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Literature Scan: Oral Tetracyclines

Month/Year of Review: May 2015

Date of Last Review: 2010
Source Document: Provider Synergies

Current Status of PDL Class:

Preferred Agents

DOXYCYCLINE HYCLATE, CAPSULE	DOXY-LEMMON™, ED DOXY-CAPS™, MORGIDOX™, VIBRAMYCIN™
DOXYCYCLINE HYCLATE, TABLET	ACTICLATE™, DOXY-LEMMON™
DOXYCYCLINE MONOHYDRATE, CAPSULE	ADOXA™, MONODOX™
DOXYCYCLINE MONOHYDRATE, SUSPENSION	VIBRAMYCIN™
TETRACYCLINE HCL, CAPSULE	ACHROMYCIN V™, ALA-TET™, SUMYCIN™

Non-Preferred Agents

DEMECLOCYCLINE HCL, TABLET	
DOXYCYCLINE CALCIUM, SYRUP	VIBRAMYCIN™
DOXYCYCLINE HYCLATE, TABLET DR	DORYX™
DOXYCYCLINE MONOHYDRATE, CAPSULE IR DR	ORACEA™
DOXYCYCLINE MONOHYDRATE, TABLET	ADOXA PAK™, ADOXA™ AVIDOXY™
MINOCYCLINE HCL, CAPSULE	DYNACIN™, MINOCIN™
MINOCYCLINE HCL, TABLET ER 24HR	SOLODYN™
MINOCYCLINE HCL, TABLET	

Conclusions and Recommendations:

- Doxycycline is the most commonly recommended tetracycline and is recommended for multiple indications as first line, second line, or as part of combination therapy base on limited, low quality evidence.
- Tetracycline is recommended for select indications based on expert opinion and low quality evidence.
- Minocycline is a potential agent for methicillin-susceptible S. aureus (MSSA) and MRSA in non-pregnant adults and children over 7 years base on limited, low quality evidence.
- Compare relative cost in executive session.

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Previous Conclusions and Recommendations:

- Recommend inclusion of one or more agents from this class including doxycycline.
- Recommend limiting use in the last half of pregnancy.
- Recommend limiting use in pediatrics under age 8 years.
- Recommend considering limiting use of demeclocycline to treatment of SIADH.

Indications for tetracyclines:

- Sexually transmitted diseases (e.g. infections due to Neisseria gonorrhoeae, Chlamydia trachomatis, etc.)
- Respiratory tract infections (e.g. Community Acquired Pneumonia)
- Urinary tract infections (e.g. due to Klebsiella species)
- Acne vulgaris
- Rosacea
- Other less common infections/illnesses cause by
    - Rickettsiae species
    - Borrelia recurrentis
    - *Haemophilus ducreyi*
    - *Yersinia pestis (plague)*
    - *Francisella tularensis*
    - *Brucella* species
    - *Bartonella bacilliformis*
    - *Calymmatobacterium granulomatis*
    - Bacillus anthracis (Anthrax)
    - Treponema pertenue (Yaws)
    - Actinomyces israelii

Methods:

A Medline OVID search was conducted with the following search terms: demeclocycline, doxycycline, minocycline, and tetracycline. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to March 2015. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. 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). Treatments for Acne vulgaris and rosacea are excluded from coverage in the Oregon Health Plan. Therefore guidelines and reviews for these indications were excluded from this evaluation.

A summary of potentially relevant trials are available in **Appendix 1**. Abstracts of these trials are available in **Appendix 2**.

New Systematic Reviews:

1. A 2012 Cochrane Collaborative report evaluated treatments for brucellosis.[1] Eight studies evaluated doxycycline plus rifampicin vs. doxycycline plus streptomycin. Doxycycline plus rifampicin was found to be less effective than doxycycline plus streptomycin (RR 1.91, 95% CI 1.07-3.42). There was no significant difference in adverse reactions. Five studies evaluating doxycylcine plus rifampicin vs. fluroquinolones vs. rifampicin found no significant difference in efficacy or adverse reactions.

New Guidelines:

1. The Infectious Disease Society of America (IDSA) published guidelines for the management of community-acquired pneumonia in children in 2011.[2] Doxycycline is included as alternative therapy for the outpatient treatment of mycoplasma pneumonia and Chlamydia infections in children over 7 years old. Doxycycline is also included as alternative empiric therapy for presumed atypical pneumonia in immunize and non-immunized children over 7 years in inpatient and outpatient settings. These recommendations are extrapolated from studies in adults.
2. The Department of Health and Human Services Center for Disease Control (CDC) published guidelines for the treatment of sexually transmitted diseases in 2010.[3] These recommendations stated that tetracyclines are no longer suitable for the treatment of *N. gonorrhoeae* in the U.S. due to the development of antibiotic resistance. Based on two studies, the CDC recommends doxycycline or tetracycline for the treatment of primary, secondary, late latent and latent syphillis in non-pregnant, penicillin-allergic patients. Doxycycline is also recommended for the treatment of granuloma inguinale, lymphogranuloma venereum, chlamydial urethritis, cervicitis, uncomplicated gonococcal infections of the cervix, urethra, and rectum, chlamydial infections in non-pregnant adults and children over 7 years old. Doxycycline is recommended for use in pelvic inflammatory disease (PID) as both step down therapy post gentamicin therapy or for mild to moderate PID with or without metronidazole. Based on one trial, doxycycline is recommended in combination with ampicillin/sulbactam for the treatment of *C. trachomatis*, *N. gonorrhoeae*, and anaerobes in women with tubo-ovarian abscess. In men, doxycycline is recommended for the treatment of epididymitis and proctitis in adult men.
3. In 2012, the CDC issued an update to the 2010 recommendations.[5] Doxycycline, in combination with ceftriaxone, was recommended for uncomplicated gonorrhea. There were no other tetracycline-related changes to treatment recommendations.
4. In 2014, the IDSA updated guidelines for the treatment of skin and soft tissue infections.[6] Recommendations for tetracycline antibiotics in this guideline are based on a limited, low quality studies. Either tetracycline or doxycycline were recommended over penicillin for treatment of mild cases of tularemia based on low quality evidence from two studies. Despite a lack of controlled trials, tetracyclines were recommended for the treatment of cutaneous anthrax. Tetracycline was identified as a potential treatment for bubonic plague, despite the lack of comparative clinical trials. Doxycycline is strongly recommended as one of several alternatives for the treatment of Impetigo and Ecthyma when methicillin-resistant S. aureus (MRSA) is suspected in penicillin allergic patients, though no references are cited. Likewise, doxycycline and minocycline are listed as potential agents for methicillin-susceptible *S. aureus* (MSSA) and MRSA in non-pregnant adults and children over 7 years. Doxycycline is recommended for the treatment of bacillary angiomatosis, glanders and mild tularemia.

New FDA Drug Approvals:

None identified.

New Formulations/Indications:

None identified.

New FDA Safety Alerts:

None identified.

Author: Ted D. Williams Date:4/27/2015

References:

1. Yousefi-Nooraie, Reza, Mortaz-Hejri S, Mehrani M, Sadeghipour P. Antibiotics for treating human brucellosis. *The Cochrane Database of Systematic Reviews*. 2012;(10). doi:10.1002/14651858.CD007179.pub2.

2. 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-e76. doi:10.1093/cid/cir531.

3. Workowski KA, Berman S, Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59(RR-12):1-110.

4. 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. doi:10.1093/cid/ciq257.

5. Centers for Disease Control and Prevention (CDC). Update to CDC's Sexually transmitted diseases treatment guidelines, 2010: oral cephalosporins no longer a recommended treatment for gonococcal infections. *MMWR Morb Mortal Wkly Rep*. 2012;61(31):590-594.

6. Stevens DL, Bisno AL, Chambers HF, et al. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2014;59(2):e10-e52. doi:10.1093/cid/ciu296.

7. Kayabas U, Karahocagil MK, Ozkurt Z, et al. Naturally Occurring Cutaneous Anthrax: Antibiotic Treatment and Outcome. *Chemotherapy*. 2012;58(1):34-43.

8. Mile B, Valerija K, Krsto G, Ivan V, Ilir D, Nikola L. Doxycycline-rifampin versus doxycycline-rifampin-gentamicin in treatment of human brucellosis. *Tropical Doctor*. 2012;42(1):13-17. doi:10.1258/td.2011.110284.

9. Baltacioglu E, Aslan M, Saraç Ö, Saybak A, Yuva P. Generalized Aggressive Periodontitis: A Pilot Study. *J Can Dent Assoc*. 2011;77:b97.

10. Cerar D, Cerar T, Ružić-Sabljić E, Wormser GP, Strle F. Subjective Symptoms after Treatment of Early Lyme Disease. *The American Journal of Medicine*. 2010;123(1):79-86. doi:10.1016/j.amjmed.2009.05.011.

Appendix 1: New Clinical Trials

Ten (10) potentially relevant clinical trials were evaluated from the literature search. Three trials studied surrogate measures, kinetics or in vitro and were therefore excluded. Two trials evaluated tetracycline as part of H. pylori eradication treatment, which is outside the scope of this review, and were therefore excluded. One trial was for parenteral therapy, which is outside the scope of this review, was also excluded. One non-controlled trials was excluded. The remaining trials are briefly described in the table below.
Full abstracts are included in Appendix 2.

Table 1: Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Analysis of clinical results of systemic antimicrobials combined with nonsurgical periodontal treatment for generalized aggressive periodontitis: a pilot study.[9]	Full-mouth scaling and root planing (FRP) alone vs. A. FRP + metronidazole 250 mg and amoxicillin 250 mg three times daily for 10 days B. FRP + doxycycline 200 mg day one and 100 mg days 2-14	18-40 years old, 20 or more teeth, clinical attachment loss and probing pocket depth of 6mm or greater at 2 or more sites in 12 or more teeth.	Changes in periodontal index values at 2 months.	PPD and CAL in the FRP + metronidazole/amoxicillin was significantly less than the other two group. PPD and CAL in the FRP + doxycycline group was significantly less than FRP alone.
Subjective Symptoms after treatment of early Lyme disease.[10]	Doxycycline 100 mg twice daily for 15 days vs. cefuroxime axetil 500 mg twice daily	Patients 15 years or older with either typical solitary erythema migrans or skin lesions less than 5cm in diameter with a recent tick bite. Exclusion: previous lyme disease, pregnant, lactating, immunocompromised, meningitis, recent antibiotic, multiple erythema migrans lesions, or allergic to either medication	Complete response at 2,6, and 12 months	No significant difference in response rates at any time interval.

Appendix 2: Abstracts of Clinical Trials

Title:
Analysis of clinical results of systemic antimicrobials combined with nonsurgical periodontal treatment for generalized aggressive periodontitis: a pilot study
OBJECTIVE:
To assess the clinical benefit of either metronidazole and amoxicillin or doxycycline administered immediately after completion of full-mouth scaling and root planing (FRP) for treatment of generalized aggressive periodontitis.
METHODS:
Patients, 18 to 40 years of age, referred to the Karadeniz Technical University department of periodontology between January 2009 and September 2009 were randomly chosen for inclusion in the study if radiographic examination showed they had > 20 teeth, clinical attachment loss and a probing pocket depth (PPD) > 6 mm at 2 sites in > 12 teeth, > 3 of which were not first molars or incisors. Patients were divided into 3 groups and received FRP alone, FRP combined with metronidazole and amoxicillin, or FRP combined with doxycycline. PPD, clinical attachment level, gingival index, gingival bleeding index and plaque index values were measured at baseline and 2 months after treatment.
RESULTS:
Thirty-eight patients with untreated generalized aggressive periodontitis participated in the study. In all 3 groups, the periodontal index values 2 months after treatment were significantly lower than baseline values ($p < 0.05$). Values for PPD and clinical attachment level were more improved in the antibiotic groups than in the FRP group, and more improved in the metronidazole and amoxicillin group than in the doxycycline group ($p < 0.05$). However, no statistically significant intergroup difference was observed in the other clinical parameters ($p > 0.05$). Systemic use of metronidazole and amoxicillin or doxycycline was clinically superior to FRP for reducing PPDs > 7 mm ($p < 0.05$).
CONCLUSION:
Treatment of generalized aggressive periodontitis with FRP alone or FRP combined with systemic antibiotics provided significant clinical benefits that reduced the need for periodontal surgery. Both antibiotic treatments had additional clinical benefits over those of FRP alone

Title:
Subjective Symptoms after treatment of early Lyme disease
BACKGROUND:
Controversy exists over the significance and even the existence of post-Lyme disease symptoms because of the high rate of similar background symptoms in the general population.
METHODS:
A European, prospective clinical trial in which doxycycline and cefuroxime axetil were compared in the treatment of adult patients with erythema migrans included a control group to address this question. Evaluations of patients were conducted at baseline, 14 days, and 2, 6, and 12 months after enrollment. Control subjects were evaluated at baseline and at 6 and 12 months. Subjective symptoms that newly developed or intensified since the onset of erythema migrans or the date of enrollment for controls were referred to as "new or increased symptoms."
RESULTS:
Doxycycline and cefuroxime axetil had comparable efficacy. At both 6 and 12 months, the frequency of new or increased symptoms in patients with erythema migrans did not exceed the frequency of such symptoms in a control group of individuals of similar gender and age without a clinical history of Lyme disease. At 12 months after enrollment, only 5 (2.2%) of 230 evaluable patients reported new or increased symptoms, and in none of the patients were these symptoms of sufficient severity to be functionally disabling.

CONCLUSION:
No significant differences were identified between doxycycline and cefuroxime axetil in the treatment of European patients with erythema migrans. The frequency of nonspecific symptoms in patients did not exceed that of a control group at > or =6 months after enrollment. We advocate inclusion of appropriate non-Lyme disease control groups in future studies in which nonspecific subjective symptoms are assessed after antibiotic therapy

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 3 2015
1. Demeclocycline/
2. Doxycycline/
3. Minocycline/
4. Tetracycline/
5. 1 or 2 or 3 or 4
6. limit 5 to (humans and yr="2010 -Current" and controlled clinical trial)