IM to a child under 5 years of age, an average peak serum level of 7 µg per ml is attained in one hour. The serum half-life of the drug is approximately 4 hours, and 8 hours after the injection the serum level falls to about 1 µg per ml. Nearly all of the administered gentamicin is excreted by the kidneys by glomerular filtration, almost entirely in the active form.

8.3 Mode of administration and dosage

Children need higher gentamicin dosages than adults to achieve similar serum levels. While the adult dose is 1.5 mg per kg every 12 hours, children under 5 years of age need 2.5 mg per kg every 8 hours.¹ The IV dose is the same as the IM dose (54). In newborn infants the dosage should be reduced to 2.5 mg per kg every 12 hours during the first week of life. Thereafter, they can be given the same dosage as children under 5 years of age (3).

Studies in experimental animals suggest that administration of the total daily aminoglycoside dose in a single injection may be equally effective and less toxic (55), but data from controlled studies in man are not yet available. Any patient who has impaired renal function needs a suitably reduced gentamicin dosage.

8.4 Toxicity

Ototoxicity, which mainly results in vestibular dysfunction but may also lead to deafness, and nephrotoxicity are the main side-effects. Both are less common in children than in adults and are unlikely to arise if a single course of treatment is given, using the doses recommended for children with normal renal function.

8.5 Clinical uses

For the treatment of pneumonia in young infants, gentamicin is used together with IM benzylpenicillin. For suspected staphylococcal pneumonia, gentamicin may be used together with cloxacillin. These drugs are often synergistic *in vitro*, but a clinical trial in staphylococcal endocarditis suggested that there may be no real benefit to be gained by adding an aminoglycoside to the penicillinase-resistant penicillin regimen (56).

Pneumonia due to *Klebsiella* and other Gram-negative species may also arise in older infants and children. If very severe pneumonia fails to respond to chloramphenicol, gentamicin and cloxacillin may be used.

¹ When gentamicin is not available, kanamycin may be used in a dose of 10mg per kg every 8 hours.

9. ERYTHROMYCIN

Erythromycin was isolated in 1952. Four preparations are available for oral administration: erythromycin base; erythromycin stearate (a salt); erythromycin ethyl succinate (an ester); and propionyl erythromycin ester lauryl sulphate (erythromycin estolate), which is the salt of an ester.

9.1 Antimicrobial activity

S. pneumoniae and *S. pyogenes* are highly susceptible to erythromycin but *S. faecalis* is less so. *S. aureus*, *S. epidermidis*, *C. diphtheriae*, and *L. monocytogenes* are also usually sensitive. Among the Gram-negative bacteria, *H. influenzae* is moderately susceptible (MIC 2.5 µg per ml) and *Legionella pneumophila* is sensitive. The enteric Gram-negative bacilli, such as *E. coli*, are usually resistant. Erythromycin is also active against *C. trachomatis* and *Mycoplasma pneumoniae*. Most organisms, in particular *S. aureus* and the streptococci, can develop resistance to erythromycin.

9.2 Pharmacology

Since erythromycin base is destroyed by acid in the stomach, tablets have been manufactured with an acid-resistant coating. In addition, enteric-coated granules or pellets of erythromycin base have been made up in capsules, and these formulations are said to offer better absorption and bioavailability. Erythromycin stearate is less easily destroyed in the stomach, and it dissociates in the duodenum, liberating active erythromycin which is absorbed.

The two erythromycin esters, ethyl succinate and estolate, are much less susceptible to gastric acid than the base and the stearate, and are more completely absorbed from the gastrointestinal tract (57, 58). For a given dose, the estolate provides higher and more lasting antibiotic activity in the serum than does the ethyl succinate, but both are antibacterially inactive until hydrolysed to free base. The estolate is hydrolysed more slowly in the body than the ethyl succinate, and circulating antibiotic levels from the estolate consist of 70-80% unchanged ester and only 20-30% of the active base. With the more rapidly hydrolysed ethyl succinate, circulating levels consist of about 45% ester and 55% active base.

The serum levels attained after single doses of erythromycin base and stearate are approximately the same. After a 250 mg dose administered to a fasting adult the peak serum level attained in 2 hours is 0.5-1.0 µg per ml. The peak serum level attained after the administration of erythromycin estolate is some 3-4 times higher. Food has no appreciable influence on the absorption of estolate, whereas the base and stearate are poorly absorbed if given with food. Even allowing for a proportion that circulates as unhydrolysed ester, the estolate gives higher levels of active erythromycin than other erythromycin preparations taken by mouth. Erythromycin is excreted partly in the urine and partly in the bile, but a large proportion seems to be inactivated in the body.

9.3 Mode of administration and dosage

The two esters of erythromycin, being tasteless and little affected by gastric acid, are best for children. In infants under 2 months of age erythromycin estolate suspension is given in a dosage of 10 mg per kg every 8 to 12 hours. The dose of erythromycin ethyl succinate is 10 mg per kg every 6 hours (59). For older infants and children, the usual dose of any erythromycin paediatric preparation is 15 mg per kg every 8 hours. Erythromycin can be given IV for the treatment of severe infections, as erythromycin lactobionate or gluceptate. Erythromycin is best not given IM since the large volume of water required to dissolve 500 mg (10 ml) makes injections very painful.

9.4 Toxicity

Nausea, vomiting, and diarrhoea may result from treatment with oral erythromycin. Hepatotoxicity is an uncommon complication that is usually associated with the estolate preparation but has been reported with other formulations. Jaundice with upper abdominal pain begins about 10 days after the start of treatment. Eosinophilia is present and liver function tests usually indicate cholestasis. On withdrawal of the drug most patients recover completely.

9.5 Clinical uses

Erythromycin is commonly given to penicillin-allergic patients for indications such as streptococcal pharyngitis, staphylococcal pneumonia, and diphtheria. The drug is also effective for chlamydial pneumonia in infancy and for *Mycoplasma* and *Legionella* pneumonia. In pertussis, erythromycin usually eliminates the organisms from the nasopharynx with the main effect of reducing transmission to the population. It may also shorten the course of the disease, but only if treatment is given early (60).

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ANNEX 1

ANTIBIOTIC ACTIVITY AGAINST COMMON RESPIRATORY PATHOGENS
USUAL (MEDIAN) MINIMUM INHIBITORY CONCENTRATION OF ANTIBIOTICS AGAINST COMMON RESPIRATORY PATHOGENS (µG/ML)

A. Pathogen	Benzylpenicillin	Penicillin V	Ampicillin	Oxacillin	Erythromycin	Chloramphenicol	Cotrimoxazole	Gentamicin
<i>Streptococcus pneumoniae</i>	0.01	0.02	0.05	0.04	0.01	3.1	1.0	6.3
<i>Haemophilus influenzae</i>	1.0	4.0	0.25	25.0	0.8	1.6	0.12	0.8
<i>Staphylococcus aureus</i> (S)	0.02	0.02	0.05	0.3	0.4	6.3	0.2	6.3
<i>Staphylococcus aureus</i> (R)	>250.0	>250.0	>25.0	0.4	>100.0	>25.0	0.2	6.3
<i>Streptococcus pyogenes</i>	0.005	0.01	0.02	0.04	3.1	0.4	6.3	
<i>Escherichia coli</i>	100.0	125.0	3.0	>1000.0	>25.0	6.3	0.2	0.6
<i>Klebsiella pneumoniae</i>	250.0	>250.0	250.0	>1000.0	>100.0	3.1	0.5	0.8
<i>Salmonella</i> spp.	10.0	125.0	1.5	>1000.0	>100.0	3.1	0.3	0.7
<i>Corynebacterium diphtheriae</i>	0.1	-	0.02	>5.0	0.025	0.8	0.4	0.4
<i>Bordetella pertussis</i>	3.1	-	1.6	-	0.09	0.8	3.0	1.0
<i>Chlamydia trachomatis</i>	1.0	-	0.25	-	0.3	10.0	-	500.0
B. Peak Serum Level ¹ (µg/ml) associated with doses recommended in this document	15.0	2.0	3.0	8.0	1.0 ² 3.0 ³	13.0	2.0	7.0

(S) = Penicillinase-negative
(R) = Penicillinase-positive.

* Levels are for trimethoprim components only.

¹ To assess whether a given antibiotic is appropriate for the treatment of a specific bacterial infection the peak serum level for that antibiotic should be compared with the MIC for the organism of that antibiotic. In most instances, for the antibiotic to be effective against an infection caused by a given organism, the peak serum level achieved should be at least double the MIC. However, for some infections such as bacterial endocarditis and meningitis, the serum level has to be much higher than this. There are also some infections which do not respond to a given antibiotic at all, even if the serum level achieved is many times higher than the MIC for the organism concerned; as an example, systemic salmonella infections do not respond to aminoglycosides although, for instance in the case of gentamicin, the peak serum level is some ten times higher than the MIC.

² Base or stearate.

³ Estolate.

ANNEX 2

Table of antibiotic doses

ANTIBIOTIC	Dose/frequency (for each dose, not total daily dose)	Form	Means of administration	Amount per dose (in tablets, capsules, or ml) according to body weight in kg				
				3-5 kg	6-9 kg	10-14 kg	15-19 kg	20-29 kg
Amoxicillin	15 mg per kg every 8 hours	250-mg tablet	oral	0.25	0.5	0.5	1	1
	15 mg per kg every 8 hours	Syrup containing 125 mg in 5 ml	oral	2.5	5	10	10	-
Ampicillin	25 mg per kg every 6 hours	250-mg tablet	oral	0.5	1	1	1	2
	50 mg per kg every 6 hours	vial of 500 mg, mix with 2.5 ml sterile water	intramuscular ^a or intravenous	1 ^a	2	3	4-5	5-6
Chloramphenicol ^b	25 mg per kg every 6 hours	vial of 1 g; mix with 4 ml sterile water	intramuscular or intravenous	0.5 ^b	1	1.5	2	2.5
	maximum 1 gram per dose	125-mg/5-ml sus- pension (palmitate)	oral	6	8	12	15	-
		250-mg capsule	oral	-	-	1	1	2
Cloxacillin, ^a flucloxacillin, oxacillin	25-50 mg per kg every 6 hours	vial of 250 mg; mix with 1 ml sterile water	intramuscular or intravenous	0.5 ^a	0.5	1	1	1.5
		250-mg capsule	oral	-	-	1	1	1
Cotrimoxazole ^c	4 mg of trimetho- prim per kg every 12 hours	Adult single strength tablet containing 80 mg trimethoprim + 400 mg of sulphamethoxazole	oral	0.25 ^c	0.5	1	1	1
	4 mg of trimetho- prim per kg every 12 hours	Paediatric tablet con- taining 20 mg of trimetho- prim + 100 mg of sulpha- methoxazole	oral	1 ^c	2	3	3	4
	4 mg of trimetho- prim per kg every 12 hours	Syrup containing 40 mg of trimethoprim + 200 mg of sulphamethoxazole per 5 ml	oral	2.5 ^c	5	7.5	7.5	-

^a Cloxacillin, flucloxacillin, oxacillin, nafcillin, methicillin, and parenteral ampicillin: for infants in the first week of life, give this dose every 12 hours; in the second through fourth weeks of life, every 8 hours.

^b Do not give chloramphenicol to premature neonates. For young infants over 1 week of age, give chloramphenicol, 25 mg/kg every 12 hours.

^c If the child is less than 1 month old, give cotrimoxazole 1/2 paediatric tablet or 1.25 ml syrup twice daily. Avoid cotrimoxazole in neonates who are premature or jaundiced.

Table of antibiotic doses (continued)

ANTIBIOTIC	Dose/frequency (for each dose, not total daily dose)	Form	Amount per dose (in tablets, capsules, or ml) according to body weight in kg					
			3-5 kg	6-9 kg	10-14 kg	15-19 kg	20-29 kg	
Gentamicin ^a intramuscular or intravenous (an aminoglycoside)	2.5 mg per kg ^d every 8 hours	vial containing 20 mg (2 ml at 10 mg/ml) undiluted	ml	1 ^e	2	3	-	-
		vial containing 80 mg (2 ml at 40 mg/ml) mix with 6 ml sterile water	ml	1 ^e	2	3	-	-
		vial containing 80 mg (2 ml at 40 mg/ml) undiluted	ml	0.25 ^e	0.5	0.75	1	1.5
Kanamycin intramuscular or intravenous (an aminoglycoside)	10 mg per kg ^d every 8 hours	vial containing 250 mg (2 ml at 125 mg/ml)	ml	0.4	0.75	1	1.5	2
Methicillin or ^a nafcillin intramuscular or intravenous	25-50 mg per kg every 6 hours	vial of 500 mg; mix with 1.7 ml sterile water vial of 1 gram; mix with 3.4 ml sterile water	ml	0.5 ^a	0.5	1	1	1.5
PENICILLIN								
Benzylpenicillin ^o intramuscular (penicillin G)	50 000 units per kg every 6 hours	vial of 600 mg (1 000 000 units); mix with 2 ml sterile water	ml	0.5 ^e	1	1	2	2
Procaine penicillin intramuscular only	50 000 units per kg daily	vials of 3 grams (3 000 000 units); mix with 4 ml sterile water	ml	0.5 200 000 units	0.75 400 000 units	1 800 000 units	1.5	2
FOR SUSPECTED STREPTOCOCCAL PHARYNGITIS (NOT FOR PNEUMONIA):								
Penicillin V oral (phenoxy- methylpenicillin)	12.5 mg/kg every 6 hours or 25 mg/kg every 12 hours	125-mg tablet	tablet	0.5	1	2	2	2
				1	2	3	3	3
Benzathine penicillin intramuscular only		vial of 1.2 million units		300 000 units	600 000 units		1.2 million units	
FOR SPECIFIC TREATMENT OF PERTUSSIS:								
Erythromycin ^f oral	15 mg/kg every every 8 hours	250-mg tablet	tablet	0.25	0.5	0.5	1	1

^d In administering an aminoglycoside, it is preferable to calculate the *exact* dose based on the child's weight and to avoid using undiluted 40 mg/ml gentamicin.

^e For the first week of life: benzylpenicillin 50 000 units/kg every 12 hours plus gentamicin 2.5 mg/kg or kanamycin 10 mg/kg every 12 hours.

^f If the child is under 2 months of age, the dose of erythromycin estolate is 10 mg per kg every 8-12 hours and the dose of erythromycin ethyl succinate is 10 mg per kg every 6 hours.
