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Month/Year of Review: January 2012
PDL Classes: Macrolides and Related Antibiotics

Date of Last Review: 2010
Source Document: Provider Synergies

Current Status of PDL Class:

- Preferred Agents: AZITHROMYCIN, CLARITHROMYCIN, ERYTHROMYCIN BASE, ERYTHROMYCIN ETHYLSUCCINATE, ERYTHROMYCIN
- Non Preferred Agents: CLARITHROMYCIN ER, DIRITHROMYCIN (DYNABAC®), TELITHROMYCIN (KETEK®), FIDAXOMICIN (DIFICID®)

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events
- Recommend inclusion of at least one medication from this group. Consider including Azithromycin or Clarithromycin for Mycobacterium Avium Complex coverage.
- Telithromycin use is limited, not considered first line therapy; consider PA criteria to limit telithromycin to use for multi-drug resistant community acquired pneumonia and allowing bridge therapy for hospitalized patients on discharge.

Methods:

A Medline OVID search was conducted with the following search terms: erythromycin, clarithromycin, azithromycin, telithromycin, acne vulgaris, endocarditis, sexually transmitted disease, chlamydia, gonorrhea, intestinal infectious disease, infection of skin, infection of subcutaneous tissue, soft tissue infection, Legionnaires Disease, Listeriosis, urethritis, Pertussis, respiratory tract infection, syphilis, community acquired pneumonia, Mycobacterium Avium infection, Duodenal Ulcer Disease, Helicobacter Pylori, gastrointestinal tract infection, COPD, otitis media, conjunctivitis, sinusitis, cervicitis, Pelvic Inflammatory Disease, diarrhea, septicemia, bacterial vaginosis, endometritis, peritonitis, Anthrax, Bartonellosis, Legionella pneumonia, Lyme Disease, Babesiosis, and Cystic Fibrosis. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to October week 2 2012.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC), the Center for Disease Control (CDC) and Infectious Diseases Society of America (IDSA).

New Trials:

A total of 210 citations resulted from the initial MEDLINE search. After review of titles and abstracts for inclusion, no relevant head-to-head clinical trials were identified. Articles were excluded due to the wrong study design (observational), comparator (placebo or other antibiotic class), or outcome (non-clinical).

New drugs:

Dificid (fidaxomicin)[1] is a new macrolide antibiotic approved in May 2011 for the treatment of Clostridium difficile associated diarrhea. Dificid was reviewed for the Oregon P & T Committee in April 2012 and made non-preferred with prior authorization criteria for use.[2]

New Formulations/Indications:
A new packaging combination of amoxicillin, clarithromycin, and omeprazole was approved in 2010. All three medications are packaged together to treat *Helicobacter pylori* infections in patients with current or former Duodenal Ulcer Disease.[3] The new packaging appears to be an attempt to increase patient convenience; there is no evidence of clinical benefit or advantage over currently available formulations.

New FDA safety alerts:
In May 2012, the FDA released a safety alert[4] regarding systemic azithromycin use. An observational study[5] published in the New England Journal of Medicine showed a significant increase in the risk of cardiovascular death in patients treated with azithromycin as opposed to patients treated with either amoxicillin, ciprofloxacin or no drug at all. The FDA acknowledged the association of macrolide use and cardiovascular effects, specifically QT prolongation. In 2011, a warning concerning the risk of QT prolongation was added to all systemic erythromycin[6], clarithromycin[7] and azithromycin[4] products' labeling. The safety alert recommends that Healthcare professionals should be aware of the potential for QT interval prolongation and heart arrhythmias when prescribing or administering macrolides.

New Systematic Reviews:
Three new or updated, relevant systematic reviews were identified.

A 2011 meta-analysis attempted to compare and evaluate the efficacy and safety of azithromycin and clarithromycin in cystic fibrosis (CF) patients. The primary efficacy outcome was the impact on the deterioration of lung function measured by changes in FEV_1; safety outcomes included adverse events and mortality. Azithromycin treatment showed a significant increase in FEV_1% (3.22%; 95% CI = 1.38 to 5.06) when compared with placebo. Adverse events were not significantly different between the azithromycin groups and the placebo group. Only one small trial with clarithromycin was included making comparisons with azithromycin difficult. [8]

A Cochrane review looking at pertussis treatment regimens was updated in 2011. In treating *Bordetella pertussis*, short-term antibiotics (azithromycin for three to five days, or clarithromycin or erythromycin for seven days) were as effective as long-term (erythromycin for 10 to 14 days) (RR 1.01; 95% CI 0.98 to 1.04), but had fewer side effects (RR 0.66; 95% CI 0.52 to 0.83). There were no differences in clinical outcomes or microbiological relapse between short and long-term antibiotics. Side effects were not compared with one antibiotic to another.[9]

A Cochrane review updated early 2012, looked at comparative treatment of genital chlamydial infections in pregnant women. Patients treated with amoxicillin, erythromycin, clindamycin or azithromycin were included. For the outcome microbiological cure, clindamycin versus erythromycin was non-significant (OR 0.42; 95% CI 0.11 to 1.68). In comparing azithromycin with erythromycin, erythromycin was more likely achieve a microbiological cure (OR 0.38; 95% CI 0.19 to 0.74). Amoxicillin was not significantly more effective than erythromycin in achieving microbiological cure (OR 0.54, 95% CI 0.28 to 1.02) but was better tolerated than erythromycin (OR 0.16; 95% CI 0.09 to 0.30).[10]

Guidelines:
Updated guidelines for COPD from the American Thoracic Society[11] and Global Initiative for Chronic Obstructive Lung Disease[12] were reviewed; as was the updated chlamydia guideline[13] from the Centers for Disease Control. Updated treatment guidelines for bacterial rhino-sinusitis[14], community acquired pneumonia[15], Lyme Disease and Babesiosis[16], and acute uncomplicated cystitis[17] from the Infectious Disease Society of America were also evaluated. No changes regarding the use of macrolides were found.

Recommendations:
- There is insufficient evidence from head-to-head studies that consistently demonstrate the superiority of one macrolide over another. No further research or review needed at this time.
- Evaluate comparative costs in executive session.

References:

1. Anon. Dificid (fidaxomicin) Prescribing Information. *Optimer Pharmaceuticals; San Diego CA*. 2011.

2. Oregon P&T Minutes. Oregon P & T Minutes 2012_04_26_PT_Minutes.pdf. Available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meeting. Accessed October 22, 2012.

3. Anon. Omeprazole, Clarithromycin, and Amoxicillin Prescribing Information. *DAVA Pharmaceuticals; Fort Lee, NJ*. 2010. Available at: http://drugs-about.com/pdf/omeprazole-apotex/omeprazole-apotex.pdf. Accessed October 21, 2012.

4. FDA. Safety Alerts for Human Medical Products > Zithromax (azithromycin): FDA Statement on risk of cardiovascular death. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm304503.htm. Accessed October 22, 2012.

5. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the Risk of Cardiovascular Death. *New England Journal of Medicine*. 2012; 366(20):1881–1890.

6. FDA. Safety Information > EES (erythromycin ethylsuccinate) Granules for oral suspension, Eryc (erythromycin delayed-release) capsules, Ery-Ped liquid and PCE (erythromycin particles in tablets) 333 mg and 500 mg film coated tablets. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm294615.htm. Accessed October 22, 2012.

7. FDA. Safety Information > Biaxin Filmtab (clarithromycin tablets, USP), Biaxin XL Filmtab (clarithromycin extended-release tablets), Biaxin Granules (clarithromycin for oral suspension, USP). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258816.htm. Accessed October 22, 2012.

8. Cai Y, Chai D, Wang R, Bai N, Liang B-B, Liu Y. Effectiveness and safety of macrolides in cystic fibrosis patients: a meta-analysis and systematic review. *Journal of Antimicrobial Chemotherapy*. 2011; 66(5):968–978.

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10. Brocklehurst P, Rooney G. Interventions for treating genital chlamydia trachomatis infection in pregnancy. In: The Cochrane Collaboration, Henderson S, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 1998. Available at: http://doi.wiley.com/10.1002/14651858.CD000054. Accessed October 22, 2012.

11. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann. Intern. Med.* 2011; 155(3):179–191.

12. Rosin R, Anzueto A, Bourbeau J, deGuia T, Hui D. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Revised 2011. GOLD_Report_2011Dec30.pdf. 2011. Available at: http://www.goldcopd.org. Accessed October 22, 2012.

13. Geisler WM. Diagnosis and management of uncomplicated Chlamydia trachomatis infections in adolescents and adults: summary of evidence reviewed for the 2010 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. *Clin. Infect. Dis.* 2011;53 Suppl 3:S92–98.

14. Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin. Infect. Dis.* 2012; 54(8):e72–e112.

15. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin. Infect. Dis.* 2011;53(7):e25–76.

16. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin. Infect. Dis.* 2006;43(9):1089–1134.

17. Gupta K, Hooton TM, Naber KG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clinical Infectious Diseases*. 2011;52(5):e103–e120.

Appendix 1

Systematic Review Abstracts

Cai Y, Chai D, Wang R, Bai N, Liang B-B, Liu Y. Effectiveness and safety of macrolides in cystic fibrosis patients: a meta-analysis and systematic review. *Journal of Antimicrobial Chemotherapy*. 2011;66(5):968–978.

Objectives To evaluate the efficacy and safety of macrolides in cystic fibrosis (CF).

Methods Randomized controlled trials (RCTs) of macrolides for the treatment of CF published in PubMed, the Cochrane Library and Embase were searched. Application of inclusion and exclusion criteria, data extraction, and assessment of methodological quality were independently performed in duplicate. The primary efficacy outcome was the impact on the deterioration of lung function (changes in FEV_1 and FVC). Safety outcomes included adverse events and mortality.

Results Eight RCTs (seven with azithromycin and one with clarithromycin) were found in the systematic review and six RCTs with azithromycin (654 patients) were included in the meta-analysis. Azithromycin treatment showed a significant increase in FEV_1% (3.22%, 95% CI = 1.38–5.06, P = 0.0006, I^2 = 0%) and FVC% (3.23%, 95% CI = 1.62–4.85, P < 0.0001, I^2 = 0%) compared with placebo. In individuals with baseline *Pseudomonas aeruginosa* colonization, both FEV_1% (4.80%, 95% CI = 1.66–7.94, P = 0.003, I^2 = 42%) and FVC% (4.74%, 95% CI = 1.92–7.57, P = 0.001, I^2 = 0%) increased significantly. The incidence rates of the main side effects (cough, headache, abdominal pain, vomiting, nausea and diarrhoea) were not significantly different between the azithromycin-treated group and the placebo group. The RCT of clarithromycin, involving 18 patients, showed its effects on clinical improvement; however, the small sample size made comparisons with azithromycin difficult.

Conclusions Long-term use of azithromycin can improve lung function, especially for *P. aeruginosa*-colonized CF patients. There was no evidence of increased adverse events with azithromycin. More data are needed to verify the best azithromycin regimen and to evaluate other macrolides in CF patients.

Altunaiji SM, Kukuruzovic RH, Curtis NC, Massie J. Antibiotics for whooping cough (pertussis). In: The Cochrane Collaboration, Altunaiji SM, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2007.

Background Whooping cough is a highly contagious respiratory disease. Infants are at highest risk of severe disease and death. Erythromycin for 14 days is currently recommended for treatment and contact prophylaxis but its benefit is uncertain.

Objectives To assess the risks and benefits of antibiotic treatment of and contact prophylaxis against whooping cough in children and adults.

Search methods We searched the Cochrane Central Register of Controlled Trials (CENTRAL Issue 4, 2010), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, the Database of Abstracts of Reviews of Effects (DARE Issue 4, 2010), MEDLINE (1966 to January Week 1, 2011) and EMBASE (1974 to 18 January 2011).

Selection criteria Randomised controlled trials (RCTs) and quasi-RCTs of antibiotics for treatment of and contact prophylaxis against whooping cough in children and adults.

Data collection and analysis Three to four review authors independently extracted data and assessed the quality of each trial.

Main results Thirteen trials with 2197 participants met the inclusion criteria: 11 trials investigated treatment regimens; two investigated prophylaxis regimens. The quality of the trials was variable. For eradicating *Bordetella pertussis* (*B. pertussis*) from the nasopharynx, short-term antibiotics (azithromycin for three to five days, or clarithromycin or erythromycin for seven days) were as effective as long-term (erythromycin for 10 to 14 days) (risk ratio (RR) 1.01; 95% confidence interval (CI) 0.98 to 1.04), but had fewer side effects (RR 0.66; 95% CI 0.52 to 0.83). Trimethoprim/sulphamethoxazole for seven days was also effective. Nor were there differences in clinical outcomes or microbiological relapse between short and long-term antibiotics. For preventing infection by treating contacts older than six months of age, antibiotics did not significantly improve clinical symptoms, nor the number of cases developing culture-positive *B.pertussis*. Side effects were reported with antibiotics and they varied from one antibiotic to another.

Brocklehurst P, Rooney G. Interventions for treating genital chlamydia trachomatis infection in pregnancy. In: The Cochrane Collaboration, Henderson S, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 1998.

Background Chlamydia trachomatis is a sexually transmitted infection. Mother-to-child transmission can occur at the time of birth and may result in ophthalmia neonatorum or pneumonitis in the newborn.

Objectives The objective of this review was to assess the effects of antibiotics in the treatment of genital infection with Chlamydia trachomatis during pregnancy with respect to neonatal and maternal morbidity.

Search methods We searched the Cochrane Pregnancy and Childbirth Group's Trials Register and added the results to Studies awaiting classification (September 2006).We updated this search on 3 January 2012 and added one additional trial report to the awaiting classification section.

Selection criteria Randomised trials of any antibiotic regimen compared with placebo or no treatment or alternative antibiotic regimens in pregnant women with genital Chlamydia trachomatis infection.

Data collection and analysis Two review authors assessed trial quality and extracted data independently. Study authors were contacted for additional information.

Main results Eleven trials were included. Trial quality was generally good. Amoxicillin appeared to be as effective as erythromycin in achieving microbiological cure (odds ratio 0.54, 95%confidence interval 0.28 to 1.02). Amoxicillin was better tolerated than erythromycin (odds ratio 0.16, 95% confidence interval 0.09 to 0.30). Clindamycin and azithromycin also appear to be effective, although the numbers of women included in trials are small.