



Month/Year of Review: November 2012
PDL Classes: Cephalosporins and Related Antibiotics

Date of Last Review: September 2010
Source Document: Provider Synergies

Table with 2 columns: Current Preferred Agents and Current Non-Preferred Agents*. Rows include 1st, 2nd, and 3rd Generation Cephalosporin, and Penicillin/Beta-Lactamase Inhibitor Combination.

Previous Recommendations:

- 1. There is no evidence to support a difference in efficacy or effectiveness.
2. Evidence does not support a difference in adverse effects or harm among each subclass.
3. Based on published studies, there is no evidence that one cephalosporin has a particular advantage or disadvantage over others among each subclass.
4. Consider prior authorization criteria to allow bridge therapy of these medications during hospitalization rather than changing medication on discharge.

PA Criteria/QL:

No prior authorization criteria required.

Methods:

A MEDLINE OVID search was conducted using all included drugs with either acute otitis media(AOM), community acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), pharyngitis, tonsillitis, gonorrhea, urinary tract infection (UTI), Lyme disease, or impetigo and limits for humans, English language, and controlled clinical trials or randomized controlled trials from 2010 to current.

New Trials:

A total of eight citations resulted from the initial MEDLINE search and after review of titles and abstracts for inclusion, no relevant head-to-head clinical trials were identified. The trials were excluded due to lack of relevant outcomes and/or comparisons and IV route medication administration.

New drugs:

The FDA approved ceftaroline (Teflaro) in October of 2010 for the indications of acute bacterial skin and skin structure infections and community-acquired pneumonia. Ceftaroline is administered by IV infusion only and is covered through the medical benefit.¹⁻³

New Formulations/Indications:

A new formulation of cefixime was FDA approved in June of 2012 as a 400mg capsule and is indicated for uncomplicated UTIs, pharyngitis, tonsillitis, AECB and uncomplicated gonorrhea. The 400 mg capsule is bioequivalent to the 400 mg tablet under fasting conditions. However, food reduces the absorption by 15% following administration of the capsule.⁴ There has been no evidence of clinical benefit or advantage over currently available formulations.

New FDA safety alerts:

There have been no new drug safety alerts for oral cephalosporins or amoxicillin/clavulanate. There was a recent drug safety communication regarding IV cefepime due to cases of nonconvulsive status epilepticus associated with its use, primarily in patients with renal impairment who did not receive appropriate dosage adjustments of cefepime.⁵

New Systematic Reviews:

Two recent systematic reviews from the Cochrane Collection were published evaluating the efficacy and adverse events between cephalosporins, as well as cephalosporins to other classes of antibiotics.

Twenty-five studies (2488 participants) assessed the efficacy and possible adverse effects of interventions to treat non-surgically-acquired cellulitis.⁶ Three of these trials compared IV cephalosporins with penicillin, 6 trials compared different cephalosporins, and one trial compared a macrolide against a first generation cephalosporin. The 6 trials that compared older cephalosporins to newer cephalosporins focused on symptom reduction or symptom free states at the end of treatment. There was no significant difference in percent of patients symptom free between the two groups (87% in older cephalosporins vs. 86.6% in newer cephalosporins, $p=0.97$). None of the studies including oral cephalosporins reported severe adverse events. The most commonly reported adverse events were nausea and vomiting. The one study that compared a macrolide to a cephalosporin analyzed cure at end of treatment which showed failure rates of 4.16% for azithromycin and 4.35% for cephalexin. The distribution of response was similar in both groups, but was not found to be statistically significant ($p=0.37$).⁶

In the other review, seventeen studies (5352 participants) assessed the evidence on the comparative efficacy of different antibiotics in alleviating symptoms, shortening duration of illness, preventing relapse and complications, and adverse effects in the treatment of streptococcal pharyngitis.⁷ Cephalosporins were compared to penicillins in 5 trials (two in adults and 3 in children) and they found there were no statistically significant differences when measuring the resolution of symptoms at the end of treatment. In four of the trials, incidence of relapse was evaluated and they found there was a benefit of treatment with cephalosporins over penicillin in the adult trials but not in the trials with children. No difference in adverse events between the treatment groups was found.⁷

Guidelines:

The Gonococcal Infections Treatment Guidelines and the IDSA skin and soft tissue infections, CAP, pharyngitis, and UTI guidelines have been updated since the date of the last review, but there have been no changes in recommendations of cephalosporin use.

Recommendations:

1. No further research or review needed at this time.
2. Further evaluate comparative costs due no difference in effectiveness or safety between agents.
3. Maintain at least one agent from each subclass (1st, 2nd, 3rd generation cephalosporins and amoxicillin/clavulanate) as well as age appropriate dosage forms.

References:

1. Corey GR, Wilcox MH, Talbot GH, et al. CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J. Antimicrob. Chemother.* 2010;65 Suppl 4:iv41–51.
2. Wilcox MH, Corey GR, Talbot GH, et al. CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J. Antimicrob. Chemother.* 2010;65 Suppl 4:iv53–iv65.
3. File TM Jr, Low DE, Eckburg PB, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. *Clin. Infect. Dis.* 2010;51(12):1395–1405.
4. Faulkner RD, Sia LL, Look ZM, et al. Bioequivalency of solid oral dosage forms of cefixime. *International Journal of Pharmaceutics.* 1988;43(1–2):53–58.
5. FDA Drug Safety Communication. Cefepime and risk of seizure in patients not receiving dosage adjustments for kidney impairment. 2012. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm309661.htm>.
6. Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database Syst Rev.* 2010;(6):CD004299.
7. Van Driel ML, De Sutter AI, Keber N, Habraken H, Christiaens T. Different antibiotic treatments for group A streptococcal pharyngitis. *Cochrane Database Syst Rev.* 2010;(10):CD004406.

Appendix 1: Abstracts of systematic reviews:

1. Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database Syst Rev.* 2010;(6):CD004299.

Background: Cellulitis and erysipelas are usually considered similar manifestations of the same condition which includes a skin infection associated with severe pain and systemic symptoms. The standard treatment for cellulitis is antibiotics, but since there are no current national guidelines in the treatment for these skin infections, a review is required to provide current best evidence and highlight gaps in research.

Objectives: To assess the efficacy and possible adverse effects of interventions to treat non-surgically-acquired cellulitis.

Methods: The Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials, MEDLINE (ovid), EMBASE, and the ongoing trials databases were searched on 4th May 2010. We included randomized controlled trials comparing two or more different interventions with the key terms cellulitis or erysipelas. Two authors independently assessed trial quality and extracted data.

Results: Twenty-five studies were included with a total of 2488 participants. No two trials examined the same drugs, therefore similar drug types were grouped together. Macrolides and streptogramins were found to be more effective than penicillins (RR 0.84, 95% CI 0.73 to 0.97). An oral macrolide compared to intravenous penicillin demonstrating that oral therapies can be more effective than iv therapies (RR 0.85, 95% CI 0.73 to 0.98). Studies comparing penicillins with cephalosporins showed no difference in treatment effect (RR 0.99, 95% CI 0.68 to 1.43). Trials that compared different generations of cephalosporin, also showed no difference in treatment effect (RR 1.00, 95% CI 0.94 to 1.06).

Conclusion: The best treatment for cellulitis cannot be defined at this time and because most recommendations are made on single trials, more studies may need to be conducted.

2. Van Driel ML, De Sutter AI, Keber N, Habraken H, Christiaens T. Different antibiotic treatments for group A streptococcal pharyngitis. *Cochrane Database Syst Rev.* 2010;(10):CD004406.

Background: Pharyngitis is a common upper respiratory tract infection with sore throat as a common symptom. Antibiotics are often prescribed to treat this condition. The review was conducted to determine the best antibiotic to treat sore throats with positive throat swabs for group A beta-hemolytic streptococci (GABHS).

Objectives: To assess the evidence on the comparative efficacy of different antibiotics in alleviating symptoms, shortening duration of illness, preventing relapse, preventing complications, and adverse effects.

Methods: The Cochrane Library, Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched. We included randomized, double-blind trials comparing different antibiotics reporting: clinical cure, clinical relapse, complications, or adverse events. Two authors independently screened trials for inclusion and extracted data.

Results: Seventeen trials were included containing a total of 5352 participants. There were no difference in symptom resolution between cephalosporins and penicillin (OR 0.79, 95% CI 0.55 to 1.12). Clinical relapse was lower with cephalosporins (OR 0.55, 95% CI 0.31 to 0.99) with overall number needed to treat to benefit (NNTB) 50. There were no differences between macrolides and penicillin. Carbacephem showed better symptom resolution post-treatment (OR 0.70, 95% CI 0.49 to 0.99; NNTB 14), but only in children. Children experienced more adverse events with macrolides (OR 2.33; 95% CI 1.06 to 5.15).

Conclusion: Evidence is insufficient to differentiate between antibiotics for GABHS tonsillopharyngitis. Limited evidence in adults suggests cephalosporins are more effective than penicillin for relapse, but the NNTB is high. Limited evidence in children suggests carbacephem is more effective for symptom resolution. Based on these results and considering the low cost and absence of resistance, penicillin can still be recommended as first choice.