1. **Summary statement of the proposal for inclusion, change or deletion**

Currently there are no oral cephalosporins on the list of essential medicines for children, although these are widely used in community outpatient practice. Hence the subcommittee on selection and use of essential medicines recommended that a full review and application be submitted for including an oral cephalosporin in the list. Accordingly, this application is to include cephalexin, a first generation cephalosporin.

Cephalexin, active against Gram positive cocci like *Staphylococcus aureus* and *Streptococcus pyogenes* and a few gram negative bacilli, is useful in treating several common community acquired infections in children. Other oral first generation cephalosporins like cefradine and cefodroxil, also have similar activity but are more expensive. The antibacterial spectrum of second generation oral cephalosporins, cefaclor and cefprozil, is similar to that of the first generation drugs, but with lesser activity against *S aureus* and better activity against *H influenzae* and *Moraxella*. Their indications for use are limited compared to first generation cephalosporins. In addition, cefaclor can cause protracted skin reactions especially in children. Cefuroxime axetil, another second generation oral cephalosporin is poorly absorbed and needs to be given with food. Third generation oral cephalosporins cefdinir and cefpodoxime proxetil are more recent introductions with extended spectrum of activity against most bacterial pathogens causing community acquired respiratory infections and skin and soft tissue infections (SSTI). These are however several times more expensive than cephalexin. International availability may also be an issue.

Cephalexin has been in use for decades. Adverse events are rare. Formulations suitable for children are available. Palatability is also documented.

Evidence based indications for cephalexin use include SSTI caused by susceptible bacteria, UTI caused by susceptible bacteria and Streptococcal pharyngitis. It can also be used to complete therapy following initial parenteral antibacterial therapy. There is no evidence to support its use in treating purulent rhinitis, sinusitis or otitis media or for its prophylactic use to prevent skin and soft tissue infections. Prevalence of SSTI and UTI caused by bacteria resistant to this antibiotic is increasing. Its efficacy
for preventing sequel like rheumatic fever is not proven. For the three indications mentioned above, other oral medicines with equal or better clinical efficacy are presently listed.

Cephalexin is widely used in paediatric out patient practice for non severe infections. In order to prevent rapid emergence of resistance to this and related drugs, it is important to restrict its use only to treatment of infections where antibacterial therapy is indicated and where cephalexin is the appropriate choice.

**Summary of issues to be considered for including cephalexin in the EML for children**

<table>
<thead>
<tr>
<th>In favour</th>
<th>Concern</th>
</tr>
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</table>
| **General** | • Good spectrum  
• Formulations  
• Palatability  
• Few adverse events  
• Less expensive  
• International availability | • Likely to be misused and so chance of driving resistance rates high |
| **Skin and soft tissue infections** | • Clinically not inferior to other oral and topical treatment  
• Recommended in guidelines | • Increasing resistance (>50% MRSA in some areas)  
• Other inexpensive oral therapies available |
| **UTI** | • *E coli* are susceptible  
• Clinical efficacy | • >25% in vitro resistance in some areas preventing empirical use  
• No recent clinical trials |
| **Respiratory infection** | • Proven effective for *Streptococcal pharyngitis* | • No evidence on ability to prevent rheumatic fever  
• No evidence for utility in other lower and upper respiratory infections |
| **Prophylactic use** | • Limited use for UTI | • No evidence for skin and superficial infections |
2. Name of the focal point in WHO submitting or supporting application

3. Names of organisations consulted and or supporting the application

4. International non-propriety name (INN generic name) of the medicine
Cephalexin

5. Formulation proposed for inclusion – paediatric
Capsules – 250mg tab-cap
Suspension or powder to be reconstituted with water – 125mg/5ml or 125mg/ml

6. International availability – sources, if possible manufacturers
250 mg tab-cap – UNFPA, IMRES, MEDS, DURBIN, JMS, ORBI, ACTION
125mg/ml – MEDS
125mg/5ml - UNFPA

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group
As individual drug (belonging to first generation cephalosporins)

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)
Cephalexin is used for the treatment of skin and soft tissue infections, urinary tract infections (UTI) and different types of upper and lower respiratory infections in children.

a. Skin and soft tissue infections
   A variety of SSTI affect children and include impetigo, cellulites, erysipelas, folliculitis and abscesses. Skin infections are the most common bacterial infections seen in children seeking primary care [1, 2].
   
   Impetigo is a contagious infection affecting mostly 2-5yr old children [1]. Incidence is higher in areas with poor hygiene and overcrowding [1]. Data from the UK show that the annual incidence of impetigo in children seen in primary practice is 2.8% in < 4 yrs and 1.6% in those between 5-14yrs [3]. In a study done in children and
youths (median age 5.3 yrs) in Australian aboriginal communities, where skin infections are very common, impetigo accounted for 65% of skin infections[4]. Nonbullous impetigo is most common and accounts for about 70% of paediatric cases[5]. Diagnosis is usually made clinically [1]. Gram stain and culture help in identifying the causative organism [1]. While simple infections can be managed with topical therapy, more extensive infections require oral therapy.

Cellulitis also occurs in children frequently, usually following a break in the skin. Prompt antibiotic therapy is required [5].

*Staphylococcus aureus* and *Streptococcus pyogenes* are the most common causative agents of these infections [1, 2, 4, 5]. Cephalexin is active against methicillin susceptible *S aureus* (irrespective of penicillinase production) and streptococci [5-8] It is therefore recommended in children for the treatment of impetigo and cellulitis requiring systemic antimicrobial therapy and also for other skin and soft tissue infections caused by *Staphylococci* or streptococci and surgical site infections following non intestinal surgeries and in areas away from perineum and axilla[9].

Cephalosporins have no action on methicillin resistant *S aureus* (MRSA). Prevalence of community acquired MRSA infections is increasing [10]. A study in the US shows that community acquired MRSA infection occurs in 18-25 individuals per 100000 population; 77% of these had SSTI [11]. The incidence is higher in children below 2 yrs of age [11]. Data from other areas also show that prevalence of MRSA in SSTI can be well above 50% [12, 13]. Although treatment failures can be expected in such cases, reports based on clinical observations from some centres show no adverse outcomes in patients treated with drugs not useful against MRSA [11, 14]. However, others recommend specific anti MRSA therapy in such cases [15].

Cephalexin was the most used oral antibiotic for non facial cellulitis in children in a study in a paediatric surgery emergency department [16]. For periorbital and orbital cellulitis following trauma also, first generation cephalosporins is recommended as one of the alternatives [17].

Cephalexin is not useful for treating necrotising infections and gas gangrene. It is not generally recommended for infections associated with bites. Other cutaneous infections like anthrax require specific therapies for the causative agents.

b. UTI

Cephalexin has action against Gram negative bacilli like *E coli*, and *Klebsiella* spp[6, 7], which are the most frequent causes of community acquired UTI. Therefore, it can be
used as one of the alternative antimicrobials in treating UTI in children usually those not requiring inpatient care [18, 19]. It is not a preferred option for prophylaxis of UTI in children but can be used if nitrofuantoin or cotrimoxazole cannot be tolerated [19]. Prevalence of bacterial resistance to cephalosporins is increasing and more than 25% of *E coli* causing UTI in children are resistant to first generation cephalosporins in many areas [20-22]. Hence cephalexin is better used for UTI only after culture and susceptibility testing.

Cephalexin is not useful for UTI due to most other Gram negative bacilli and in nosocomial infections. Enterococci are also not susceptible. Data on proportion of children with UTI receiving this drug currently could not be obtained.

c. Respiratory tract infections

The only evidence based indication is tonsillopharyngitis caused by *S pyogenes*. It is recommended for use as an alternative in children allergic to penicillin, developing streptococcal sore throat [23-25] and is FDA approved for this indication [23]. It can also be used for persistent *S pyogenes* throat infections [23].

Although there is no evidence to recommend its use for other respiratory infections, it is used widely in community out patient practice for all types of upper and lower respiratory tract infections including those in children [26] since it has action on most agents causing community acquired lower and upper respiratory infections like *Streptococcus pneumoniae* (except penicillin resistant *S pneumoniae*), *Haemophilus influenzae*, *Moraxella (Branhamella) catarrhalis* and *Streptococcus pyogenes* [6, 7]. It does not form part of currently accepted guidelines for the treatment of sinusitis, acute or chronic otitis media or lower respiratory infections.

d. Other infections

Cephalexin may be effective in treating infections associated with external pin fixation in children [27]. For uncomplicated osteomyelitis, it can be used for oral therapy following parenteral therapy in children [28].

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

Cephalexin is administered orally without regard to meals, is acid-stable, and rapidly absorbed from the GI tract [6, 7]. Following a 250 or 500 mg oral dose of cephalexin, average peak serum concentrations of 9 or 15—18 mcg/ml, respectively, are achieved.
within 1 hour and mean serum concentrations decline to 1.6 or 3.4 mcg/ml, respectively, at 3 hours post-dose. Cephalexin is distributed into most body tissues and fluids but does not reach therapeutic levels within the CSF. Cephalexin is largely excreted unchanged into the urine which leads to high urinary concentrations. Specific data related to children and neonates could not be obtained.

The usual recommended dose for susceptible infections is 25 to 50mg/kg/day in divided doses. For streptococcal sore throat, twice daily dosing for 10 days is recommended [24]. For skin and soft tissue infections, four doses per day [9] for 3-14 days is required. For UTI, four doses per day for 7-14 days is recommended [19]. For UTI prophylaxis, 12.5 mg/kg as single dose at night [29] is used.

**Guidelines**

- Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Infectious Diseases Society of America - Medical Specialty Society. 2005 [9]
- Diagnosis and treatment of respiratory illness in children and adults Institute for Clinical Systems Improvement (ICSI). 1994 Jun (revised 2007 Jan) [23]
- Evidence-based care guideline for medical management of first urinary tract infection in children 12 years of age or less. Cincinnati Children's Hospital Medical Center. 2006 [19].

**10. Summary of comparative effectiveness in a variety of clinical settings:**

**Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)**

The Cochrane library was searched for reviews and other clinical trials using cephalexin for various indications. A Medline search was also done for studies documenting clinical efficacy using cephalexin/cefalexin and trial as search terms. In general there was paucity of clinical trials, especially recent ones and those evaluating cephalexin in children. Most trials showed non inferiority as compared to other drugs.
SSTI

A Cochrane review (2003) on impetigo showed that for non bullous impetigo, topical treatment with mupirocin brings about better cure rates as compared to placebo (OR 6.49; 95% CI 3.93 – 10.73) [8]. There were no significant differences between mupirocin or oral therapy with cephalexin or other oral cephalosporins [8]. For bullous impetigo, there was no significant difference between cephalexin and dicloxacillin (OR 3.39; 95% CI 0.62 – 18.49) [8]. For secondary impetigo, there was no difference between cephalexin and enoxacin[8]. There was insufficient data to understand recurrence rates and development of bacterial resistance. Studies where cephalexin was used are shown in table 1.

Although recent in vitro data suggest superiority of other oral cephalosporins [30] for this indication, clinical trials show that Cephalexin is still effective in treating uncomplicated skin and soft tissue infections [31] and secondary infections following trauma [32]and dermatitis [33]. The latter two trials however, show that topical therapy can be equally effective. A recent trial on management of abscesses shows that following incision and drainage cephalexin therapy and placebo had similar outcomes [34] in a population with high incidence of MRSA.

Treatment failure was recorded in 8.9% of children with cellulitis treated with cephalexin and was similar to those treated with cefazolin and probenicid [35].

Tonsillopharyngitis

Clinical trials show that cephalexin can eradicate *S pyogenes* from throat and can bring about clinical cure comparable to penicillin [36, 37]. However, evidence on its ability to prevent rheumatic fever is inadequate. Treatment failures can occur, but is less than that following treatment with penicillins [38].

For sinusitis, antibiotics have only a limited role [39]. Cephalosporins have no proven efficacy over aminopenicillins for this indication. Cephalexin is not FDA approved for this indication [23].

UTI

Earlier studies showed that cephalexin is useful in treating UTI [40, 41]. However, prevalence of bacterial resistance to cephalexin has increased since then. Studies using cephalexin for treatment of infections in children are summarised in table 2 and other recent studies in table 3.
11. Summary of comparative evidence on safety
Adverse reactions are rare with first generation cephalosporins [42]. Product literature on Keflex state that safety and effectiveness have been established in children using suspensions and capsules [7].

The important probable adverse reaction is hypersensitivity, but is very rare. About 5 - 10% of individuals hypersensitive to penicillin can have hypersensitivity to cephalosporins [6, 29, 42]. Anaphylaxis can occur in 0.0001% to 0.1% of individuals. Rash is more common but occurs only in <2% [42].

Most common adverse effects are GI related and occur in about 5%[42]. Diarrhoea is most common. Nausea vomiting, dyspepsia and gastritis can occur. These events may be severe enough to discontinue therapy. Mild to severe antibiotic associated diarrhoea is reported [29]. Intestinal and vaginal candidiasis is also a possibility [42]. Cholestatic hepatitis is also described. [29, 43]

Since these drugs are primarily eliminated through kidneys, dosage needs to be modified in case of renal impairment [29].

Cephalosporins can cause a fall in prothrombin activity and so those at risk should be monitored [7]. These drugs are also reported to trigger seizures and cause sleep disturbances and hallucinations. Abnormalities like elevated bilirubin, elevated LDH, pancytopenia etc are also reported [7, 29].

Renal clearance of metfromin can be delayed. Cephalexin excretion is inhibited by probenecid

Cephalosporin use can cause false positive Coombs test. This can also occur in new born babies of mothers on cephalosporins. It can also cause a false positive glucose in urine test [7].

12. Summary of available data on comparative cost and cost effectiveness within the pharmacological class or therapeutic group
As per International Drug Price Indicator Guide, a range of prices are there. Median prices in US $ is shown below.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalexin</td>
<td>250 mg capsule</td>
<td>0.043/capsule</td>
</tr>
<tr>
<td></td>
<td>125mg/ml suspension</td>
<td>0.0076/ml</td>
</tr>
<tr>
<td></td>
<td>125mg/5ml suspension</td>
<td>0.0070/ml</td>
</tr>
</tbody>
</table>
Cefuroxime
250mg cap  0.2381/cap

Cefadroxil
250 mg/5ml  0.015/ml
125 mg/5ml  0.0127/ml
500 mg tab - cap 0.09/cap

Cefradine is not listed in the drug price indicator guide
Cefaclor is not listed in the drug price indicator guide
Cefpodoxime is not listed in the drug price indicator guide

According to BNF C,
Cephalexin - 21 cap pack is approx £4, 125mg/5 ml 100 ml-£ 3
Cefradine – 250 mg 20 cap – £4.26, 250 mg/5ml 100 ml £4.22
Cefpodoxime - 10 tab pack £10, 100ml £12
Cefprozil. 20 tab – £14.95, 250mg/5 ml 100 ml – £15.22
Cefaclor -50 cap pack £26, 100 ml £7.5
Cefadroxil . 20 cap pack £5.64, 125mg/5ml 60 ml – £1.75

13. Comparative cost effectiveness presented as range of cost per routine out come
(cost per case, cost per cure, cost per month of treatment, cost per case prevented,
cost per clinical event prevented, cost per quality adjusted life years gained, if
possible and relevant)
Therapy for 10 days with Cephalexin 250 mg 4 times a day - Approximately $1 – 2
Using suspension – approx $ 3
This is the least expensive oral cephalosporin

14. Summary of regulatory status
Cephalexin is FDA approved. The approved label recommends it for use in children
BNF C recommends it for use in children

15. Availability of pharmacopoeial standards
Reference standards and monographs are listed in European and US pharmacopoeia
16. Proposed text for the WHO Model Formulary

Cephalexin

Cephalexin is an oral first generation cephalosporin with good activity against methicillin susceptible *S.aureus* and streptococci. It also has activity against *H influenzae*, penicillin susceptible *S pneumoniae* and some *E coli* and Klebsiella spp

Tablets/ capsules  250mg
Oral suspensions  125mg/5ml and 125mg/ml

Uses in children

1. Infections of skin and related structures caused by susceptible bacteria - in those requiring systemic antibiotics, as an alternative to penicillin group of drugs.
2. UTI caused by susceptible bacteria – to be used based on susceptibility data.
3. Streptococcal tonsillo pharyngitis in children allergic to penicillin, as an alternative to erythromycin

Caution

- To check emergence and spread of resistance, use only for infections strongly suspected or proven to benefit from cephalexin. Inform patients about appropriate use
- There is insufficient data on its ability to prevent rheumatic fever/carditis.

Contraindications

Proven immediate hypersensitivity to penicillin or carbapenems.

Precautions

Hypersensitivity reactions can occur in individuals with penicillin hypersensitivity
Super infection with non susceptible microorganisms can occur during therapy
The dose has to be reduced in renal impairment.
Can cause false positive Coombs test results and urine glucose results

Dosage

<table>
<thead>
<tr>
<th>Children</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of infection</td>
<td>25 -50 mg/kg/day</td>
<td>2-4 divided doses</td>
</tr>
<tr>
<td>Prophylaxis for UTI</td>
<td>12.5 mg/kg (max 125mg) at night</td>
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</tr>
</tbody>
</table>

Adverse reactions

Adverse reactions are rare.
GI related symptoms like nausea, vomiting and diarrhoea are the commonest
Allergic rash and anaphylaxis can occur.
Confusion can follow large doses in patients with renal impairment
References


19. Evidence-based care guideline for medical management of first urinary tract infection in children 12 years of age or less. Cincinnati Children's Hospital Medical Center., 2006.


<table>
<thead>
<tr>
<th><strong>Participants</strong></th>
<th><strong>Interventions</strong></th>
<th><strong>Outcomes</strong></th>
<th><strong>Notes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bass 1997 Hawaii Allocation concealment - B Outpatients only impetigo av age 3.8 yrs, S. aureus 41/48</td>
<td>1. cephalexin 50 mg/kg/day in 3 dd + placebo ointment, 10 days 2. mupirocin ointment 2%, 3td + liquid oral placebo 3. bacitracin ointment 500 units/g, 3td + liquid oral placebo</td>
<td>8-10 days, cure</td>
<td>Lost to follow up (LTFU) 6/32, (5 mupirocin) Side effects- not reported</td>
</tr>
<tr>
<td>Demidovich 1990 Hawaii Allocation concealment - B Outpatients, only impetigo 5 m-15 yrs (av 3 yrs) S. aureus 45/73, GABHS 6/73, both 14/73,</td>
<td>1. penicillin V 40-50 mg/kg/day in 3 dd, 10 days 2. cephalexin 40-50 mg/kg/day in 3 dd, 10 days 3. erythromycin 30-40 mg/kg/day in 3 dd, 10 days</td>
<td>8-10 days, failed</td>
<td>LTFU: 2/ 75 SE: nil reported</td>
</tr>
<tr>
<td>Dillon 1983 USA Allocation concealment - B only impetigo (bullous 57/70) av age 3.2 yrs, MF 41/37, S. aureus: 64/70</td>
<td>1. cephalexin 50 mg/kg/day in 2 dd (&gt;20 kg: 500mg 2td) 2. dicloxacillin 15 mg/kg/day in 4 dd (&gt;40 kg: 125 mg 4td)</td>
<td>Prompt cure</td>
<td>LTFU: C: 5/40, D: 3/38</td>
</tr>
<tr>
<td>Fujita 1984 Japan Allocation concealment - B outpatients Age 16-84 yrs M/F 120/84</td>
<td>1. enoxacgin 500 mg, 3td 2. cephalexin 500 mg 2td (double dummy)</td>
<td>cured/imp roved</td>
<td>LTFU 20/224 SE: E 11 of 113, C 4 of 110 (mainly GI)</td>
</tr>
<tr>
<td>Hains 1989 USA Allocation concealment - B outpatients child hospital only impetigo 1-18 yrs, S. aureus 35%, GABHS 12% both 54%</td>
<td>1. cefadroxil 30 mg/kg/day, max 1 g., in 1 dd, 10 days 2. cephalexin 30 mg/kg/day, max 1 g., in 2 dd, 10 days</td>
<td>14 days, cured</td>
<td>SE none reported</td>
</tr>
<tr>
<td>Kiani 1991 multicentre USA admitted + outpatients S. aureus 152/179,</td>
<td>1. azithromycin 500 mg day 1, 250 mg, day 2-5, 5 days</td>
<td>11 days, cured/imp</td>
<td>253 entered, 179 evaluable (41</td>
</tr>
<tr>
<td>Allocation B</td>
<td>Participants</td>
<td>Interventions</td>
<td>Outcomes</td>
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</tr>
<tr>
<td>Tack 1997 multicentre US Allocation - C</td>
<td>S. pyogones 29/179</td>
<td>2. cephalexin 500 mg twice daily, 10 days</td>
<td>roved</td>
</tr>
<tr>
<td>Tack 1998 multicenter USA Allocation concealment - B</td>
<td>0-13 yrs (median 5.4) M/F 217/197 S. aureus 284/394</td>
<td>1. cefdinir 7 mg/kg, twice a day 10 days 2. cephalexin 10 mg/kg four times a day 10 days</td>
<td>7-14 day, cure</td>
</tr>
<tr>
<td>Tack 1998 multicenter USA Allocation concealment - B</td>
<td>13-88 yrs, M/F 564/388 (all participants), S. aureus 308/382 (all participants)</td>
<td>1. cefdinir caps 300 mg, 2 times a day, 10 days 2. cephalexin caps 500 mg, 4 times a day, 10 days</td>
<td>7-16 days, cure/improved</td>
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<tr>
<td>Study</td>
<td>Methods</td>
<td>Participants</td>
<td>Interventions</td>
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</tr>
<tr>
<td>Disney FA[36], 1992, USA</td>
<td>Randomized, double-blind, crossover</td>
<td>Tonsillitis or pharyngitis and throat cultures with GABHS Children and</td>
<td>1. cephalaxin 2. penicillin (27 mg/kg per day) Four doses for 10 days.</td>
</tr>
<tr>
<td></td>
<td>study Multicentric</td>
<td>adolescents (525)</td>
<td></td>
</tr>
<tr>
<td>Curtin C, 2003[37]</td>
<td>Prospective open-label, observational</td>
<td>Children with acute tonsillo-pharyngitis with laboratory confirmed GABHS</td>
<td>1. Cephalaxin twice (54) 2. three times daily (94) 3. Cefadroxil once daily</td>
</tr>
<tr>
<td></td>
<td>cohort study Intention to treat</td>
<td></td>
<td>(70)</td>
</tr>
<tr>
<td>Stillerman M[44], 1984,</td>
<td>Double-blind, randomized Multicenter</td>
<td>GABHS pharyngitis</td>
<td>1. Cephalaxin 1.0/ 0.5 g daily bid (82) 2. qid (75) for 10 to 14 days</td>
</tr>
<tr>
<td>Pediatrics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tarpay MM [45], 1984 USA</td>
<td>Double-blind controlled study</td>
<td>GABHS pharyngitis in 65 children</td>
<td>1. cephalaxin b.i.d. 2.q.i.d.</td>
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</tr>
<tr>
<td>Study</td>
<td>Methods</td>
<td>Participants</td>
<td>Interventions</td>
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</table>
| Matsen JM [46] 1974      |                                | Children with streptococcal pharyngitis. All but six had GABHS isolated from throat cultures (128). | 1. cephalaxin for 10 days (66)  
2. phenoxyemethyl penicillin for 10 days (34)  
3. a single injection of benzathine penicillin (28) | Similar cure rates - 96.7, 97.1, and 96.4%  
Bacteriological failures - cephalexin 2, one each with oral penicillin and IM penicillin. |                      |
| Skin related infections   |                                |                                                                              |                                                                                                         |                                                                                               |                                     |
| Tack KJ[47], 1997 USA    | Multicenter Randomized Controlled Trial investigator-blind | Children with impetigo and secondary infection of preexisting dermatitis.(394) | 1. Cefdinir, 7 mg/kg twice a day (165)  
2. Cephalexin, 10 mg/kg four times a day (156), each for 10 days. The most common pathogens were *S aureus* and *Strept pyogenes* | Microbiologic eradication  
Cefdinir 99.4%, Cephalexin 97.4% (P = 0.14).  
Clinical cure rates Cefdinir 98.3%, Cephalexin 93.8% (P = 0.056). | 16% cefdinir, 11% cephalexin (P = 0.11)  
diarrhea most common - 8% cefdinir 4% cephalexin |
| Linder[48] 1993, USA      | Randomized, Multicenter       | Pyoderma children and adolescents (1-18 years).  
*S aureus* (56%)  
*Strept pyogenes* (39%). | 1. Cefadroxil single oral daily dose 30 mg/kg, (156)  
2. Cephalexin 30 mg/kg/day in 2 divided doses,(133) for 10 days | Bacteriologic response  
Statistically greater in the patients treated with cefadroxil (96% versus 89%; P = 0.042).  
Clinical response cefadroxil-94%, cephalexin 92% - (P = 0.476). | Compliance 95% cefadroxil, 65% cephalexin (P < 0.0001).  
Adverse events were infrequent and mild |
| Mallory SB[49] 1991, USA  | Randomized Controlled third-party-blinded Multicentric | Skin and skin structure infn (148). Mainly *S aureus* and | 1. Azithromycin (500 mg on day 1, 250 mg/day on days 2-5)  
2. Cephalexin (500 mg | Clinical cure azithromycin - 99%, cephalexin 96%  
On completion of therapy, both treatments had eradicated | Both agents were well-tolerated |


<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcome</th>
<th>Adverse events</th>
</tr>
</thead>
</table>
| hospital                    | Randomized Controlled clinical Trial         | Children with impetigo (73) (62% - S aureus only, 19% - S aureus and GABHS, 8% GABHS only, and 11% others) | 1. Penicillin V  
2. Cephalexin 40 to 50 mg/kg per day  
3. Erythromycin 30 to 40 mg/kg per day. All were given in 3 divided doses for 10 days. | Treatment failure penicillin V -24%, erythromycin -4% and none with cephalexin                    |                                                     |
| Demidovic h[50],1990 Hawaii | Follow up examiners blinded                  |                                                                              |                                                                                 |                                                                                                    |                                                     |
| Mouallem R [51] 1976        | Randomized, double-blind study               | Bacterial infections (lobar pneumonia or skin infections) in children 4 months – 11yrs (162) | 1. Cephradine - 25-110 mg/kg per day  
2. Cephalexin - 25-150 mg/kg per day for five to fifteen days. | Clinical and bacteriologic responses nearly identical in the two groups | Both equally safe for use in paediatric practice.                                                  |
| UTI and others              |                                               |                                                                              |                                                                                 |                                                                                                    |                                                     |
| Helin I[41] 1984            | prospective                                  | children with acute lower urinary tract infection                            | 1. Cephalexin, 25-50 mg/kg x 3-days (19)  
2. Nitrofurantoin, 3-4 mg/kg/day x 10 days (24) | Cure rates 90% and 96%, respectively. Relapse – 2 and 1 respectively  
Reinfection on follow-up 7-8 months - 2 cephalexin and 4 nitrofurantoin | No side effects in either of the treatment groups.                                               |
| Russo RM [40], 1977         | Double blind, comparative study              | Children with initial episodes of UTI(100)                                  | 1. Cephalexin  
2. Sulfisoxazole | Cephalexin - clinical cure rate 86%  
bacterial cure rate 84%  
Sulfisoxazole – 82% and 92%  
high rate of failure in _Proteus mirabilis_ infections (4/8) | Minimal untoward effects                                                                        |
| Stechenberg BW [52]         | randomized                                   | Children with otitis media Bacteriologic                                   | 1. Cephalexin  
2. Ampicillin | No overall statistically significant differences; Poor response in 20 on |                                                     |
<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976, USA</td>
<td>diagnosis by needle tympanocentesis (179)</td>
<td></td>
<td></td>
<td>cephalixin and 5 on ampicillin.</td>
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<td></td>
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<td><em>H. influenzae</em> as cause- 50% on cephalixin and none on ampicillin had poor response (P&lt;.05)</td>
</tr>
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<td>Parish, LC [53]</td>
<td>Prospective, randomised, double-blind trial.</td>
<td>Adults with uncomplicated skin infections (401)</td>
<td>1. Oral moxifloxacin 400 mg OD for 7 days</td>
<td>Clinical outcome evaluated in 351 Moxifloxacin as effective as cephalixin</td>
</tr>
<tr>
<td>2000 multicentre</td>
<td></td>
<td></td>
<td>2. Cephalexin - 500 mg three times daily for 7 days</td>
<td>Clinically (90% and 91% respectively) Bacteriologically eradicating</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>S aureus (92% and 93%, respectively). Streptococcus spp. (90% and 82%,</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>respectively)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Adverse events comparable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Most frequent - moxifloxacin- nausea cephalixin- headache</td>
</tr>
<tr>
<td>Giordano PA [31]</td>
<td>Randomized Investigator blinded</td>
<td>Adults and adolescents (&gt;13 yrs) with mild to moderate uncomplicated skin and skin structure infections</td>
<td>1. cefdinir 300 mg twice daily x 10 days</td>
<td>Discontinued in 3% moxifloxacin 4% cephalixin treated patients</td>
</tr>
<tr>
<td>2006 USA.</td>
<td></td>
<td></td>
<td>2. cephalexin 250 mg four times daily x 10 days</td>
<td>Both well tolerated.</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>diarrhea (10% &amp; 4% p = 0.017),</td>
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<td></td>
<td></td>
<td>nausea (3% &amp; 6%, p = 0.203), vaginal mycosis (3% &amp; 6% p = 0.500).</td>
</tr>
<tr>
<td>Free A [32]</td>
<td>Randomized Controlled Trial double</td>
<td>patients with secondarily infected traumatic lesions</td>
<td>1. topical retapamulin 1% twice daily x 5 days</td>
<td>Safety similar</td>
</tr>
<tr>
<td>2006, USA</td>
<td></td>
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<td>Noncompliance 8.0%</td>
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**Table 3 Recent trials using cephalixin**

- **Parish, LC [53] 2000 multicentre**
  - Prospective, randomised, double-blind trial.
  - Adults with uncomplicated skin infections (401)
  - 1. Oral moxifloxacin 400 mg OD for 7 days
  - 2. Cephalexin - 500 mg three times daily for 7 days
  - Clinical outcome evaluated in 351 Moxifloxacin as effective as cephalixin Clinically (90% and 91% respectively) Bacteriologically eradicating S aureus (92% and 93%, respectively). Streptococcus spp. (90% and 82%, respectively).
  - Adverse events comparable
  - Most frequent - moxifloxacin- nausea cephalixin- headache
  - Discontinued in 3% moxifloxacin 4% cephalixin treated patients

- **Giordano PA [31] 2006 USA.**
  - Randomized Investigator blinded
  - Adults and adolescents (>13 yrs) with mild to moderate uncomplicated skin and skin structure infections
  - 1. cefdinir 300 mg twice daily x 10 days
  - 2. cephalexin 250 mg four times daily x 10 days (391 patients well matched)
  - Clinical response – 89% in both groups – even those with MRSA infections improved Cefdinir - convenience higher
  - Enrollment probably skewed towards those with abscesses. Incision and drainage, spontaneous drainage, and needle aspiration are likely to have contributed to clinical response
  - Adverse events comparable
  - Both well tolerated. diarrhea (10% & 4% p = 0.017), nausea (3% & 6%, p = 0.203), vaginal mycosis (3% & 6% p = 0.500).

- **Free A [32], 2006, USA**
  - Randomized Controlled Trial double
  - Patients with secondarily infected traumatic lesions
  - 1. topical retapamulin 1% twice daily x 5 days
  - Cure -89.5% in retapamulin; 91.9% for cephalixin
  - Safety similar
  - Noncompliance 8.0% with cephalixin,
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Setting</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Parish LC[33], 2006 USA | Randomized Controlled Trial     | Patients with secondarily infected dermatitis     | 1. topical retapamulin 1% twice daily x 5 days  
2. oral cephalexin x 10 d | Clinical success rates: 85.9% and 89.7%, respectively  
Both safe and tolerated                                                                                      |
| Rajendran[34]    | Randomized, double-blind, placebo-controlled trial | Outpatients with skin and soft tissue abscesses S. aureus 70.4% (87.8% MRSA) | 1. placebo (84)  
2. cephalexin 500 mg orally 4 times for 7 days (82) after incision and drainage | Clinical cure 7 days  
Placebo - 90.5% (95% CI 0.82 to 0.96)  
Cephalexin 84.1% (95% CI, 0.74 to 0.91) (difference in the two proportions, P = 0.25).  
Antibiotics may be unnecessary after drainage of uncomplicated skin and soft tissue abscesses |
| Casey[38]        | Retrospective                    | GABHS tonsillopharyngitis 1080 children (2-18yrs) | 1. penicillin,  
2. amoxicillin,  
3. first-generation Ceph  
4. β-lactamase stable antibiotic all for 10 d | Frequency of symptomatic relapses within 5 days of completing therapy  
Rank-order for failures P, A, 1st Ceph, β-lactamase stable (P = .005).  
Symptomatic relapse after retreatment more with P than ceph (P = .02). |