Literature Scan: Cephalosporins and Related Beta-lactam Antibiotics

Month/Year of Review: January 2015   **Date of Last Review:** November 2012
PDL Classes: Cephalosporins and Related Antibiotics, oral   **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:

Current Preferred Agents[1]	Current Non-Preferred Agents
Oral Cephalosporins, 1st Generation	Oral Cephalosporins, 1st Generation
Cephalexin cap (*Keflex*)	Cefadroxil cap (*generic*)
Cephalexin susp (*generic*)	Cefadroxil tab (*generic*)
	Cefadroxil susp (*generic*)
Oral Cephalosporins, 2nd Generation	Cephradine cap [DSC]
Cefprozil tab (*generic*)	
Cefprozil susp (*generic*)	Oral Cephalosporins, 2nd Generation
Cefuroxime tab (*Ceftin*)	Cefaclor cap (*generic*)
Cefuroxime susp (*Ceftin*)	Cefaclor ER tab (*generic*)
	Cefaclor susp (*generic*)
Oral Cephalosporins, 3rd Generation	Loracarbef cap [DSC]
Cefdinir cap (*generic*)	Loracarbef susp [DSC]
Cefdinir susp (*generic*)	
	Oral Cephalosporins, 3rd Generation
	Cefditoren tab (*Spectracef*)
	Cefixime cap (*Suprax*)
	Cefixime chew tab (*Suprax*)
	Cefixime susp (*Suprax*)
	Cefixime tab (*Suprax*)
	Cefpodoxime tab (*generic*)
	Cefpodoxime susp (*generic*)
	Ceftibuten cap (*Cedax*)
	Ceftibuten susp (*Cedax*)
Oral Penicillin/Beta-Lactamase Inhibitor Combination	Oral Penicillin/Beta-Lactamase Inhibitor Combination
Amoxicillin/clavulanate tab (*Augmentin*)	Amoxicillin/clavulanate ER tab (*Augmentin XR*)
Amoxicillin/clavulanate chew tab (*Augmentin*)	
Amoxicillin/clavulanate susp (*Augmentin*)	

Abbreviations: cap = capsule; chew = chewable; DSC = discontinued product; ER = extended release; susp = suspension; tab = tablet

Previous Conclusions and Recommendations:[2]

- Evidence does not support a difference in efficacy or safety between cephalosporins.
- Maintain at least one agent from 1st, 2nd and 3rd generation cephalosporins and amoxicillin/clavulanate as well as age appropriate dosage formulations.

Conclusions and Recommendations:

- Maintain at least one oral agent from 1st, 2nd and 3rd generation cephalosporins and amoxicillin/clavulanate as well as age appropriate dosage formulations due to similar effectiveness and safety between these agents.
- Make cefuroxime oral suspension preferred on the PDL due to cost effectiveness.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) comparing oral cephalosporins or oral beta-lactams with beta-lactamases to active controls was conducted with limits for humans and English. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) and Infectious Disease Society of America (IDSA) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines for this class scan. Prospective RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources and if the RCT directly compares antibiotics with clinically relevant outcomes (i.e., cure rate, resolutions of symptoms, etc).

New Systematic Reviews:
A Cochrane Collaboration systematic review compared antibiotics used for community-acquired pneumonia (CAP) in children. There were few comparisons involving cephalosporins; however, the authors concluded that for the treatment of patients with CAP in ambulatory settings, cefpodoxime may be an alternative second-line drug. One multi-centered, open-label study (n=348; ages 3 months to 11.5 years) compared cefpodoxime to amoxicillin/clavulanic acid and found similar response rates after 10 days of treatment (OR 0.69; 95% CI 0.18 to 2.60). Another open-label study (n=140) compared ceftibuten with cefuroxime in children with radiographically confirmed CAP. Sequence generation for randomization and methods to conceal allocation were not clear. Cure rate (OR 0.32; 95% CI 0.11 to 0.94) and failure rate (OR 6.81; 95% CI 1.46 to 31.70) were significantly better in children receiving cefuroxime. However, the review concluded several antibiotics as viable alternative to first-line amoxicillin or trimethoprim/sulfamethoxazole for CAP in children treated in the outpatient setting, including amoxicillin-clavulanate, macrolides, or cephalosporins (cefpodoxime, ceftibuten or cefuroxime) due to lack of robust data demonstrating any clinical differences.[3]

Another review from the Cochrane Collaboration examined the effectiveness of antibiotics in relieving symptoms for breastfeeding women with mastitis. Overall, the authors found insufficient evidence to confirm the effectiveness of antibiotic therapy for the treatment of mastitis. Only two trials met inclusion criteria. One small trial (n=25) found no significant difference in symptom relief or abscess formation between amoxicillin and cephradine.[4]

New Guidelines:
The updated clinical practice guideline from the Infectious Diseases Society of America (IDSA) for the treatment of community acquired pneumonia is projected to be available in fall of 2015.[5]

The IDSA recently published a clinical practice guideline for acute bacterial rhinosinusitis (ABRS) in children and adults. Amoxicillin-clavulanate, rather than amoxicillin alone, is recommended for empiric first-line antimicrobial therapy of ABRS in children (*Strong Recommendation, Moderate-quality Evidence*) and adults (*Weak Recommendation, Low-quality Evidence*). Amoxicillin-clavulanate is also recommended for first-line empiric treatment of ABRS rather than a respiratory fluoroquinolone (*Weak Recommendation, Moderate-quality Evidence*). Empiric therapy should be initiated as soon as ABRS is diagnosed (*Strong Recommendation, Moderate-quality Evidence*). "High-dose" amoxicillin-clavulanate, at a dose of 2 g orally twice daily or 90 mg/kg/day orally twice daily, is recommended in both children and adults with ABRS who live in geographic areas with high rates (≥10%) of penicillin-resistant *S. pneumonia*, those with severe infection, attendance at day care, age <2 or >65 years, recent hospitalization, antibiotic use within the past month, or who are

immunocompromised (*Weak Recommendation, Moderate-quality Evidence*). Duration of empiric treatment is 5-7 days in adults and 10-14 days in children (*Weak Recommendation, Low-Moderate-quality Evidence*).[6]

The IDSA recommends penicillin or amoxicillin for treatment of Group A streptococcal pharyngitis based on narrow spectrum of activity, infrequency of adverse reactions and modest cost (*Strong Recommendation, High-quality Evidence*). In patients with penicillin allergies not anaphylactically sensitive, a first generation cephalosporin, clindamycin or clarithromycin is recommended for 10 days, or azithromycin for 5 days (*Strong Recommendation, Moderate-quality evidence*).[7]

In 2012, the CDC released an update to the Sexually Transmitted Diseases Treatment Guidelines from 2010 which no longer recommends first-line treatment with oral cephalosporins for gonococcal infections. Current guidelines recommend combination therapy with a single intramuscular dose of ceftriaxone 250 mg plus either a single dose of azithromycin 1 g orally or doxycycline 100 mg orally twice daily for 7 days. A single oral 400 mg dose of cefixime is recommended as second-line treatment with either azithromycin or doxycycline if ceftriaxone is not available.[8]

The American Academy of Pediatrics guideline on the diagnosis and management of acute otitis media (AOM) was updated in 2013. High-dose amoxicillin is recommended as first-line treatment for AOM when a decision to treat with antibiotics has been made and the child has not received amoxicillin in the past 30 days, does not have concurrent purulent conjunctivitis, or is not allergic to penicillin (*Grade B Recommendation*). Additional β-lactamase coverage with amoxicillin-clavulanate at 90 mg/kg/day of amoxicillin and 6.4 mg/kg/day of clavulanate (amoxicillin to clavulanate ratio, 14:1) in 2 divided doses for AOM is recommended if the child has received amoxicillin in the last 30 days, has concurrent purulent conjunctivitis, or has a history of recurrent AOM unresponsive to amoxicillin (*Grade C Recommendation*). Alternative initial oral antibiotics include cefdinir 14 mg/kg/day in 1 or 2 doses, cefuroxime 30 mg/kg/day in 2 divided doses, or cefpodoxime 10 mg/kg/day in 2 divided doses. The optimal duration of therapy is uncertain but studies generally favor the standard 10-day therapy for children younger than 2 years and children with severe symptoms. A 7-day course is appropriate for older children with mild or moderate AOM.[9]

New drugs:
None.

New Formulations/Indications:
A new dosage formulation of cefixime 500 mg/5 mL oral suspension (Suprax) was approved by the FDA in February 2013 for the treatment of otitis media, acute exacerbation of chronic bronchitis, uncomplicated urinary tract infections, uncomplicated gonorrhea and pharyngitis/tonsillitis. Two bioequivalence studies were reviewed by the FDA for approval; the FDA used previous findings of safety and effectiveness to support the new dosage form. The new oral suspension formulation is more concentrated than the 100 mg/5 mL and 200 mg/5 mL suspensions already marketed by the manufacturer.[10]

New FDA safety alerts:
None.

New Trials:
Sixty-nine potentially relevant RCTs were evaluated from the literature search. After further review, 66 RCTs did not meet pre-specified criteria and were therefore excluded. The remaining 3 RCTs are briefly described in the table below. Full abstracts are included in the appendix.

Table 1: Description of Randomized Controlled Trials.

Study	Comparison	Population	Primary Outcome	Results
Pallin, et al.[11] RCT, DB	Cephalexin + trimethoprim/sulf amethoxazole (C+TMP/SMX) vs. cephalexin alone (C) for 7-14 days	Patients with cellulitis, without abscess (n=146, median age 29 years, range 3-74)	Clinical cure (defined as resolution of symptoms other than slight erythema or edema)	Clinical Cure: C + TMP/SMX: 62/73 (85%) C: 60/73 (83%) Difference 2.7%; 95% CI, -9.3% to 15%
Casey, et al.[12] RCT, SB	Amoxicillin/clavul anate (A/C) 80 mg/kg/day x 10 days vs. cefdinir (C) 14 mg/kg/day x 5 days	Children 6-24 months with acute otitis media (n=330, mean age 13.1 months)	Clinical cure (defined as afebrile, improved tympanic membrane on exam at 11-14 days)	Clinical Cure: A/C: 141/165 (86.5%) C: 115/165 (71.0%) (p=0.001)
Hooten, et al.[13] RCT, DB, NI	Cefpodoxime 100 mg BID x3 days vs. ciprofloxacin 250 mg BID x 3 days	Adult women with acute uncomplicated cystitis	Clinical Cure (defined as not requiring antibiotics at 30-day follow-up)	Clinical Cure: Cefpodoxime: 123/150 (82%) Ciprofloxacin: 139/150 (93%) Difference 11%; 95% CI, 3% to 18% (CI upper limit >10% demonstrating cefpodoxime is not non-inferior to ciprofloxacin; p=0.57)
Key: CI = confidence interval; DB = double blinded; NI = non-inferiority trial; RCT = randomized controlled trial; SB = single blinded				

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uncomplicated cystitis: a randomized trial. *JAMA* 2012;307:583-9. doi:http://dx.doi.org/10.1001/jama.2012.80.

Appendix:

Abstracts:

Pallin DJ, Binder WD, Allen MB, et al. Clinical trial: comparative effectiveness of cephalexin plus trimethoprim-sulfamethoxazole versus cephalexin alone for treatment of uncomplicated cellulitis: a randomized controlled trial. *Clinical Infectious Diseases*. 2013; 56:1754-62.

BACKGROUND: Community-associated methicillin-resistant S. aureus (CA-MRSA) is the most common organism isolated from purulent skin infections. Antibiotics are usually not beneficial for skin abscess, and national guidelines do not recommend CA-MRSA coverage for cellulitis, except purulent cellulitis, which is uncommon. Despite this, antibiotics targeting CA-MRSA are prescribed commonly and increasingly for skin infections, perhaps due, in part, to lack of experimental evidence among cellulitis patients. We test the hypothesis that antibiotics targeting CA-MRSA are beneficial in the treatment of cellulitis.

METHODS: We performed a randomized, multicenter, double-blind, placebo-controlled trial from 2007 to 2011. We enrolled patients with cellulitis, no abscesses, symptoms for <1 week, and no diabetes, immunosuppression, peripheral vascular disease, or hospitalization (clinicaltrials.gov NCT00676130). All participants received cephalexin. Additionally, each was randomized to trimethoprim-sulfamethoxazole or placebo. We provided 14 days of antibiotics and instructed participants to continue therapy for >1 week, then stop 3 days after they felt the infection to be cured. Our main outcome measure was the risk difference for treatment success, determined in person at 2 weeks, with telephone and medical record confirmation at 1 month.

RESULTS: We enrolled 153 participants, and 146 had outcome data for intent-to-treat analysis. Median age was 29, range 3-74. Of intervention participants, 62/73 (85%) were cured versus 60/73 controls (82%), a risk difference of 2.7% (95% confidence interval, -9.3% to 15%; P = .66). No covariates predicted treatment response, including nasal MRSA colonization and purulence at enrollment.

CONCLUSIONS: Among patients diagnosed with cellulitis without abscess, the addition of trimethoprim-sulfamethoxazole to cephalexin did not improve outcomes overall or by subgroup.

Casey JR, Block SL, Hedrick J, et al. Comparison of amoxicillin/clavulanic acid high dose with cefdinir in the treatment of acute otitis media. *Drugs*. 2012; 72:1991-7.

BACKGROUND: 10 days of amoxicillin/clavulanic acid high dose and 5 days of cefdinir have been the preferred first- or second-line antibiotics for treatment of children with acute otitis media (AOM) since 2004, as recommended by the American Academy of Pediatrics in the USA, but no head-to-head comparison study has been done.

OBJECTIVE: The purpose of the study was to compare the clinical efficacy of amoxicillin/clavulanic acid high-dose therapy for 10 days with cefdinir therapy for 5 days for AOM at recommended doses.

METHODS: This was an investigator-blind trial in young children 6-24 months old with no history of recurrent AOM who were randomly assigned to amoxicillin/clavulanic acid (80 mg/kg/day amoxicillin) or cefdinir (14 mg/kg/day), both in two divided doses. The diagnosis of AOM was based on specific clinical criteria by validated otoscopists at two AOM research centres. The outcome measure for clinical cure was resolution of all symptoms and signs of AOM except for persistence of middle-ear effusion at test-of-cure (TOC) 11-14 days after initiation of antibiotic treatment. Clinical failure was defined as persistence of symptoms and signs of AOM and the need for additional antibiotic therapy. Subjects lost to follow up or who had not taken at least 80% of the prescribed medication were classified as having an indeterminate response. Compliance was monitored using Medical Electronic Monitoring System (MEMS) caps and antibiotic bottle volume measurement at the TOC visit. A logistic regression model was used to estimate the association of age with cure rate. Full interactions in terms of age with treatment were included to estimate any age gradient differential.

RESULTS: A total of 330 children (average age 13.1 months) with AOM were studied. At TOC, 256 children had clinical cure, 69 had clinical failure, and 5 were lost to follow-up. High-dose amoxicillin/clavulanic acid-treated children had a better cure rate (86.5%) than cefdinir-treated patients (71.0%; p=0.001). Cefdinir was correlated with less frequent cure outcomes as children increased in age between 6 and 24 months. The odds ratios for clinical cure per increasing month of age estimated from a logistic regression model for amoxicillin/clavulanic acid high dose and cefdinir treatment groups was 0.992 (95% CI 0.932, 1.056), p>0.05 and 0.932 (95% CI 0.881, 0.986), p=0.01. The differences in the odds ratios are

significant at p<0.002, indicating a stable clinical cure rate across the ages of children studied for amoxicillin/clavulanic acid and decreasing clinical cure rates as children increased in age for cefdinir.

CONCLUSION: In children with bona fide AOM for whom clinical outcomes are assessed by validated otoscopists, 10 days of high-dose amoxicillin/clavulanic acid is significantly more effective than 5 days of cefdinir as therapy for AOM. Because of the identified age effect (correlated to child weight), higher doses of cefdinir may have led to a different conclusion; 10 days of cefdinir may also have led to a different conclusion.

Hooton TM, Roberts PL, Stapleton AE, et al. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. *JAMA*. 2012; 307:583-9.

OBJECTIVE: To determine whether cefpodoxime is noninferior to ciprofloxacin for treatment of acute cystitis.

DESIGN, SETTING, AND PATIENTS: Randomized, double-blind trial of 300 women aged 18 to 55 years with acute uncomplicated cystitis comparing ciprofloxacin (n = 150) with cefpodoxime (n = 150); patients were from a student health center in Seattle, Washington, and a referral center in Miami, Florida. The study was conducted from 2005 to 2009 and outcomes were assessed at 5 to 9 days and 28 to 30 days after completion of therapy. Intent-to-treat and per-protocol analyses were performed; 15 women in the ciprofloxacin group and 17 women in the cefpodoxime group were lost to follow-up.

INTERVENTIONS: Patients were given 250 mg of ciprofloxacin orally twice daily for 3 days or 100 mg of cefpodoxime proxetil orally twice daily for 3 days.

MAIN OUTCOME MEASURES: Overall clinical cure (defined as not requiring antimicrobial treatment during follow-up) at the 30-day follow-up visit. Secondary outcomes were clinical and microbiological cure at the first follow-up visit and vaginal Escherichia coli colonization at each follow-up visit. The hypothesis that cefpodoxime would be noninferior to ciprofloxacin by a 10% margin (i.e., for the difference in the primary outcome for ciprofloxacin minus cefpodoxime, the upper limit of the confidence interval would be <10%) was formulated prior to data collection.

RESULTS: The overall clinical cure rate at the 30-day visit with the intent-to-treat approach in which patients lost to follow-up were considered as having clinical cure was 93% (139/150) for ciprofloxacin compared with 82% (123/150) for cefpodoxime (difference of 11%; 95% CI, 3%-18%); and for the intent-to-treat approach in which patients lost to follow-up were considered as having not responded to treatment, the clinical cure rate was 83% (124/150) for ciprofloxacin compared with 71% (106/150) for cefpodoxime (difference of 12%; 95% CI, 3%-21%). The microbiological cure rate was 96% (123/128) for ciprofloxacin compared with 81% (104/129) for cefpodoxime (difference of 15%; 95% CI, 8%-23%). At first follow-up, 16% of women in the ciprofloxacin group compared with 40% of women in the cefpodoxime group had vaginal E coli colonization.

CONCLUSIONS: Among women with uncomplicated cystitis, a 3-day regimen of cefpodoxime compared with ciprofloxacin did not meet criteria for noninferiority for achieving clinical cure. These findings, along with concerns about possible adverse ecological effects associated with other broad-spectrum beta-lactams, do not support the use of cefpodoxime as a first-line fluoroquinolone-sparing antimicrobial for acute uncomplicated cystitis.