WHO Model List of Essential Medicines for Children currently lists two macrolides, azithromycin and erythromycin. Azithromycin (cap 250/500 mg and oral liquid 250mg/5ml) is only for treating trachoma, in children above 6 months. Oral (tab-cap 250 mg, powder for oral liquid 125 mg, as stearate or ethyl succinate) and parenteral (500 mg powder as lactobionate per vial) erythromycin is also listed. This review is to decide on the appropriate macrolide to be included in the list and to judge safety in neonates.

Summary
Erythromycin (base, stearate, ethyl succinate), azithromycin and clarithromycin are available internationally. The latter two are approved for use only in children above 6 months. Their in vitro spectrum of activity is similar. Clinical evidence on superiority in safety and efficacy for different indications and age groups is scanty. While erythromycin needs to be administered as multiple daily oral doses, azithromycin can be given as single daily oral dose and clarithromycin as twice daily oral doses. The latter two have much less GI related side effects and so are better tolerated. Penetration into tissues is good especially for azithromycin and clarithromycin. Since azithromycin does not inhibit CYP3A, drug interactions are less compared to erythromycin and clarithromycin.

Indications where macrolides are used as first line drugs include trachoma, neonatal infections due to C trachomatis, pertussis, Campylobacter enteritis and legionnaires disease. Azithromycin is recommended for trachoma and erythromycin for eye infections and pneumonia caused by C trachomatis in the neonates. For pertussis, current guidelines recommend azithromycin even in children below 1 month, since erythromycin use is associated with infantile hypertrophic pyloric stenosis (IHPS). Erythromycin is approved for this indication in neonates. IHPS has recently been reported with azithromycin. However, this complication is infrequent with both drugs. Legionellosis can be treated with any macrolide. Clarithromycin and azithromycin are
among the primary drugs for treatment and secondary prophylaxis of disseminated MAC infection in HIV infected children. All three are recommended as second line drugs for many common childhood infections like acute otitis media (AOM) and community acquired pneumonia (CAP). They are also useful for treating streptococcal infections, diphtheria etc in children with serious penicillin hypersensitivity. FDA approved (Zithromax label) indications for azithromycin use in children above 6 months are AOM, CAP, tonsillo-pharyngitis and acute bacterial sinusitis (ABS) and for clarithromycin (Biaxin label), tonsillo-pharyngitis, CAP, AOM, ABS, uncomplicated skin and soft tissue infections and MAC (>20 months) infections. Erythromycin is least expensive followed by azithromycin and clarithromycin. All three have unpleasant taste, but erythromycin is the most palatable. Parenteral preparations have limited use in children and the use is associated with thrombophlebitis.

**Recommendations**

**Azithromycin** –
- Review age restriction - since it is recommended in CDC approved guidelines for those below 1 month, limited available data show it to be effective and safe
- Remove statement on trachoma – since there are other indications where this is one of the primary drugs in children eg pertussis, other *C trachomatis* infections, campylobacter enteritis

**Erythromycin** –
- Remove injection- since oral therapy is recommended in most situations and parenteral use is associated with thrombophlebitis

**Clarithromycin** may be considered for MAC and similar mycobacterial infections

**Introduction**
Clinically useful macrolides currently available in the US include erythromycin, azithromycin, and clarithromycin (Drugs@fda). International Drug Price Indicator Guide also lists erythromycin (oral suspension, tab/cap and powder for injection), azithromycin (tab/cap and suspension) and clarithromycin (tab/cap and suspension). Telithromycin, a derivative of erythromycin is a ketolide with better activity against macrolide-resistant Gram positive organisms, for use in those above 18 yrs. This
though available in the United States, is not listed in the International Drug Price Indicator Guide. Dirithromycin was discontinued.

Erythromycin has been in use since 1950s for several indications in children and infants [1]. Erythromycin base is acid labile and so is used as enteric coated capsules. Esters like stearate, estolate, and ethylsuccinate have improved acid stability, and their absorption is less altered by food [2]. These are administered as four divided doses per day. Azithromycin and clarithromycin are semisynthetic derivatives of erythromycin with improved acid stability, tissue penetration and broader spectrum of activity. Clarithromycin may be given 12 hrly or as extended release tablets once daily. It is absorbed rapidly after oral administration. Azithromycin is also absorbed rapidly and is administered as single daily doses. Macrolides penetrate well into all tissues except brain and CSF. Azithromycin concentrations within tissue or secretions and cells (including phagocytes) exceed serum concentrations [2].

All three have unpleasant taste, erythromycin being most palatable [3]. Erythromycin is less expensive as compared to others.

**Spectrum**

Spectrum of activity of macrolides is similar to that of penicillin. Activity against micro-organisms causing common infections where macrolides are used in children is shown in table. Cross resistance between macrolides is complete.

<table>
<thead>
<tr>
<th>Respiratory pathogens</th>
<th>In vitro</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S pneumoniae</strong></td>
<td>Azithromycin least active Resistance coexists with penicillin resistance</td>
<td>All effective for AOM, CAP due to these agents [5] Recommended in children</td>
</tr>
<tr>
<td>Resistance rates can vary in different areas. Recent US data 34% resistant. Higher rates in children [4]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>H influenzae</strong></td>
<td>Modest activity Azithromycin better</td>
<td></td>
</tr>
<tr>
<td><strong>M pneumoniae</strong></td>
<td>Good activity[6]</td>
<td></td>
</tr>
<tr>
<td><strong>L pneumohila</strong></td>
<td>Good activity</td>
<td>Usually adults, Any macrolide [7]</td>
</tr>
<tr>
<td><strong>S pyogenes</strong></td>
<td>Azithromycin least active</td>
<td>Children allergic to penicillin. No evidence on ability to prevent rheumatic fever [10]</td>
</tr>
<tr>
<td>Resistance varies in different areas from &lt;10 to &gt;40% [8, 9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Status</td>
<td>Treatment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>B pertussis</td>
<td>Active</td>
<td>Azithromycin or erythromycin in children below 1 m any macrolide above that [11]</td>
</tr>
<tr>
<td>C diphtheria</td>
<td>Active</td>
<td>Erythromycin in penicillin allergy[1]</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C trachomatis</td>
<td>Active</td>
<td>Azithromycin recommended</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td></td>
<td>Azithromycin better activity, azithromycin or erythromycin recommended[12]</td>
</tr>
<tr>
<td>H pylori</td>
<td></td>
<td>Clarithromycin is effective [13], usually in adults</td>
</tr>
<tr>
<td>Non-tuberculosis mycobacteria and protozoa eg T gondii</td>
<td></td>
<td>Azithromycin and clarithromycin effective</td>
</tr>
</tbody>
</table>

Although they are active against Gram positive cocci, susceptibility of S aureus is not predictable. There is no activity against enteric group of Gram negative bacilli.

**Adverse events**[2, 13-16]

Safety of azithromycin and clarithromycin in children below 6 months is not established and so are not approved in this age group [13, 15]. Data on clarithromycin in children is scanty as compared to azithromycin and erythromycin. However serious adverse events are rare. With azithromycin <1% children and with clarithromycin <2% discontinued treatment because of adverse events [13, 15].

Most events are GI related. These are more frequent with erythromycin as compared to azithromycin and clarithromycin. Oral erythromycin frequently is accompanied by epigastric distress, which may be quite severe. This is more common in children and young adults. IV erythromycin may also cause similar symptoms. Only about 2-3 % children on azithromycin and clarithromycin develop GI related events [13, 15].

Cholestatic hepatitis is caused primarily by erythromycin estolate and rarely by the ethylsuccinate or the stearate. Hepatic dysfunction with elevated enzymes can occur, but infrequently, with azithromycin and clarithromycin [13, 15].

Erythromycin and clarithromycin inhibit CYP 3A and so interact with several drugs. Azithromycin is relatively free of this effect [2].
IHPS is associated with erythromycin use. IHPS requiring pyloromyotomy occurred in 7 (5%) of 157 neonates receiving pertussis prophylaxis with erythromycin. This effect may be dose dependant with a risk of 5% for infants on treatment for 8-14 days and 10% for those on therapy for 15 to 21 days [14]. Data on azithromycin and clarithromycin in this age group are scanty. An early study using azithromycin in a small number of infants showed no major adverse events [17]. No IHPS was observed in 58 neonates receiving azithromycin and 18 receiving erythromycin for prophylaxis of pertussis [18]. However there is at least a case report of two neonates developing IHPS following azithromycin [19].

Severe thrombophlebitis can follow IV administration of erythromycin. Rapid IV administration can cause serious ventricular arrhythmias (Australian Medicines Handbook). IM is not recommended.

Allergic reactions, mild to severe can occur and include fever, eosinophilia, skin eruptions and anaphylaxis.

Head ache is also reported in 2-3% of children

Cardiac arrhythmias, including QT prolongation with ventricular tachycardia can occur with macrolides especially in those with underlying cardiac disease

Transient auditory impairment is reported

Superinfection including antibiotic associated diarrhoea can occur with all three drugs

Tooth and tongue discoloration and taste disturbances occur more commonly clarithromycin.

Uses

Macrolides are used in children for many indications. However, in those below 6 months, indications are limited to therapy or prophylaxis of pertussis and therapy of eye infection or pneumonia due to *Chlamydia trachomatis*. (BNF C 2006 gives dosage for neonates and children below 6 months for erythromycin and clarithromycin only).

*Chlamydia trachomatis* infections

*Trachoma*: Blindness due to trachoma is a public health problem. Single dose azithromycin is as effective as conventional topical tetracycline [20]. A recent randomised controlled clinical trial showed 96% clinical cure with single oral dose of azithromycin [21]. Mass therapy of individuals above one year with single dose
azithromycin is also evaluated as a method of trachoma eradication [22]. WHO recommends either oral azithromycin as single dose or tetracycline eye ointment for trachoma treatment. It also recommends annual mass therapy in certain areas [23]. This is not FDA approved indication.

*C trachomatis infections in the new born* include conjunctivitis and pneumonia. About 20-50% of infants born to infected mothers develop conjunctivitis and 5-20% pneumonia [24]. Erythromycin is recommended (Australian Medicines Handbook) [25] and systemic therapy is preferred even for conjunctivitis since the possibility of infections at other sites exists. A study on small number of infants less than 1 month showed azithromycin also to be effective and safe [17].

**Pertussis**

Although effective vaccines are available, cases and out breaks still occur[26]. In areas where vaccination rate is high young infants and older children, adolescents and adults have higher incidence[26, 27]. This infection is associated with high case fatality rate [11, 27]. Macrolides are the drugs of choice for therapy and post exposure prophylaxis [11]. There is no clinical evidence for better efficacy or safety for any one drug. Although not approved for use in children below 6 months, azithromycin is recommended as the preferred macrolide in children including those below 1 month, in guidelines approved by American Academy of Paediatrics and CDC [11, 28]. A few clinical trials in this age group show safety and efficacy (28). Clarithromycin can be used in children above 1 month. FDA approved erythromycin label states that it can be used in neonates if benefits outweigh risks.

**Legionnaires disease** – This disease is more common among adults and most reports are from developed countries [29, 30]. A macrolide is recommended as first line therapy[7]. Azithromycin and clarithromycin are preferred [7] although clinical evidence for their superiority is lacking. For severe infections, although IV macrolides can be used, there are other options [7].

**Campylobacter jejuni:** Macrolides are recommended for this infection [12]

**MAC:** Using clarithromycin in HIV infected patients with disseminated MAC or M kansasii infection prolongs survival [13, 31, 32]. Macrolides however, are not used as
monotherapy and antiretroviral therapy is required [31]. Clarithromycin or azithromycin can be used, but clarithromycin has the greatest invitro activity (Australia Medicines Handbook) and so preferred by some [31] but is not recommended below 20 months for this treatment [13]. Incidence of opportunistic infections including disseminated non tuberculosis mycobacterial infections are decreasing in children and is about 0.2 cases per 100 patient years [33].

Respiratory infections
Acute respiratory infections form one of the major indications for antibiotic use in children. Several bacterial pathogens causing this group of infections including *M. pneumoniae* are susceptible to macrolides. A trial (1997) showed that azithromycin can bring about bacteriological and clinical cure in children (6m-12yrs) with AOM, sinusitis, CAP and tonsillitis[5]. The drug was well tolerated and only about 6% developed side effects, mostly GI related. In Canada, while overall antibiotic use decreased over a period of time, macrolide use increased considerably. The increase was mostly with the use of azithromycin, followed by clarithromycin [34]. Most frequent indication was upper respiratory tract infections. Frequent use of azithromycin for respiratory infections and AOM contributes to selection of resistant strains.

Macrolides are not recommended as first line drugs for most respiratory infections.

*AOM:* Recent trials (2007) show that clinical cure rates with azithromycin are similar to that of amoxicillin, ceftriaxone [35] and co-amoxyclovulanic acid [36]. Data from 4 trials in children using azithromycin single dose therapy for AOM show that end of therapy clinical success rate was 88% (544/619) [37]. Guidelines for treatment of AOM in children however include azithromycin and clarithromycin only as second line drugs to be used in those with beta lactam allergies, recurrence and persistent AOM despite antibiotic therapy etc [38]. Penetration of erythromycin to middle ear fluid is not good.

*Acute bacterial sinusitis:* When antibiotics are indicated, a macrolide is not the first choice. It can be used in type 1 hypersensitivity to penicillin [39].

*Streptococcal sore throat:* Macrolides, especially azithromycin can be used as an alternative in children with serious penicillin allergy to eradicate streptococci [40, 41].
It is also recommended to prevent recurrent attacks of rheumatic fever in patients with serious hypersensitivity. However, there is no clinical evidence to support this [10].

Lower respiratory infections: Macrolides are effective for non severe lower respiratory infections requiring oral antibacterial therapy. A Cochrane review on antibiotics for CAP in children did not find difference between azithromycin and Co amoxyclavulanic acid and between azithromycin and erythromycin [42]. Co-amoxyclavulanic acid was better than amoxicillin alone. In a guideline from the US, a macrolide is recommended as first line therapy for children above 5yrs with CAP [43]. These are not useful as single agents for severe infections and in children with risk factors like cystic fibrosis.

Diphtheria- In addition to antitoxin, erythromycin can be used in children with serious penicillin allergy, to eradicate the organism.

Syphilis – As an alternative in severe penicillin allergy macrolides can be used

H pylori – Macrolides especially clarithromycin aid in eradication of H pylori [13, 44]

Macrolides can be used for treating skin and soft tissue infections, but resistance is very high among potential pathogens

References

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14. *Erythromycin ethyl succinate label*. Abbott laboratories, USA.


38. *Evidence based clinical practice guideline for medical management of acute otitis media in children 2 months to 13 years of age.* Health Policy and Clinical Effectiveness Programme, Cincinnati Children's Hospital Medical Centre, 2004.


43. *Evidence based care guideline for community acquired pneumonia in children 60 days through 17 years of age.* Cincinnati Children's Hospital Medical Center. Cincinnati, 2006.