Reviewer No. 1: checklist for application of: Cefalexin

In the WHO Essential Medicines List for Children

(1) Have all important studies that you are aware of been included?
   Yes ☑ No ☑

(2) Is there adequate evidence of efficacy for the proposed use?
   Yes ☑ No ☐

(3) Is there evidence of efficacy in diverse settings and/or populations?
   Yes ☑ No ☐

(4) Are there adverse effects of concern?
   Yes ☑ No ☐

(5) Are there special requirements or training needed for safe/effective use?
   Yes ☐ No ☑

(6) Is this product needed to meet the majority health needs of the population?
   Yes ☐ No ☑

(7) Is the proposed dosage form registered by a stringent regulatory authority?
   Yes ☑ No ☐

(8) What action do you propose for the Committee to take?

Reject the application for inclusion of the following presentations of cefalexin:
- Tablets/capsules 250mg
- Oral suspensions 125mg/5ml and 125mg/ml

(9) Additional comment, if any.

In order to identify any additional literature, the following broad and sensitive search was conducted using the PubMed Clinical Query application: (cephalexin OR cefalexin AND
Only one small additional study was identified, which looked at the provision of prophylactic antibiotics in patients presenting to an urban children's hospital with trauma to the distal fingertip, requiring repair. In a prospective randomised control trial, 146 patients were enrolled, of which 69 were randomised to the no-antibiotic group, and 66 were randomised to the antibiotic (cefalexin) group. No difference in the primary outcome measure (the rate of infection at 7 days after repair) was detected between the cefalexin group (1.5%; 95% CI 0.04%-8.16%) and the control group (1.45%; 95% CI 0.04%-7.81%). The authors concluded that “routine prophylactic antibiotics do not reduce the rate of infection after repair of distal fingertip injuries”.

In order to be included in the EML, rather than remain listed only as an alternative in WHO guidelines, cefalexin would have to demonstrate either increased effectiveness, lower incidence of adverse effects or lower cost. An additional factor in its favour would be evidence of reduced rates of resistance associated with its use, or at least evidence that resistance developed more slowly against this agent than against comparator antimicrobials.

The initial application made the following points (emphasis added): “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.”

Two additional resources in relation to efficacy were identified. An extensive narrative review on the rational approach to the therapy of staphylococcal skin infections in children was published in 2005. In this review, Ladhani and Garbash characterized the value of the first-generation cephalosporins in these terms: “With the exception of cefadroxil, the first-generation cephalosporins (cefalexin, cefradine, and cefaclor) have serum elimination half-lives of ≤1 hour and hence have to be administered three to four times daily. The newer agents all have longer half-lives and can be given once or twice daily. Among the first generation cephalosporins, cefaclor is least favored because of its more frequent dose administration, decreased absorption with food, relatively low β-lactamase stability, lower activity against Gram-negative bacteria, and higher rates of adverse effects, including hypersensitivity reactions. On the other hand, cefalexin has been shown to be as effective as the penicillinase-resistant penicillins given four times a day for the treatment of skin and soft tissue infections in children, with treatment success rates of >85% - along with the added advantage of having a twice daily dose regimen. Cefadroxil is at least as effective as cefalexin,[131] and can be given
once daily, but is more expensive. A randomized, multicenter study of children aged 1–18 years given either cefadroxil 30 mg/kg once daily (n = 156) or cefalexin 30 mg/kg/day twice daily (n = 133) [maximum dose 1g for both antibacterials] for 10 days showed that bacteriologic response was greater in the patients treated with cefadroxil (96% vs 89%; p = 0.042), with better treatment completion (95% vs 65% took 100% of their medication; p < 0.0001), although the clinical response in both groups was similar (94% vs 92%; p = 0.48), as were the adverse effects.[121]” The bottom line message from this review was as follows: “The treatment of choice for oral antibacterials remains the penicillinase-resistant penicillins such as flucloxacillin. Cefalexin and erythromycin are suitable cost-effective alternatives with broader cover, although care must be taken with the use of macrolides because of development of resistance to multiple families of antibacterials, particularly the lincosamides. Other cephalosporins such as cefadroxil and cefprozil are also effective, can be given once daily and have a better tolerability profile -- while azithromycin has a further advantage of a 3-day course. However, all of these agents are more expensive.”

A meta-analysis of cephalosporin versus penicillin-based treatment of group A β-haemolytic streptococcal (GABHS) tonsillopharyngitis in children was published in 2004. Trials were only included if they met the following criteria: patients <18 years old, bacteriologic confirmation of GABHS tonsillopharyngitis, random assignment to antibiotic therapy of an orally administered cephalosporin or penicillin for 10 days of treatment, and assessment of bacteriologic outcome using a throat culture after therapy. Primary outcomes of interest were bacteriologic and clinical cure rates. A total of 35 studies (involving 7125 patients) were included, but none had been published after 1999. The odds of bacteriologic cure were greater with the cephalosporins than with the penicillins (OR 3.02; 95% CI 2.49-3.67), taken as a group, and this also held for the individual cephalosporins (cefalexin, cefadroxil, cefuroxime, cefpodoxime, cefprozil, ceftixime, cefditoren, and cefdinir). A similar result was shown in terms of clinical cure rate (OR 2.33; 95% CI 1.84-2.97). The authors felt that there was “a trend for diminishing bacterial cure with penicillin over time, comparing the trials published in the 1970s, 1980s, and 1990s”. The authors concluded that “the likelihood of bacteriologic and clinical failure of GABHS tonsillopharyngitis is significantly less if an oral cephalosporin is prescribed, compared with oral penicillin”. This meta-analysis was strongly criticized on methodological grounds in a subsequent letter to the same journal, with these authors stating that “the problem is the inevitable “contamination” of streptococcal pharyngitis trials by patients who are chronic pharyngeal streptococcal carriers with intercurrent viral pharyngitis. Because cephalosporins are clearly more active than penicillin for eradication of the chronic carrier state, this “contamination” of treatment groups by carriers often contributes to an appearance of superior activity of cephalosporins compared with penicillin in groups of enrollees thought to have bona fide streptococcal pharyngitis”. Their argument is worth repeating in detail: “Recommending cephalosporins as a treatment of choice for GABHS pharyngitis undoubtedly would lead to aggressive marketing and increased prescriptions of all groups of cephalosporins for GABHS pharyngitis, including those that are 20 to 30 times the cost of penicillin and have broad spectra of antimicrobial activity, thus greatly increasing the selection pressure on flora that results in resistant organisms. We believe the situation is analogous to
current efforts to preserve amoxicillin as the drug of choice for acute otitis media and sinusitis in children in the face of mounting marketing pressure to switch to more expensive broad-spectrum cephalosporins and macrolides. Although the use of cephalosporins for group A streptococcal pharyngitis could reduce the number of patients (mostly merely chronic carriers) who continue to harbor the organism in their throats after completing therapy, the economic and ecologic costs involved would make this a Pyrrhic victory for those who advocate a cephalosporin as a drug of choice for streptococcal pharyngitis. Penicillin has stood the test of time satisfactorily for 5 decades, and there are compelling reasons to continue to recommend it as the drug of choice. Its narrow antimicrobial spectrum, inexpensive cost, and impressive safety profile all offer substantial benefits to our patients and society. Casey and Pichichero advocate a major change in the treatment of streptococcal pharyngitis. We believe that, as observed by Bertrand Russell, change is not necessarily progress, and in this instance it certainly would not be”.

Apart from the result itself, what the Casey and Pichichero meta-analysis points to is the problem of comparing bacteriological or clinical cure rates over time, when susceptibility patterns may have changed.

A more recent study, and therefore not included in the 2004 meta-analysis, looked at the comparative efficacy and safety of a short (5-day) cefaclor and the standard (10-day) amoxycillin treatment of group A streptococcal pharyngitis in children. In a randomized trial in 384 children, although adherence was somewhat higher in the children treated with cefaclor (100 vs. 95.1%; p = 0.003), rates of clinical success were similar (91.4% vs. 91.9%; p = 0.974), as were rates of bacteriological success (85.7% vs. 89.6%; p = 0.348) and adverse effects (8.3% vs. 9.4%; p = 0.857).

None of these data present strong evidence to vary the summary presented in the initial application, in relation to efficacy, safety and the development of resistance.

Cefalexin is included in the WHO Pocket Book of Hospital Care for Children as an alternative to cotrimoxazole treatment for UTI, together with ampicillin, amoxicillin, with choice to be based on local sensitivity data. Another reason for exercising this choice might be hypersensitivity to the other alternative agents (the aminopenicillins). In this regard, Pichichero and Casey have published a meta-analysis of trials that compared allergic reactions to a cephalosporin in penicillin-allergic and non-penicillin-allergic patients. Although the number of studies included was small, and the number of participants in each study was limited, the following results were stated: “A significant increase in allergic reactions to cephalothin (odds ratio [OR] = 2.5; 95% confidence interval [CI] = 1.1 to 5.5), cephaloridine (OR = 8.7; CI = 5.9 to 12.8), and cephalexin (OR = 5.8; CI = 3.6 to 9.2), and all first generation cephalosporins plus cefamandole (OR = 4.8; CI = 3.7 to 6.2) were observed in penicillin allergic patients; no increase was

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1 The same data also appeared to be published in the following form: Pichichero ME. Use of selected cephalosporins in penicillin-allergic patients: a paradigm shift. Diagn Microbiol Infect Dis. 2007 Mar;57(3 Suppl):13S-18S.
observed with second generation cephalosporins (OR = 1.1; CI, 0.6 to 2.1) or third generation cephalosporins (OR = 0.5; CI = 0.2 to 1.1).” The authors summarized this evidence as follows: “First-generation cephalosporins have cross-allergy with penicillins, but cross-allergy is negligible with second- and third-generation cephalosporins.” The evidence in relation to cefalexin in particular was drawn from only 1 study (published in 1978) in which penicillin allergy was classified on the basis of history alone (in which 19/291 penicillin-allergic patients reacted to cefalexin, compared with 87/7819 non-penicillin-allergic patients), and 1 study (published in 2005) in which the classification was based on a history confirmed by a skin test (in which 1/28 penicillin-allergic patients reacted, compared with 0/36 non-penicillin-allergic patients). If anything, this meta-analysis underlines the possibility of cross-allergy between cephalosporins, including cefalexin, and penicillins. A recent publication has also pointed out that adverse events associated with antibiotics are implicated in 19% of all emergency department visits for drug related adverse events in the US per year. While penicillins were responsible for the 36.9% (95% CI 34.7%-39.2%) of such emergency department visits, cephalosporins were responsible for 12.2% (95% CI 10.9%-13.5%).

The initial application also expressed concern about the potential for inappropriate use of cefalexin: “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.”

Given the lack of strong evidence showing a major benefit from the more widespread availability of this agent, and the potential for inappropriate use, it would seem prudent not to recommend for its inclusion on the WHO EML for children at this time.

References